Microdosimetry and nanodosimetry for internal emitters

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Abstract
In this review, the multiscale approach in radiation dosimetry in relation to biological effects is first briefly introduced. The need of dosimetry in microscopic regions, for example in cells, is then addressed, followed by a review of the basic microdosimetric quantities of internal emitters. The requirement of understanding the molecular biological effects of radiation leads to the dosimetric concept in the nanometer ranges, where the initial events produced at the molecular level cause the subsequent cellular and tissue effects that may lead to cancer. Track structure theory is particularly introduced in nanodosimetry for internal emitters. The relationship between the quantities in macroscopic dosimetry, e.g. absorbed dose, the microdosimetric quantities, e.g. specific energy and lineal energy, and the nanodosimetric characteristics, the track structures is inherently established in a derivational way. The significance of microdosimetric and nanodosimetric quantities in understanding and interpreting the mechanisms of radiobiological effects is addressed. Several applications of microdosimetry and nanodosimetry for internal emitters in radon and thoron progeny dosimetry and risk analysis, in targeted radionuclide therapy, in modelling of DNA damages and as a tool in the potential interpretation of dose-response relationship at low doses and dose rates are given. Finally, the potential future development of internal microdosimetry and nanodosimetry is outlined.

1 Introduction
In radiation research, radiation induced biological effects and cancer development are multistage processes, therefore, radiation doses in different scales or levels (multiscale dosimetry) are needed for understanding the mechanisms and quantification of the dose-response relationship. From the historical point of view, just a few months after the discovery of x-rays in 1895 by W.C. Röntgen, adverse effects, for example, dermatitis and radiation damages to the hands and fingers of early experimental investigators in the United Kingdom and in Germany, from high exposure of x-rays were reported (Clarke and Valentin, 2005). In 1925 the International Commission on Radiation Units and Measurements (ICRU) was formed and attempted to quantify a quantity termed "roentgen" for description of the energy deposition in the living body after irradiation (ICRU, 1928). However, "roentgen" was late in 1956 redefined as a quantity for the measurement of the exposure of x-rays, and a new term "absorbed dose" was established as a quantity for measuring the energy imparted and deposited in a volume (ICRU, 1954). The unit "roentgen" was then used as a measure of a quantity "exposure dose" (ICRU, 1957) and later of the quantity "exposure" (ICRU, 1962) with the SI unit "C kg^{-1}". After the Second World War in 1950, the International of Commission on Radiological Protection (ICRP) set up six sub-committees including one on the permissible dose for internal radiation (ICRP, 1955), and published explicitly a recommendation on permissible dose for internal radiation (ICRP, 1959).

The concept "absorbed dose" is used as a quantity to describe the energy deposited per unit of mass in a volume of interest. However, also the spatial distribution of the radiation greatly influences the radiation physical conditions. Zirkle (Zirkle, 1940) introduced the concept of linear energy absorption which was later called *linear energy transfer* (LET) (Zirkle et al., 1952) to describe the energy transfer including excitation and ionization along particle tracks. LET was applied to interpret the biological effects in terms local energy deposition. Due to the secondary electrons along the tracks, the LET must be clarified with energy transfer less than some specified value Δ, L_Δ, or with all

transfer energy possible, L_∞ (ICRU, 1970). In current practice, the mean organ absorbed dose is commonly applied in internal dosimetry and LET is used to define the quality factor.

Interpretation of biological effects of internal emitters requires the energy deposition in a small volume, say cellular size, other than mean absorbed dose in organs and tissues. It was recognized in the 1950s by Rossi and coworkers that the average "absorbed dose" failed to assess the radiobiological detriment effect in the micrometer or even smaller level, like mutation, chromosome aberrations and carcinogenic risk. They tried to measure the energy deposition and found the fluctuation of absorbed dose in these small microscopic volumes. They proposed the "event size, Y" (later named as "lineal energy, *y*") for radiation quality (Rossi, 1959) and "local energy density, Z" (later named as "specific energy, *z*") to replace the use of absorbed dose in a microscopic volume (Rossi et al., 1961). The microscopic distribution of energy imparted to cellular levels, which was then termed "microdosimetry"- though the microdosimetry founder Harald Rossi proposed alternative terminology (Goodhead, 1987; Rossi, 1968)- was proposed as a new radiation quantity and it was theoretically completed subsequently by Kellerer (Kellerer, 1970). Microdosimetry was successfully used to explain the dose response relationship in cellular microenvironment. The distributions of microdosimetric quantities can be solved by so-called compound Poisson process (Kellerer, 1985).

This microscopic dosimetric concept, initially used for external dosimetry, was directly applied for internal dosimetry and was indicated as "internal microdosimetry" by Roesch (Roesch, 1977, 1978) for especially quantifying the radiation energy received by a single cell from internal alpha and beta emitters. Internal microdosimetry was successfully applied in radon and thoron inhalation dosimetry and risk estimation (Aubineau-Laniece et al., 1998; Fakir et al., 2005; Hofmann et al., 2007; Hofmann and Steinhäusler, 1979; Hofmann et al., 2014 ; Hui et al., 1990; Li and Zheng, 1996), as well as for alpha emitters in lungs (Aubineau-Laniece et al., 2002; Chouin and Bardies, 2011; Fisher, 1988; Polig, 1983). Recently, the microdosimetric concept has been extensively used in targeted radionuclide therapy for quantification of cellular doses (Jadvar, 2017; Williams et al., 2008), such as in the new alpha radiopharmaceuticals (Amato et al., 2015; Hobbs et al., 2012; Sgouros et al., 2010) and the beta emitting radiopharmaceutical ^{90}Y microsphere (Pasciak et al., 2016). Besides this medical use, microdosimetry is continually being applied in radiation protection.

Biological effects, however, were recognized as a result from damages of small molecules, e.g. deoxyribonucleic acid (DNA), like double strand breaks (DSBs) which can be experimentally measured. The microdosimetric quantities could not describe the energy or events occurring in the space of DNA, genetic damages and chromosome aberrations (Goodhead, 1987; Paretzke, 1978). In fact, parallel to the development of the concept of microdosimetry, "tracks" generated by radiation in living material were addressed as the primary events, which lead to genetic damages, even early in the 1940s by Lea (Lea, 1946, 1956). Energy deposition in nanometer scale, not micrometer range, can provide the spatial energy deposition events or doses in nanometer volumes as in DNA. Direct simulation of interaction of radiation tracks along the DNA helix is needed. Track structure calculations, which were proposed by Paretzke (Paretzke, 1987), were applied in the radiation molecular biology as a physical tool for studying the mechanism of radiation actions on molecular level. Recently, nanodosimetry was proposed explicitly as a dosimetric tool to explore the radiation molecular mechanism to distinguish it from the microdosimetry, which is dedicated more to the cellular level (Grosswendt, 2004, 2005, 2006; Rabus and Nettelbeck, 2015). The term "nanodosimetry" has been used in the early times by others (Baum et al., 1973; Holt, 1978).

Nanodosimetry and track structure calculations can provide radiation dose information in molecular scale for interpreting and understanding the mechanism of the radiation and further for quantifying the risk. The details of track structures of radiation in the nanometer scale can be simulated by the event-by-event Monte Carlo simulation technique and measured by particular nanodosimeter instruments. The cross sections of different types of radiation in liquid water (taken frequently as a surrogate for biological materials) and complex biomolecules (considering the target heterogeneity on nanometer scale) serve as basic input to Monte Carlo track structure simulation programs, e.g. PARTRAC and Geant4-DNA, and play an important role; their determination is a rather arduous work. Radiation

chemical diffusion in living tissues and biological effects modelling are research fields in nanodosimetry, which, however, will not be included in this review, because it is a dosimetry based review. Nanodosimetry and track structure calculations are continuing to contribute to the debate of linear no-threshold (LNT) hypothesis regarding risk of low doses and low dose rates which has recently been raised again in radiobiology and medicine. A combination of radiobiology, epidemiology and modelling is supposed to be a promising strategy to solve this issue.

In microdosimetry and nanodosimetry, the temporal and spatial distributions of radionuclides in the targeted cells and molecules are needed as input for determining the specific energy and physical tracks; these provide a research field for microdosimetric biokinetic modelling, especially for internal emitters.

