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Microdosimetry: Principles and applications

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ABSTRACT

Aim: to present the most important aspects of Microdosimetry, a research field in radiation biophysics.
Background: microdosimetry is the branch of radiation biophysics that systematically studies the spatial, temporal and spectral aspects of the *stochastic nature* of the energy deposition processes in microscopic structures.
Materials and Methods: we briefly review its history, the people, the formalism and the theories and devices that allowed researchers to begin to understand the true nature of radiation action on living matter.
Results and Conclusions: we outline some of its applications, especially to Boron Neutron Capture Therapy, attempting to explain the biological effectiveness of the boron thermal neutron capture reaction.

1. Background and Aim

The early target theories[1,2] attempted to describe the discrete acts of energy transfer, termed "hits" identifying them with individual ionizations or clusters of ions. The spatial correlation of these events was not considered, and target theory in this earliest form could not explain the relative biological effectiveness of different types of ionizing radiation. A far more realistic treatment emerged in the work of Lea,[3] who attempted a more detailed description of the "random" configurations of energy deposition in the tracks of charged particles. He used the term "energy dissipation" which was later called "Linear Energy Transfer" or LET, by Zirkle et al.[4]

Microdosimetry,[5–10] in its present sense, was founded entirely on an original approach introduced by Harald H. Rossi (1917–2000), when he recognized the fundamental difference between macroscopic absorbed dose and the energy deposition in microscopic structures. He realized that the important quantities that described the problem at microscopic scale were inherently "stochastic variables". He and his colleagues proceeded then to develop sophisticated techniques for measuring the random fluctuations of energy deposition, to construct a novel conceptional and mathematical framework, and to apply the new concepts and methods to radiobiology.

1.1. *Why microdosimetry?*

- Ionizing radiations interact in a discontinuous form with matter; dose and dose rate are statistical averages that disregard the inherent random fluctuations.

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- The knowledge of the macroscopic absorbed dose gives little information about the energy deposited in cellular and subcellular structures.
- Fluctuations are more substantial for smaller volumes, smaller doses and for more densely ionizing radiations.

2. Materials and methods

2.1. Formulations of microdosimetry

Two different formulations were developed,[11] depending on the need of considering a detailed description of the inchoate distribution of energy deposited by charged particles in a microscopic sensitive volume, or site:

Regional microdosimetry (or the microdosimetry of Rossi counters): This approach considers the process of energy deposition in a site of specified dimensions without regard to the microscopic distribution of energy transfers, that is, the "pattern" of ionizations produced by the charged particle trajectory. This formulation is especially important because it involves quantities that can, in principle, be measured and correlated with biological effects.

Structural microdosimetry: This more advanced alternative, by the contrary, permits a detailed description of the microscopic pattern of energy absorption, or inchoate distribution. The immediate effect of radiation is essentially determined by the intersection of this pattern and that of sensitive components in irradiated matter. It makes strong use of Integral Geometry and Geometric Probability.[12,13]

2.2. Microdosimetric quantities and distributions

In regional microdosimetry, two fundamental quantities are defined as the microscopic, stochastic analogs of dose and LET: specific energy (z) and lineal energy (y). These two quantities are random variables and can be experimentally measured under certain conditions. The *specific energy*, z (Gy), is the quotient of ε by m, where ε is the energy imparted by one or more events in a site of mass m. The *lineal energy* y (keV/μm) is defined as the energy imparted **in one event** divided by the *mean chord length* that results from the random intersection of the site by straight lines. Under an isotropic and uniform field of random straight lines, the mean chord length $\bar{l}$ of a convex body is given by the Cauchy's formula $\bar{l} = 4(V/S)$, V being its volume and S its surface area.

Usually, the energy deposited in a microscopic site spans several orders of magnitude; a large number of events in a site typically occurs in the low energy region and a few but important high LET events in the high energy region. One possibility for visualizing the distribution is to use a semi-logarithmic representation; usually the distribution is "rebinned" on a histogram with logarithmic intervals. This procedure has several advantages, other than providing a better visualization of the spectrum. The statistical representations are the *frequency* distribution and the *dose* distribution, $f(y)$ and $yf(y)$, both multiplied by y after logarithmic rebinning. In the $yf(y)$ vs. log y representation (frequency distribution), equal areas under the curve represent equal fraction of events. In the $y^2f(y)$ vs. log y representation (dose distribution), equal areas under the curve represent equal fractional doses.