In the future, microdosimetry could be strengthened in targeted radionuclide therapy and radiation therapy for cancers and non-cancer diseases. Nanodosimetry may contribute to the application of nanoparticles in nuclear medicine and radiotherapy; in this case, the radiation is applied externally, while the conjugated nanoparticles are delivered to the tumor, and local doses in nanometer range are needed for assessing the biological response. Cross sections, in particular of low energy electrons in living materials, need validation by experimental data. The improvement and inclusion of chemical and effects modules in the nanodosimetry codes need more work. The reduction of uncertainties of cross sections in different nanodosimetry codes requires further comparison work. In the following sessions, we will guide the reader through the development of microdosimetry and nanodosimetry and the applications for internal emitters, finally discussing the future perspective of this research field.

2 Multiscale dosimetry – macrodosimetry, microdosimetry and nanodosimetry

The development of radiation dosimetry was a history of understanding the relationship between the quality and energy deposited and transferred in the regions under interest with the induced biological effects. Radiation dosimetry deals with the measurement of absorbed dose / dose rate resulting from the interaction of ionizing radiation with matter, which was later used as a quantity for the calculation of the energy deposited in a point and a volume by radiation. In this section, the main concepts during the development of quantification of dosimetry in different scale are introduced and definitions of some dose related quantities are given.

In the early time, a quantity “roentgen” was used to measure that quantity produced by x-rays and denoted as “r”. Later, it was recognized that the quantity expressed by “roentgen” actually should be appropriately defined by absorbed dose, D. The “roentgen” is used to measure the exposure (Parker and Roesch, 1962; Roesch and Attix, 1968). A new term “absorbed dose” was defined to describe the energy deposition of radiation in living tissues. This quantity was used to quantify the energy produced by radiation in a large volume or mass and try to relate this dose to the harm effects and skin cancer observed in the early time. It is interesting to note that long before radiation was discovered, the term “dose” was used as an amount of medicine delivered to patients and it can be traced back to Paracelsus in 1538 with his statement “Dosis sola facit venenum” – the dose makes the poison (Rühm, 2016). The definition of “absorbed dose” was at first established by ICRU in 1954 (ICRU, 1954) and is recently revised in ICRU Report 85a (ICRU, 2011).

Absorbed dose, D

The *absorbed dose, D*, is the quotient of $d\bar{\varepsilon}$ by d*m*, where $d\bar{\varepsilon}$ is the mean *energy imparted* by ionizing radiation to matter of mass d*m*, thus $D = \frac{d\bar{\varepsilon}}{dm}$ with unit of J kg^{-1}. The special name for the unit of absorbed dose is gray (Gy). It should be noted here, the absorbed dose, *D*, is considered a point quantity, although it should be recognized that the physical process does not allow d*m* to approach zero in a strict mathematical sense. In the limit of a small domain, the mean specific energy $\bar{z}$ is equal to the absorbed dose D.

Energy imparted ε

The energy imparted, ε, to the matter in a given volume is the sum of all *energy deposits* in the volume, thus: $\varepsilon = \sum_i \varepsilon_i$ with unit: J, where the summation is performed over all energy deposits, ε_i, in that volume.

Energy deposit, ε_i

The energy deposit, ε_i, is the energy deposited in a single interaction, i, thus: $\varepsilon_i = \varepsilon_{in} - \varepsilon_{out} + Q$, with Unit: J, where ε_{in} is the energy of the incident ionizing particle (excluding rest energy), ε_{out} is the sum of the energies of all charged and uncharged ionizing particles leaving the interaction (excluding rest energy), and Q is the change in the rest energies of the nucleus and of all elementary particles involved in the interaction (Q>0: decrease of rest energy; Q<0: increase of rest energy).

In internal dosimetry, the mean organ absorbed dose is commonly calculated and related to biological effects in tissue, with the related quantities organ equivalent dose and effective dose. They are used to predict the risk to a person who incorporated radionuclides. The absorbed dose in regions like organs and tissues may be regarded as macrodosimetry.

However, absorbed dose is a statistic average quantity and disregards the random fluctuations and the biological effects are related to the energy deposit and event in cellular region. If the volume under investigation becomes smaller, the absorbed dose becomes fluctuant or random. If the fluence and absorbed dose in a unit mass are kept constant, the biological effectiveness produced by different type of radiation depends on its quality. A concept of *linear energy transfer* was introduced by Zirkle (Zirkle et al., 1952) to describe this radiation quality.

Linear energy transfer, LET

The *linear energy transfer* or *restricted linear electronic stopping power*, L_Δ, of a material, for charged particles of a given type and energy, is the quotient of dE_Δ by dl, where dE_Δ is the mean energy lost by the charged particles due to electronic interactions in traversing a distance dl, minus the mean sum of the kinetic energies in excess of Δ of all the electrons released by the charged particles, thus: $L_\Delta = \frac{dE_\Delta}{dl}$. Unit: J m^{-1}.

Although LET is a proper quantity for description of radiation quality, LET is, by definition, an average property of particles and it does not take into account the random nature of energy loss along a track, for example, the secondary electrons. This can result in wide variations in energy deposition by identical particles passing through small volumes (Goodhead, 1987). The early biological results and scientific guess (Lea, 1946; Zirkle, 1932) have already addressed that the microscopic changes of molecular and genetic changes play a great role for the final macroscopic effects. The interactions and energy transfer of radiation with matters occurred at the atomic levels, and the frequently number and types of atomic processes are proportional to specific energy, which was defined as energy deposited in micrometer-sized volume.

Microscopic quantities, lineal energy and specific energy and their distributions were proposed by Rossi and co-workers as they measured a large statistical fluctuation in patterns of radiation energy deposition over micrometer distances with a low-pressure proportional counter (Rossi and Rosenzweig, 1955). Goodhead (Goodhead, 1987) gave a useful working definition of microdosimetry "could be the study of the physical microscopic properties of ionizing radiations, their interactions, and their patterns of energy deposition, with particular emphasis on the inhomogeneities and stochastic nature of the interactions".

Lineal energy, y

The *lineal energy*, y, is the quotient of ε_S by $\bar{l}$, where ε_S is the energy imparted to the matter in a given volume by a single energy-deposition event, and $\bar{l}$ is the mean chord length of that volume, thus $y = \frac{\varepsilon_S}{\bar{l}}$ with unit: J m^{-1}.

Specific energy, z

The *specific energy* (imparted), *z*, is the quotient of ε by *m*, where ε is the energy imparted by ionizing radiation to matter in a volume of mass *m*, thus $z = \frac{\varepsilon}{m}$ with unit: J kg^{-1}. The special name for the unit of specific energy is gray (Gy).

The biological experiments showed that DNA strand breaks, nucleotide damages, cell inactivation, and mutation were analyzed in terms of energy concertation in 10 to 100 nanometers ranges. These findings demonstrated that the energy deposited in nanometer ranges or volumes were important to the primary lesions in somatic effects. Paretzke (Paretzke, 1987) developed track structure theory to calculate the energy deposition in a DNA volume and relate the initial event to the later effects of radiations. To generate track structures of radiation passing through matters, the cross sections are essential as input parameters.

Cross section, σ

The *cross section*, σ, of a target entity, for a particular interaction produced by incident charged or uncharged particles of a given type and energy, is the quotient of *N* by Φ, where *N* is the mean number of such interactions per target entity subjected to the particle fluence Φ, thus $\sigma = \frac{N}{\Phi}$ with unit: m^2. A special unit often used for the cross section is the barn, b, defined by 1 b = 10^{-28} m^2. It should be noted here, that a full description of an interaction process requires, among other things, the knowledge of the distributions of cross sections in terms of energy and direction of all emergent particles resulting from the interaction. Such distributions, sometimes called *differential cross sections*, are obtained by differentiations of σ with respect to energy of emergent particles and solid angle.

The track structures of radiation in living materials can be calculated based on the available cross sections by using Monte Carlo simulation programs. The tracks provide detail information of energy deposition and transferred, if the tracks are superimposed upon the structure model of target molecules, e.g. DNA, the damages of molecules, like DNA strand breaks and fragments can be modelled (Friedland et al., 1998). The physical tracks interact with liquid water and produce chemical radical, which can attack DNA directly and lead to strand breaks (von Sonntag, 2006).

Taking the molecular radiation biology processes like, DNA damages, chromosome aberrations, cellular deaths or transformation, and the extension to somatic effects of radiation interactions in the human body into account, biological mathematical models are developed for assessment of the health risk exposed to radiation (Rühm et al., 2017). This is an up-to-date research topic, which may contribute to the debate of LNT model at low doses (Siegel et al., 2017; Weber and Zanzonico, 2017).

3 Internal microdosimetry

The concept of microdosimetry was developed by Rossi and coworkers (Rossi, 1959; Rossi et al., 1961) as they tried to analyze the biological effects by absorbed dose in a smaller volume. Rossi proposed terms “event size Y” and “local energy density, Z” to quantify the measured results instead of using LET and absorbed dose. This quantity Z was later redefined as specific energy *z*. They even setup tissue equivalent proportional counter to measure the absorbed dose in small volume elements. The measured “absorbed dose” in very small diameter volume demonstrates the distribution of dose of neutrons, proton and x-rays (Rossi, 1968). Kellerer (Kellerer, 1970, 1985) completed the theory of structural microdosimetry. Roesch (Roesch, 1977) applied these concepts to the internal emitters and developed an appropriate method named internal microdosimetry, especially for alpha- beta- and low x-rays.

We start from the lineal energy *y*. By definition, y is the quotient of ε_S by $\bar{l}$, where of ε_S is the energy imparted to the matter in a volume by a single energy-deposition event and $\bar{l}$ is the mean chord length of that volume. In addition to specific energy, z, we define a single event specific energy, z_1 as the quotient of ε_S by *m*. Because the single energy-deposition event ε_S is a stochastic quantity, y and z_1 are

represented by the distributions *f(y)* and $f_1(z)$. It is obvious to find out the relationship for a single even in a volume:

$z_1 = \frac{y}{\rho d^2}$ and $z(Gy) = 0.204 \frac{y(keV/\mu m)}{[d(\mu m)]^2}$ where ρ is the density and d the diameter of the sphere.

$f(y) = (S/4) f(z_1)$ where *V* and *S* are the volume and surface area for a convex site, respectively.

The average specific energy produced by an event and multiple events in a site at an absorbed dose, *D*, can be calculated as:

$\bar{z}_F = \int_0^\infty z f_1(z) dz$ with the average number M=$\bar{v}$ of events is equal to D/ $\bar{z}_F$.

$\bar{z} = \int_0^\infty z f(z; D) dz$ with $D = \lim_{n\to\infty} \bar{z}$.

If the specific energy produced by *n* single events is z. and the increment of the *n*th single event is z_1, then the specific energy produced by (n-1) single events is ($z-z_1$). The probability density in specific energy of ($z-z_1$) produced by the (n-1) single events is denoted $f_{n-1}(z-z_1)$. Because of the stochastic nature of the energy deposition event by a particle crossing the target site, the specific energy increment produced by the *n*th event, z_1 can be any value *z*', between 0 and z. The probability density of the value *z*' being the single event density $f_1(z)$. Therefore the probability density $f_n(z)$ of specific energy, z, which is produced by exactly n single events, can be calculated by:

$$f_n(z) = \int_0^z f_1(z) f_{n-1}(z - z') dz'$$

This formula can be rewritten as a *n*-fold convolution of $f_1(z)$: $f_n(z) = [f_1(z)]^{*n}$.

At an absorbed dose, *D*, the probability of exactly n events occurring inside the target site follows the Poisson distribution as the events are assumed to be independent:

$$p(n) = \frac{M^n}{n!} e^{-M}$$

The dose-dependent specific energy distribution, *f*(z; D), i.e. *f*(z) at the absorbed dose *D*, is determined by summing up the product $p(n) \bullet f_n(z)$ upon all numbers of events between 0 and *n* which may occur in the site.

$$f(z; D) = \sum_{n=0}^{\infty} \frac{M^n}{n!} e^{-M} [f_1(z)]^{*n} \qquad (1)$$

This equation (1), which is the central equation in microdosimetry, describes a compound Poisson process. In particular, when no event occurred, i.e. no energy was deposited inside the target site, the probability density, *f*(0) is defined as delta function $\delta(z)$ at z = 0. This indicates the probability that the target site is missed by radiation. For point sources of internal emitters, the single event density can be replaced by a source-target distance, r, dependent function, $f_1(z;r)$, the mean number of event, $M=a_i w_i$, where a_i is mean number emitted by the point source and w_i is the probability that the particle emitted by this point source hits the target site (Roesch, 1977).

To solve the equation (1), one needs to calculate the singe-event specific energy distribution, $f_1(z)$. It is difficult to measure the microscopic spectra in a site of diameter less than 0.3 μm. Indeed, it is an ambitious task to compute the energy imparted to a small volume with diameter of nanometer range. Kellerer (Kellerer, 1970, 1985) proposed a method applying so-called energy-loss straggling problem given by Landau (Landau, 1965) and Vavilov (Vavilov, 1957). However, from the view of track structure, the single-event distribution can be computed from Monte Carlo-simulated tracks for any circumstance of radiation types and geometries of target sites (Wilson, 1977; Wilson and Paretzke, 1980).

In order to condense the complete energy transfer points in tracks to a microdosimetric parameter or function for analysis of radiation effect mechanism, it is useful to consider a particular summation of the energy deposits in the track *j* of a charged particle of specified type and energy like:

$$\tilde{T}_j(x) = \sum_i \sum_k \varepsilon_i \varepsilon_k \Big/ \sum_i \varepsilon_i$$

where i runs over all energy transfer points of the track and k runs over all transfer points within a distance up to x from the transfer point, t_i, $T_j(x)$ is a function of the distance, x, which reflects the proximity of the transfer points of the track j, where j runs over all n tracks in the selected volume. The expectation value of $T_j(x)$ is the integral proximity function, $T(x)$.

$$T(x) = \lim_{n\to\infty} \frac{1}{n} \sum_{j=1}^{n} \tilde{T}_j(x)$$

The integral proximity function, $T(x)$, is a weighted mean energy imparted to a spherical volume of radius x, centered at an arbitrary transfer point of an arbitrary track. $t(x)$ is the derivative of $T(x)$ with respect to x. It is called the differential proximity function.

$$T(x) = \int_0^x t(x')dx'$$

$T(x)$ can be also named as point-pair distance distributions, of the geometric objects T and S. $t(x)$ can be understood as distance distribution of energy transfers multiplied by total energy of the tracks.

4 Internal nanodosimetry

The main task of microdosimetry developed by Rossi (Rossi, 1968) and Kellerer (Kellerer, 1970, 1985) or internal microdosimetry extended by Roesch (1977, 1978) is to determine the distribution of specific energy and lineal energy and related these quantitate directly to biological radiation effects of radiation. It is the hypothesis of dual radiation action which postulates that cellular lesion production is found to depend on two terms that are proportional to the first and the second power of the absorbed dose in micrometer volumina (Paretzke, 1978). The fundamental shortcoming of quantities such as lineal energy and specific energy is that they contain no information on the spatial pattern of energy deposition with the simulate volume. However, experimental data show that these internal patterns are very important in determining the biological effectiveness of radiation and the experimental measurement of y and z is usually limited to a simulated tissue volume of 0.3 μm diameter, whereas it is known that much smaller dimensions are important in biological mechanism of radiation actions. Further limitation of application of y and z is that the averaged quantities of distribution are used and it is impossible to deduce from z_F and z_D the frequency of a given volume being hit or missed (Goodhead, 1987). Nevertheless, the microdosimetric quantities do have practical application in the cellular level, hit probability calculation, the dose distribution in cellular region. From a development point of view, the y and z is a classification and a reduction of data produced by track structure calculations and can be regarded as a phase of developing period from conventional dosimetry to nanodosimetry.

To overcome the limitation of y and z quantities, radiation tracks, especially those of protons and heavier ions have been described in terms of their average track profiles of energy density perpendicular to their direction of travel (Katz et al., 1972). These have been applied to radiation chemistry, physical track detectors, and cellular biological systems. The approach has sometimes been called “track structure” but this terminology is misleading since the individual tracks are represented as continuous, amorphous distributions of average energy deposition with no account being taken of the statistical fluctuations of individual secondary electrons or of primary interactions. Track profiles are sometimes subdivided into regions of core and penumbra. Mozunder and Magee (Mozunder and Magee, 1966) introduced spatial patterns of energy transfer along radiation tracks which can be classified approximately as spurs, blobs, and short tracks by these concepts have been applied in radiation chemistry and recently to simple biological systems.