The so-called "multi-event" distribution accounts for the fact that a given amount of energy can be deposited in a site by one or more concurrent events. It is therefore the composition of a homogeneous spatial compound Poisson process with intensity $n = D/Z_F$ (the mean number of events in the site) and the specific energy densities for "exactly" ν events in a site:

$$f(z, D) = \sum_{\nu=0}^{\infty} \frac{e^{-n} n^{\nu}}{\nu!} f_{\nu}(z), \tag{1}$$

The quantity Z_F is the first moment of the specific energy single-event density, the dose-mean specific energy. The density $f_{\nu}(z) = \int_0^z f_1(x) f_{\nu-1}(z-x)dx$ can be obtained from the single event density by convolution with itself, $f_{\nu}(z) = \int_0^z f_1(x) f_{\nu-1}(z-x)dx$. For completeness, $f_0(z) = \delta(z)$, the Dirac delta function at $z = 0$.

2.3. Experimental microdosimetry

Nowadays, instrumentation for microdosimetry and nanodosimetry covers a great number of devices and techniques,[11] but the classical instrument designed by Rossi and still in use today for characterizing complex radiation fields is the Tissue-Equivalent (spherical) Proportional Counter, or TEPC. It is based on a relationship that, under certain conditions, relates the energy deposited in a gas-filled, centimeter-sized cavity (g) with that actually deposited in a micrometer-sized site of living tissue (t):

$$\overline{\Delta\varepsilon} = \Delta x_g \left(\frac{S}{\rho}\right)_g \rho_g = \Delta x_t \left(\frac{S}{\rho}\right)_t \rho_t \tag{2}$$

where Δx is the distance traveled by a particle, S/ρ the mass-stopping power and ρ the density, either in the gas cavity or in the tissue microscopic site. If the detector cavity is made of "tissue equivalent" gas and walls, the mass-stopping power cancels out and a direct relationship arises that permits obtaining microdosimetric spectra representative of the actual energy deposition in a microscopic site.

2.3.1. Neutrons and photons

Neutrons and photons constitute some of the most important types of radiation, for radiotherapy and radiation protection. Elastic and inelastic scattering, nonelastic reactions, capture and spallation are possible reactions that a neutron of certain energy can produce in tissue. In a (nearly) monoenergetic beam of 14 MeV neutrons, for example, it is possible to observe several distinct regions of the measured microdosimetric spectrum indicating the contribution from protons, alpha particles and heavy recoils to the total absorbed dose, which is proportional to the area under the curve. The first important characteristic is the proton recoil peak, which ends slightly above 100 keV/μm. This cut-off, known as *proton edge*, represents the maximum energy that can be deposited by a recoil proton along a diameter of the gas cavity. Above 2.5 MeV, (n,α) reactions become important and an alpha edge is also visible at 360 keV/μm. At lineal energies greater than the alpha

edge, events due to heavy recoil of carbon, nitrogen and oxygen are also noticeable.

Photons deposit energy usually by photoelectric emission, Compton scattering and pair production interactions, although for very high energies, nuclear reactions can also occur. Similar to neutrons, the photon spectra also show distinctive features depending on the photon energy, showing a narrow shape for low energies and a more dispersed structure for higher energies.

3. Results

3.1. *Radiation biophysics within the framework of Compound Dual Radiation Action (CDRA) theory*

The theory of Compound Dual Radiation Action[14–16] states that lethal lesions are produced either by simple chromosome breaks or by pairwise combination of Double Strand Breaks (DSBs), leading to a 2-Break Aberration (2-BA). The spatial scales associated with each case are of the order of nanometers and micrometers, respectively. The concentration of DSBs in Dual Radiation Action is postulated to be proportional to z, the specific energy deposited in the sensitive matrix of the cell. Thus, the yield of 2-BA resulting from pairwise combination of lesions is proportional to the square of the specific energy deposited either by a single event or by two independent events. These yields, when averaged with the multi-event density, give rise to a Linear-Quadratic (LQ) dependence of the mean number of lethal events with dose (see Fig. 1).