However, the general limitation of these alternatives to microdosimetry is their ignoring fluctuations in energy deposition and electron track structures and did not include information on what microscopic concentration of energy are critical in determining biological effects. The track structure theory addressed by Paretzke (Paretzke, 1974; Paretzke, 1987) with Monte Carlo simulation programs

provided most detailed description of the microscopic pattern of radiation interaction with matters and energy deposition in a nanometer scale. Radiation track structure theory and Monte Carlo radiation transport simulation gives a full history of radiation passing through matter. The importance of radiation tracks structure in biological effects was demonstrated already by Lea in his monography "Thus the ionization in tissue irradiated by x-rays of 1.5 Å is not distributed at random but is localized along tracks as in" a Wilson-chamber photographs (page 10, 2nd 1956). Tracks and initial events lead to molecular damages. The diameter of DNA helix is about 2 nm. In the track structure simulation, the interaction sites between track and DNA moiety and its backbone are even relevant other than the doses, the energy deposited in the volume of molecule is usually used, based on biological assumptions, to produce damages. Grosswendt (Grosswendt, 2004, 2005, 2006) and Rabus and Nettelbeck (Rabus and Nettelbeck, 2015) proposed nanodosimetry for the target volume based on the track structure calculations.

To calculate the track structure generated by radiation in living materials, the cross sections (Section 2) of different radiation types are primarily required. To calculate the cross sections, the interaction processes of radiation with matters should be studied. In the early time, the calculation of cross section of radiation transport in water vapor as surrogate of tissues. For internal dosimetry, photons, electrons and alpha particles are more relevant than proton and neutrons and heavy ions. Generally cross sections should be validated by experimentally measurements.

Photons interact with molecules in three main processes: photoelectric effect, Compton scattering and electron-positron pair production event. The fourth process, elastic photon interaction, also Rayleigh scattering is important at low energies below 100 keV, and this event changes the direction of photon and the energy deposition of location of the next inelastic event (Evans, 1955; Paretzke, 1987). The cross sections for the processes in liquid water and other materials are well calculated and available to quantify the energy deposition in the biological materials (Berger et al., 2010).

The energy of an electron is mainly transferred to matter through interaction of electric field of moving electrons with that of electron bound in the medium (Bethe, 1930; Inokuti, 1971). The interactions lead to electronic ionizations and ionizations and the slow down electron with residual energy lower than 10 eV will lose energy by direct excitation of rotational, translational or vibrational modes of molecular affected. Elastic, excitation and ionization cross sections for electrons were calculated for water vapor (Paretzke, 1988), liquid water (Dingfelder et al., 1999), and DNA molecular moiety (Bernhardt and Paretzke, 2003; Tan et al., 2004) to mimic the interactions of electrons in biological tissues.

An α-particle is a charged heavy particle and is not very penetrating. Therefore α-particle is important in cellular level in lungs and other organs especially through inhalation. In biological material, energy transfer of α-particle occurs preliminarily through excitations and ionizations and is described by stopping power which is defined average energy loss per unit distance along its path. However, the lost energy by α-particle transfers to the secondary radiation, like electrons and photons which penetrate to distance from the particle tracks.

Track structures are in general simulated by using Monte Carlo (MC) simulation program which are imbedded calculated cross sections. Investigators should implement the geometry of the targets and radiation types under study into these MC programs for specific problems. There are several well developed MC programs which are mostly used in the community of track structure calculations and nanodosimetry, e.g. PARTRAC (Friedland et al., 2011), Geant4-DNA (Incerti et al., 2016), PENELOPE (Salvat, 2014), NASIC (Li et al., 2015). Experimental biological endpoint effects, like DNA DSBs, chromosomal aberrations and cell survival fractions are useful for comparison to the theoretical simulations.

In experimental nanodosimetry, some particular characteristics of the track structure, namely the cumulative probabilities F_1, F_2 and F_3 of measuring at least 1, 2 or 3 ionizations in the target volume,

are almost uniquely determined by the mean cluster size of the ionization cluster size distribution, independent of its particular shape (Conte et al., 2017). This experimental investigation aims at establishing a new concept of radiation quality that builds on measurable characteristics of the particle track structure at the nanometer scale.

5 Microdosimetric and nanodosimetric biokinetic modelling

Internal dosimetry is usually calculated based on the distribution of radionuclides around the targets, for example, organs and tissues for absorbed dose, cells for microscopic doses and DNA molecules for nanoscale doses. The radionuclide distribution in human body as a function of time is generally studied by biokinetics and biokinetic modelling. As Roesch applied microdosimetry in internal dosimetry (Roesch, 1977), the phenomena of inhomogeneous distribution of radionuclides in and around cellular environment was addressed as one of the reasons why a microdosimetric approach should be used. The evitable step for calculating specific energy is to determine the $f_1(z;D)$ firstly, and this needs the quantitative distribution of radionuclides in the cells. For this purpose, microdosimetric biokinetic modeling is proposed as a technical tool in microdosimetry. For the similar reason, nanodosimetric biokinetic modelling is designed as a tool in nanodosimetry. The use of "microdosimetric" and "nanodosimetric" instead of "micro" and "nano" is to emphasize the objective of biokinetic modeling for dosimetric purposes.

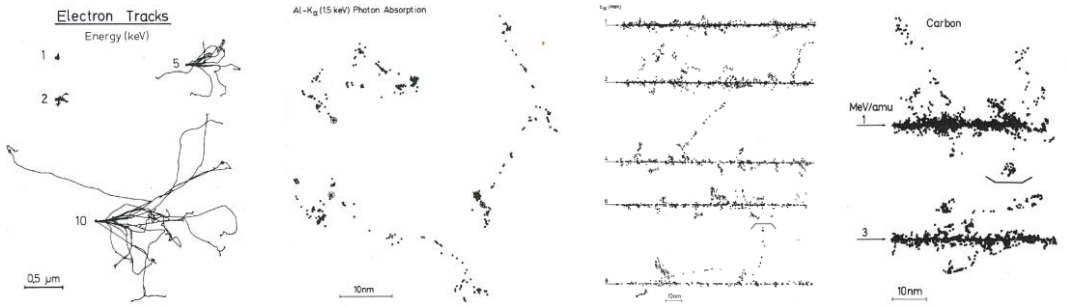
The dynamic distribution of radionuclides in organ, tissue, and cell are the basis for biokinetic modelling. For this purpose, imaging is an important method for determining the kinetics of the radionuclides in cells. Based on images, a model can be setup to simulate the kinetics of the radionuclides. Microdosimetric biokinetic modeling is currently practical for the new approved targeted radiopharmaceuticals with alpha and beta emitters. For example, biokinetic distributions of decay products are needed for ^{227}Th decays to ^{223}Ra if the new ^{227}Th alpha-emitter is used for cancer treatment. Recently some nanoparticle-based targeted molecular imaging and therapeutic tracers were developed. The kinetics of the tracers with DNA or other molecules can well be established by nanodosimetric biokinetic modeling.

6 Relationship of absorbed dose, specific energy and track structures

Depending on the biological endpoint effects investigated in different scale, the doses in different levels are needed for establishing a dose-response relationship. The biological effects are initiated from the molecular damages, for example DSBs, to chromosomal aberrations, cell killing and cell death, tissue effect, to somatic effect or later developed cancer. Especially for low doses and low dose rates, the cancer is a long development process from the initial event. However, the initial physical events and chemical radicals, occurred during 10^{-16}-10^{-12} seconds after irradiation (Adams and Jameson, 1980), usually cannot be measured but are theoretically simulated. The experimentally measured biological endpoints, like DSBs and SSBs, cell survival fractions are generally later effects days or weeks after irradiation. Transferring or converting the initial events, track structures and DNA hits, to the later corresponding specific energy in cellular level and absorbed dose in the tissue level is needed.

Starting from the cross sections of different radiation types, applying Monte Caro simulation technique, radiation tracks are described as any event that occurred during the ionizations and excitations as radiations and particles traverse the materials: the coordinates of the interactions, interaction types, energy deposited, energy transferred and etc. are recorded (Fig. 1). By implementing the molecular targets, the interactions with the backbone or base of the DNA, are further recorded. The chemical radicals are sometimes classified also to the initial events, but not to the physical tracks. These radiation tracks are used to predict the interactions of radiation with targets in nanometer ranges. These damages can be further modelled through chemical interactions and further to biological endpoint effects, e.g. DNA and chromosome aberrations, DNA fragmentation,

gene mutation (e.g. *hprt* and *p*53), and so on. These biological processes can be further used by mathematical modelling to predict cellular and tissue effects and even risk estimation.



a b c d

Fig. 1. Simulated track structures of electrons (a), photons (b), alpha partciles (c) and heavy ions (d) in water vapor (Paretzke, 1987)

From tracks to specific energy

These simulated physical tracks are a huge data set and contain valuable information of all the events produced by radiation. The data reduction is needed to identify the important parameters as descriptors that relate to further processes and phenomena. For this reason, the tracks can be classified and discriminated according to absorbed dose concept, energy and volume or to locations and types of events, new chemical species. Based on the absorbed dose concept, the tracks can be classified to microdosimetric quantities, z and y and the related distributions *f*(*z*) and *f*(*y*) if a small volume of element is defined (Paretzke, 1987), especially, the $f_1(z)$ which is essential for resolution of the compound Poisson process, can be easily calculated. Another relationship between track structures and microdosimetric concept is the proximity function $T(r)$ (Section 2), which can be calculated from the spatial distribution of the energy transfer position along the tracks.

From specific energy to mean absorbed dose

It is quite obvious, if the energy imparted inside a large volume representing organ or tissues can be classified, the absorbed dose, D can be directly obtained from the energy deposition of the tracks. Alternatively, absorbed dose can be derived by the integral from *f*(*z*): D= $\bar{z} = \int_0^\infty zf(z)dz$.

From specific energy to cell survival fraction

Carlson et al. (Carlson et al., 2008) proposed a microdosimetric method for determining survival fractions. Starting from classical cell survival fraction $S(D) = \exp(-\alpha D - \beta D^2)$, replace the intra-track effects term with $\alpha = \theta\Sigma + \kappa\bar{z}_F\Sigma^2$ and the inter-track term with $\beta = (\kappa/2)\Sigma^2$, one get:
$S(D) = \exp(-(\theta\Sigma + \kappa\bar{z}_F\Sigma^2)D - ((\kappa/2)\Sigma^2)D^2)$,
where θ and κ are cell or tissue specific parameters related to biological processing DNA damage. Σ is the number of DSB per Gy per cell, this parameter can be estimated from dedicated MC program, for example PARTRAC code (Friedland et al., 2011); $\bar{z}_F$ is the mean specific energy of single event, which can be obtained from microdosimetry.

7 Applications

In this section, several examples are given to demonstrate the strength of microdosimetry and nanodosimetry in the modern radiation research with addresses on internal radionuclide therapy, modeling of DNA damages and risk assessment at low doses.

7.1 Microdosimetry of radon and thoron progeny in human respiratory tracts

Hofmann and Steinhäusler applied microdosimetric concept to assess the specific energy in the human lung as microdosimetry was introduced into internal radon dosimetry (Hofmann and Steinhäusler, 1979), It is noted that in 1970, James and Kember (James and Kember, 1970) measured the frequency distribution of alpha-particle incidence in targets of similar dimensions to cell nuclei, which is similar

to the distribution of lineal energy. Hui et al. (Hui et al., 1990) calculated distribution of specific energy of radon decay products applying Monte Carlo technique by taking into account the two cells at risk in the human respiratory tract. Thereafter several investigate develop computer codes to analyze the distribution of inhaled radon products in human respiratory tracts and calculate the microdosimetric distributions (Aubineau-Laniece et al., 1998; Aubineau-Laniece et al., 2002; Balásházy and Hofmann, 2000; Fakir et al., 2005; Hofmann et al., 2007; Li and Zheng, 1996). Microdosimetry of thoron progeny was also calculated recently (Hofmann et al., 2014). In this session, the principle method of calculating microdosimetric distribution and dose conversion factor for radon is presented here as an example.

Physical decay of ^{222}Rn

The naturally occurring noble gas ^{222}Rn decays into the so-called short-lived radon progeny ^{218}Po, ^{214}Pb, and ^{214}Bi/^{214}Po. Among them, only two are alpha emitters: ^{218}Po: E = 6.0 MeV, R(tissue) = 47 μm, and ^{214}Po: E = 7.69 MeV, R(tissue) = 72 μm. Basal and secretory cells are currently considered as the sensitive target cells in the bronchial epithelium as potential progenitor cells of bronchial carcinomas (ICRP, 1994). The radiological and environmental parameters of the radon progeny in the inhaled air which eventually determine the exposure of these target cells are activity concentrations, aerosol size distributions of attached and unattached, and corresponding attached and unattached fractions.

Quantification of surface activities of radon progeny

The steady-state surface activities of both ^{218}Po and ^{214}Po nuclides on bronchial airway surfaces, which represent the alpha particle sources for the irradiation of basal and secretory cells, are produced by the initial deposition of the inhaled radon progeny and their subsequent clearance by mucociliary action. The first step in lung dose calculations is the deposition of the attached and unattached nuclides on bronchial airway surfaces. The individual personal parameters which determine their deposition in human airways are the anatomy of the lung, such as size and structure of the branching airway system as well as total lung volume, and breathing parameters, such as breathing frequency and inhaled tidal volume. The primary physical deposition mechanisms acting upon an inhaled radon progeny are diffusion and impaction, depending on particle diameter and flow rate. Once radon progeny are deposited on airway surfaces, the mucociliary action starts to transport them upstream to the mouth. Mucociliary clearance velocities depend on airway diameter, decreasing in an exponential fashion from the highest value in the trachea down to the smallest (about four orders of magnitude) value in the most distal terminal bronchioles.

Interaction of sources and targets

Alpha particles emitted from the steady-state activities on bronchial airway surfaces can hit the basal and secretory cells in the bronchial epithelium, located either at the same side as the emission site (near wall) or on the opposite side (far wall), provided that the distance between the emission site and the target site is within the range of the alpha particles. Due to the short ranges of the alpha particles in tissue there exists a strong geometric correlation between alpha emission sites and target cells. Thus the energy deposition in a cell nucleus located at a given depth in tissue depends on the probability that an alpha particle actually hits that nucleus (distance between emission site and target sit) and, in case of a hit, on the energy deposition as a function of the alpha particle range (Bragg curve).

Two macroscopic sources of randomness contribute to the microscopic energy deposition in the nuclei of sensitive target cells: the inter- and intra-subject variability of radon progeny surface activities in a given airway generation, and the depth distribution of target cells within the epithelial tissue. As a result of the inherent variability of bronchial airway dimensions in a given airway generation, the resulting variability of deposition fractions and mucociliary clearance velocities leads to a wide distribution of uniformly distributed ^{218}Po and ^{214}Po surface activities (Hofmann et al., 2000a). This source variability is further enhanced by the variable thickness of the bronchial epithelium and the depth distribution of target cells within epithelial tissue. The effect of the biological variability on resulting steady-state surface activities and energy deposition in sensitive target cells has been modeled by the Monte Carlo deposition, clearance and dosimetry code IDEAL (Hofmann et al., 2010).

Experimental and CFD simulation studies for inhaled attached and unattached radon progeny in bronchial airway bifurcation models have demonstrated that inhaled nuclides are preferentially deposited within bifurcation zones, exhibiting hot spots in the vicinity of the peak of the carinal ridge (Balásházy and Hofmann, 2000). This inhomogeneous source distribution further increases the randomness of cellular energy deposition.

Single event and specific energy distribution

Microscopic sources of the energy deposition in microscopic targets are the random track lengths of alpha particles, either traversing the target (crossers) or stopping within the target at the end of the alpha particle range (stoppers), the random energy deposition along its path as a result of the LET as a function of the alpha particle range (Bragg curve), and the probability of single and multiple hits following a Poisson distribution.

For low bronchial tissue doses, energy deposition in single cells or cell nuclei is caused by the action of single alpha particle hits and hence characterized by the single-event distribution $f_1(z)$. However, higher tissue doses or local accumulations of the radon progeny at the carinal ridge can lead to multiple hits in these target cells. For example, specific energy spectra in bronchial secretory and basal cells located in an asymmetric bronchial airway bifurcation, corresponding to bronchial airway generations 3 and 4, are presented in Figure 2 (Fakir et al., 2005) for ^{218}Po and ^{214}Po activities characteristic for residential radon exposures. This figure illustrates the effects of hot spots (T) vs. uniform (R_2) nuclide distribution and of shallow secretory cells (20 µm) vs. deeper lying basal cells (40 µm).

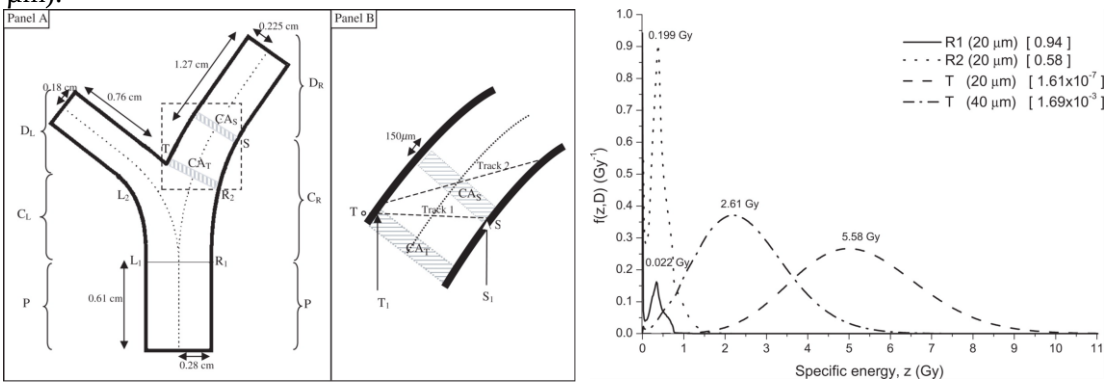


Figure 2: Dose-dependent specific energy spectra in at three different target locations T (carinal ridge), R_1 (transition zone) and R_2 (cylindrical tube) in a bronchial airway bifurcation for secretory cells (20 µm depth) and basal cells (40 µm depth). The numbers in parenthesis are the probabilities of zero events, indicating the fraction of cells not hit at all (Fakir et al., 2005).

Several approaches have been proposed to relate microdosimetric distributions specifically to radon lung cancer risk, such as the threshold model (Fisher et al., 1992; Sedlak, 1996) or the effect-specific track length model (Fakir et al., 2006; Hofmann et al., 2000b). The basic assumption of the threshold models is that there exists a value of the specific energy above which the deposited energy is lethal to the cell or below which the cell may survive and thus may be available for oncogenic transformation. However, the function to relate carcinogenic risk to specific energy has yet to be determined from experimental in-vitro data or epidemiological studies. In the effect-specific track length model, the random chord lengths of alpha particle tracks through spherical cell nuclei are related to cell killing and oncogenic transformation probabilities by probabilities-per-unit-track-length derived from experimental in vitro studies as function of LET (lineal energy). This allowed the calculation of transformation frequencies in secretory and basal cells as a function of radon progeny exposure.

7.2 Microdosimetry in targeted radionuclide therapy and radiotherapy

Targeted radionuclides, alpha- beta- and Auger-emitters conjugated with or unconjugated with targeting molecules, were directed to tumor cells to study and understand the response and effects of therapy. In this case cellular doses to tumorous cells and healthy neighboring cells are needed in order to assess this kind of therapy and for dose control to the patients (Allen et al., 2014; Jadvar, 2017; Williams et al., 2008; Zukotynski et al., 2016). The potential advantage of these radionuclides is the ability to deliver therapeutic doses to individual tumor cells while minimizing the dose to the surrounding normal tissues. However, the dosimetry of these radionuclides is challenging because the dose must be characterized on a scale that is comparable to the range of these emissions, i.e. millimeters for beta particles, micrometers for alpha particles, and nanometers for Auger electrons (Roeske et al., 2008). Microdosimetry takes into account the stochastic nature of energy deposited in small targets for a-particle dosimetry. The stochastic variations of energy deposited within the target must be considered when the relative deviation of the local dose exceeds 20%. For example, a small cell nucleus with a diameter of 5 mm irradiated by α-particles would require an average dose of at least 100 Gy for the relative deviations to be less than the 20% threshold. Thus, the necessity for microdosimetric methods will depend on the source distribution, the target size and shape, and the expected mean dose. For small average doses, such as those expected by non-targeted tissues, microdosimetry may be important in characterizing the pattern of energy deposition and in understanding how this pattern relates to clinical outcomes (Sgouros et al., 2010).

Microdosimetry has been applied in the radionuclide therapy, especially in radioimmunotherapy (Humm, 1986; Humm, 1987; Humm et al., 1993). Akabani (Akabani et al., 2003) did microdosimetric analysis for the treatment of EMT-6 lung tumor colonies in nude mice with lung histological images and autoradiography data for microdistribution and alpha particle Monte Carlo transport and evaluated survival fraction based microdosimetric distributions. Hobbs et al. (Hobbs et al., 2012) recently simulated cellular dosimetry by creating simple spheres representing marrow cavities and positioning ^{223}Ra on the trabecular bone surface or in the endosteal layer (Fig. 3). The interior of the sphere was divided into cell-size voxels and the energy was collected in each voxel and interpreted as dose cell histograms. The results from the marrow cavity model differ markedly from a standard absorbed fraction method which represents average dose values. The marrow cavity model offers an explanation for the clinical evidence suggesting that the average absorbed dose will not reflect biological outcome in the case of ^{223}Ra therapy.

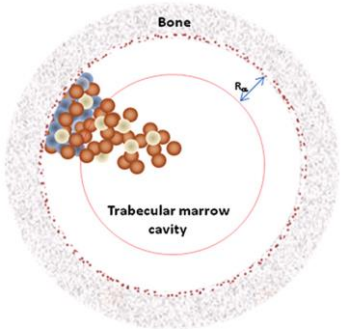


Figure 3. Representation of the marrow cavity model. The cavity is represented by a sphere of radius R_c. R_α is the range of the α-particles from ^{223}Ra decay. The blue spheres are osteoprogenitor cells, while the brown spheres are hematopoietic stem and progenitor cells and the white spheres are adipose cells. The 10 μm endosteal layer is represented by the brown speckled ring.

Amato et al. (Amato et al., 2015) developed a computational model of solid-tumor microenvironment around a blood capillary vessel, and simulated the transport of radiation emitted by ^{223}Ra, ^{111}In, ^{131}I and ^{177}Lu using the Geant4 Monte Carlo code. For each nuclide, several models of radiopharmaceutical dispersion throughout the capillary vessel were considered. This microdosimetric approach can quantify dose distributions at the microscopic level around a simple model of tumor capillary vessel for some therapeutic radionuclides by taking into account the differences between irradiation properties of the alpha, beta and Auger emissions. The results can help to characterize the dose inhomogeneities in solid tumor therapies with radiopharmaceuticals, taking into account the interplay between drug distribution from vasculature and range of ionizing radiations.

Microdosimetry is continuing to play an important role in the radiotherapy for determining the RBE for high LET radiation and for low-LET radiation as well (Wambersie et al., 1990). The recent applications of gold nanoparticles in radiotherapy by x-rays and proton beams raise the question of the RBE values for this new preclinical radiation therapy. Study showed that the effectiveness of proton radiotherapy for the killing of prostate tumor cells was increased by approximately 15%–20% for those cells containing internalized gold (Polf et al., 2011).

7.3 Track structure calculations and nanodosimetry in modelling DNA damages

Radiobiological experiments measured cell survival fractions, chromosomal aberrations and DNA strand breaks. The requirement of precise radiation dose at the cellular level can still be attained by applying microdosimetric methods. However, for molecular targets, mostly in nanometer size, only the track structure-based nanodosimetry can provide the spatial and temporal detailed energy depositions.

Track structure calculations

For example, in radioiodine therapy, ^{131}I is used to cure thyroid cancers, however x-rays can damage healthy tissues in around, if ^{125}I can be used instead, because of its on average 20 Auger electrons released per decay, less x-rays released. Assumed the two isotopes of iodine are distributed in a small volume to simulate a tumor. The track structure can be simulated by using Monte Carlo biophysical code, PARTRAC, the energy deposited and the dose in tumor and heathy tissue can be scored. Fig. 4 shows the track structures of these two radioisotopes of iodine in liquid water, in sphere of diameter of 100 μm, the energy of ^{125}I deposits completely inside the sphere and the decay energy of ^{131}I. Other physical quantities, like single-event distribution, electron degradation spectra, and spatial relationship of inelastic events, like the nearest-neighbor distance distributions and *S* values used in nuclear medicine can be calculated (Li et al., 2001).

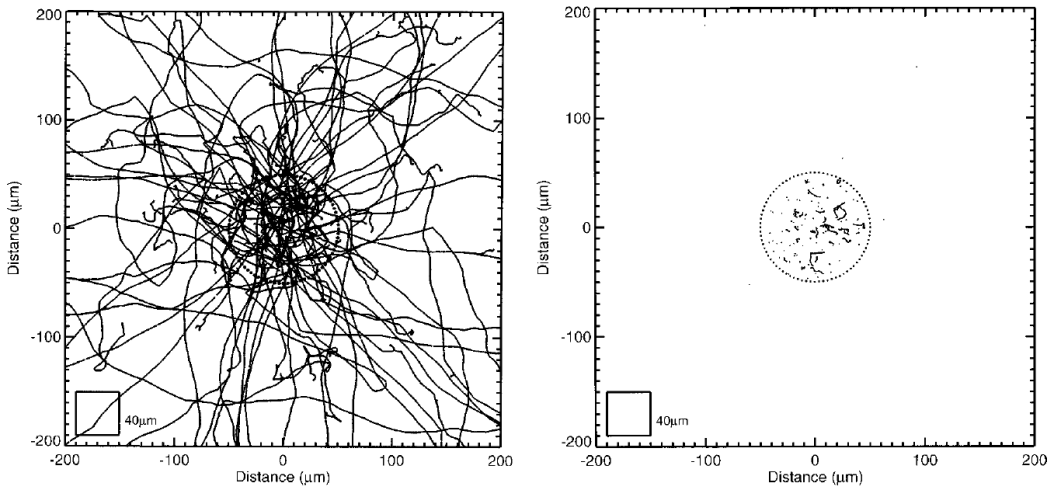


Fig. 4. Track structures of decays of ^{131}I and ^{125}I in liquid water in micrometer range

^{125}I as a radioprobing to detect the structure of DNA-protein complex and the DNA damages

Another example of application of track structure calculations shows that ^{125}I can be used as a radioprobing for DNA distortions. It has been shown in experiments that ^{125}I can be used to study fine conformational changes of DNA within DNA-protein complexes (Karamychev et al., 1999). In a related simulation study (Li et al., 2004), ^{125}I was incorporated into a pyrimidine in a small piece of DNA with as specific base pair sequence into an *E. coli* catabolite gene activator protein (CAP)-DNA complex. DNA strand breaks induced by direct (tracks) and indirect (chemical radicals) effects were simulated with PARTRAC. Direct effects included those due to direct interaction of the emitted radiations with the molecules, as well as DNA damage caused by the charge neutralization processes associated with the Auger cascade process was found to be primarily responsible for the damage caused within 5-7 base pairs of the decay site. The simulated results are in good agreement with

experimental data in the literature. Fig. 5 shows the site in which ^{125}I is incorporated, and the radiation direct interactions with the CAP-DNA recorded, and the chemical radical attacks to the DNA reproduced the detailed structure in nanometer range.

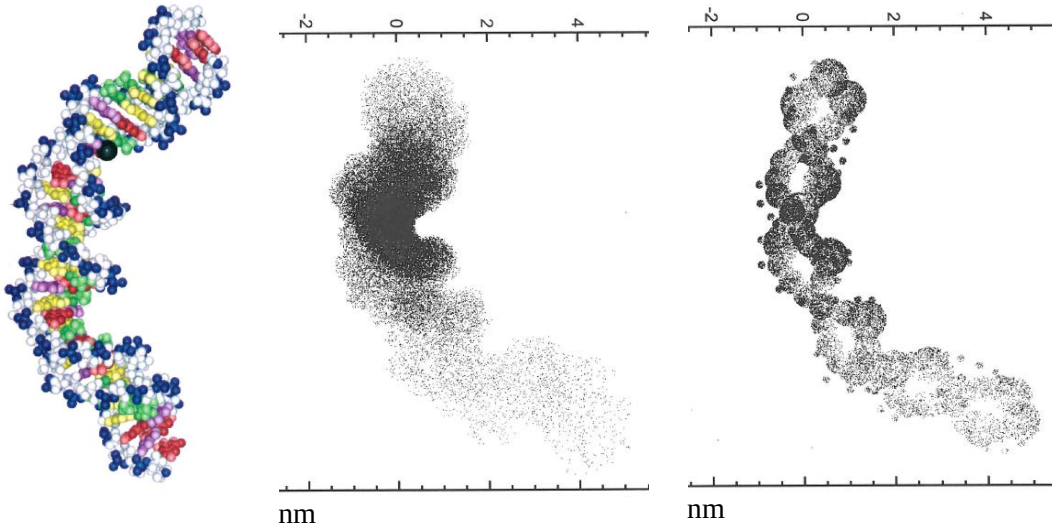


Fig. 5. DNA atomic model and track structures and chemical radical diffusion of targeted molecular radioiodie ^{125}I decay in liquid water

Nanodosimetry of antibody conjugated gold nanoparticles in radiotherapy

The third example showed the potential use of nanodosimetry in innovative breast cancer radiotherapy by using antibody-conjugated gold nanoparticles (Xie et al., 2015). As shown in Fig. 6, gold nanoparticle in size about of 50 nm diameter were successfully conjugated with cmHsp70.1 antibody (Gehrmann et al., 2015), this conjugate can be used as targeting drug which can be delivered into the tumor in mice, irradiated then by x-rays to kill the tumor by the secondary and Auger electron produced by interaction of gold and x-rays. The detailed nanodosimetric calculation demonstrated that the radiation doses 10-1000 nm around the gold nanoparticles are much higher, up to 500-fold than without gold nanoparticles. If the gold nanoparticles, which are conjugated to antibody, can research the surface of the cell nucleus, the DNA double strand breaks caused by this enhanced dose can reach up to 1.5 fold higher than normal x-rays therapy (Fig. 7).

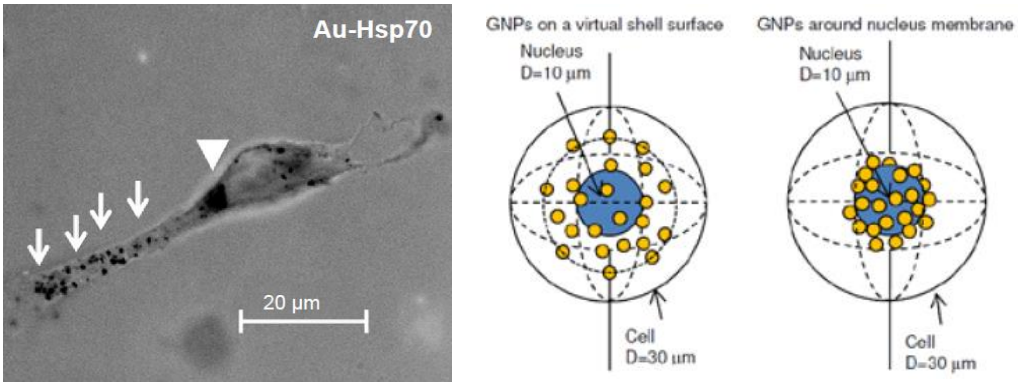


Fig. 6. Imaging of distribution of conjugate of cmHsp70.1 and gold nanoparticles and the computer geometric setup for simulation

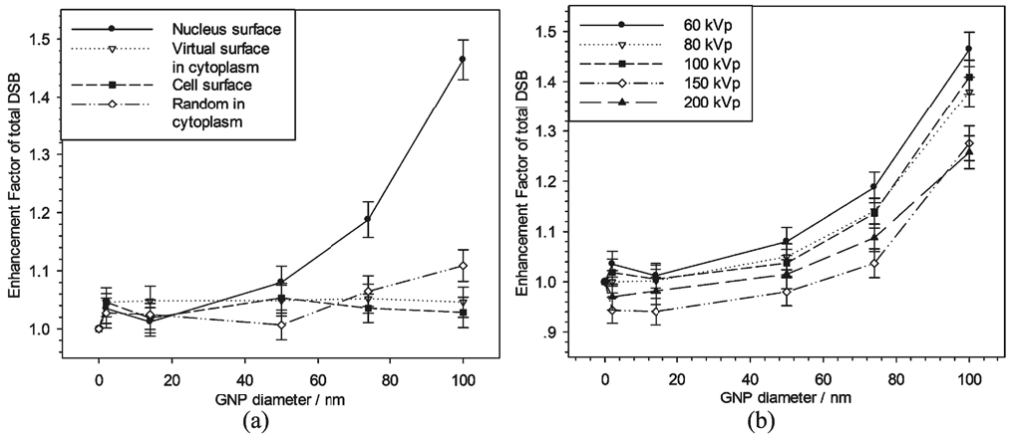


Fig. 7. Enhanced DNA DBSs by gold nanoparticles

7.4 Track structure theory and nanodosimetry in interpretation of dose-response relationship at low doses and low dose rates

For many years, the radiation risk at low doses and low dose rates is in debate (BEIR, 2006; Brenner and Sachs, 2006; ICRP, 2006; Siegel et al., 2017; Tubiana and Aurengo, 2006; Tubiana et al., 2009) (Fig. 8 right). Radiation hormesis at the lowest doses of radiation that overwhelms the homeostatic system makes the debate even more complicated. From epidemiological effects, low doses are usually difficult to be quantified and to be related the finding effects; furthermore the estimated doses are subject to a large uncertainty. The attempt to start from the initial physical and chemical events in the molecular targets and to integrate those early events with later genetic damage, like *hprt* locus (Friedland et al., 2001) and *p53* gene (Ma et al., 2005) and chromosomal aberrations (Friedland and Kundrát, 2013; Friedland and Kundrát, 2015) and even cellular communication (Mariotti et al., 2010) for example, bystander effects (Hall, 2003) and apoptosis (Kundrát et al., 2012), and tissues effects (Friedland and Kundrát, 2014) for risk analysis (Kaiser et al., 2016; Rühm et al., 2017) has been extensively developed.

In the low dose risk assessment, along with molecular radiobiological experimental and molecular epidemiology investigation (Kreuzer et al., 2015; Little et al., 2008), track structure calculation and cancer mathematical modeling can integrate the mechanism processes of cancer development from the initial stages through molecular and cellular and tissue effects to risk assessment and can contribute to the interpretation of the relationship of dose response at low doses. Here we propose a project plan in which the tracks simulations and mathematical cancer modeling can add the essential information for modeling and the quantitative doses that may related to the risk estimation.

The risk at low dose range, say below 100 mSv, is uncertain and is in debate (Hall, 2004). The epidemiology has provided phenomenological information on cancer risk, however, the molecular mechanisms and processes and development of cancer can be revealed only by from molecular radiobiology. In both above approaches, the radiation doses in different levels, e.g. in a targeted molecule, in a cell and in an organ are uncertain, especially the initial events which lead DNA damages, or cell membrane damage, mitochondrial DNA damages are difficult to be experimentally quantified. At this stage, the track structure based nanodosimetry can implement the molecular structures and the targets in the physical track simulation and provide the information needed for cancer modelling to explore the dose-response relationship at very low dose level (Brenner, 2009). In this project plan, it is important to simulate and provide the macrodosimetry and microdosimetry for the experimental investigations in vivo or in vitro, so that cancer modeling can integrate the radiobiological analysis and initial events and nanodosimetry to later development of cancer.

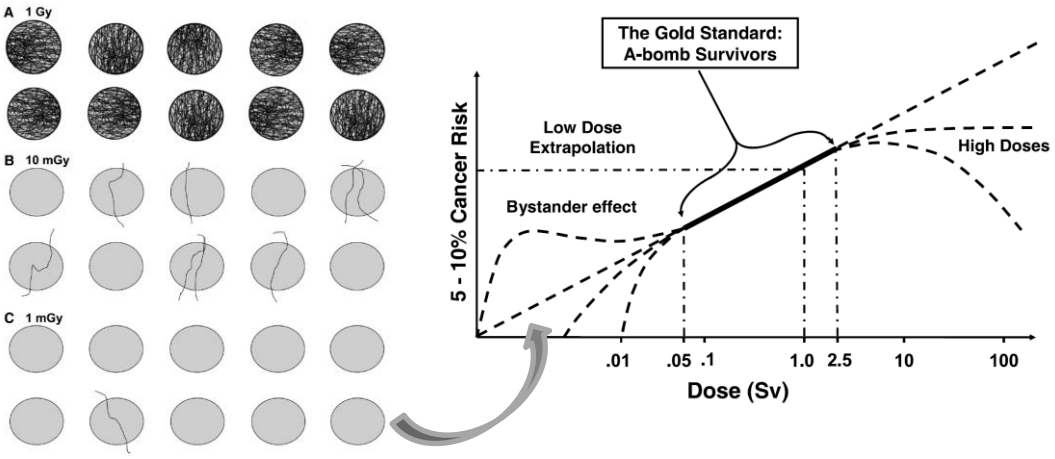


Fig. 8 Application of track structure theory to interpret the dose response relationship at low doses and low dose rates

8 Future development

Microdosimetry and nanodosimetry, as a special theme in radiation dosimetry, was born from linear energy transfer and absorbed dose, and has developed for 50 years since the first Symposium on Microdosimetry in 1967. Here we account for nanodosimetry as further development of microdosimetry and consider them both as one domain. The conventional use of absorbed dose and liner energy transfer will be continued in the radiation protection as well in the radiation medicine, because the primary index for organ risk is based on organ absorbed dose for internal dosimetry.

The concepts of specific energy and radiation track structures significantly contribute to the closely related research areas of radiobiology and radiation medicine and they improve our understanding of the radiation quality and quantify the health risk in radiation protection. As a subtopic in radiation dosimetry, internal dosimetry extended its dosimetric research into cellular and molecular regions with the advanced applications of micro- and nanodosimetry. Furthermore RBE derived from microdosimetric quantity links the doses in micro- and nanoscale directly to the cellular and molecular radiobiological effects. The quantification of RBE values is relevant for the optimization of the benefit of particle therapy, hence is considered as a future research topic.

The microdosimetric quantities, z and y can be regarded as averaged quantities or data classification of radiation track structures. Therefore, the microdosimetry-based biophysical models and radiation risk analyses might be influenced by the detail of the radiation tracks in the nanometer ranges of different radiation quality. The theoretically calculated cross sections of low energy radiation of DNA moiety and its backbone and the experimental validation can be subjects in nanodosimetry research as well as the uncertainty analysis of cross sections which were implemented in different nanodosimetric codes. The physicochemical processes, although not belong to dosimetry, however should be experimentally investigated and integrated into the nanodosimetric transport codes for a full description of radiobiological effects.

The experimentally investigations of cross sections as well as track structures can be a research subject for establishing some new concepts of radiation quality that builds on measurable characteristics of the particle track structures at the nanometer scale. Similarly, the complexity of quantities in radiation dosimetry, especially the radiation quality for ion therapy is required to be quantified and the related experimental investigations.

The advanced development in molecular targeted radionuclide therapy needs detail distributions of radiopharmaceuticals in and around cells and molecules. This is a challenge for micro- and nanodosimetric biokinetic modelling together with clinical and preclinical investigations. Application of nanoparticles, aptamer, and mRNA in molecular targeted therapy need to determination of RBE

and radiation quality for those new pharmaceuticals of alpha-, beta- and Auger-emitters, these clinical needs provide a space of applications of micro- and nanodosimetry in precision radiotherapy.

Track structure calculation in nanodosimetry is a power tool in a continue contribution to understanding the mechanism of radiation effects from the initial events to cell communication. Furthermore, track structure based risk estimation models provide much comprehensive mechanism to the radiation effect and risk than the solely epidemiological data based risk estimation. Since radiation proteomics and epigenetics of diseases are developing rapidly, micro- and nanodosimetry can serve as a tool to explore the underlying mechanisms and provide precision dosimetry. Track structure based nanodosimetry; together with mathematical cancer modelling can continually provide insight into the molecular dosimetry for understanding of the dose-response relationship at low doses and low dose rates.

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