3.1.1. *Synergism*

A system that is described by Dual Radiation Action must manifest synergism when it is exposed to different kinds of radiations.[11] Radiations A and B will produce a number of sublesions proportional to the specific energy deposited by each one. Both groups can then interact to form lesions at a rate given by $\varepsilon(z_A, z_B) = k(c_A z_A + c_B z_B)^2$ that integrated with $f(z_A, z_B, D_A, D_B)$ results in

$$\varepsilon(D_A, D_B) = \alpha_A D_A + \alpha_B D_B + \beta_A D_A^2 + \beta_B D_B^2 + 2\sqrt{\beta_A \beta_B} D_A D_B, \quad (3)$$

where the last term expresses the synergistic effect.

3.2. *The microdosimetry of the boron neutron capture reaction*

The major ambition of Boron Neutron Capture Therapy (BNCT) is to deliver a highly localized dose to tumor cells while preferentially sparing normal cells by means of the selective production of ^{10}B thermal neutron (n_{th}) capture reactions

$$^{10}B + n_{th} \Rightarrow {}^{4}He + {}^{7}Li + 2.79\,MeV$$

Nevertheless, the short ranges in tissue of the high-LET alpha and ^{7}Li particles (about 8 and 4 μm respectively in soft tissue) and the particular microdistribution that the ^{10}B compound exhibits at the cellular level, make calculation of the ^{10}B microdosimetry a difficult task. Departure from a uniform ^{10}B distribution makes the deposited energy strongly dependent on the shape of the sensitive site, precluding the use of KERMA since Charged Particle Equilibrium (CPE) conditions are not fulfilled. Moreover, the inherent stochastic character and the small number of ^{10}B reactions needed to deliver therapeutic doses are factors that affect the dose distribution among identical microscopic sites even for nominally uniform ^{10}B distributions. In order to describe and understand these aspects, several investigators[17–21] had developed theoretical, numerical and stochastic approaches, always arriving at the conclusion that a detailed description of the

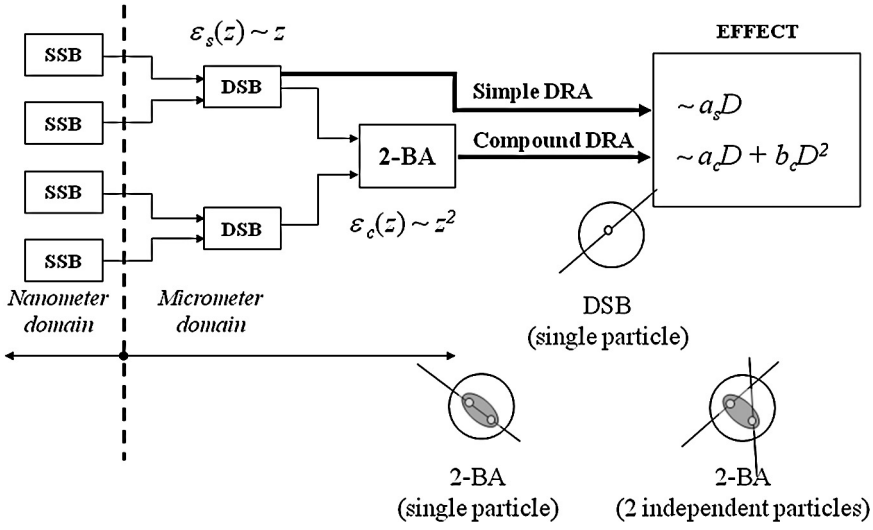

Fig. 1 – DSBs arise from Single-Strand Breaks (SSBs) produced at nanometer scale by a single particle at typical doses. Their yield is proportional to the specific energy accumulated in a micron-size volume by one or more independent particles. After averaging with an incoherent radiation field, the effect will be proportional to *D*. If the possibility of formation of a 2-BA with an additional DSB exists (with a yield proportional to the square of z), the effect will have a linear component due to 2-BA produced by a single particle and a quadratic component due to interaction between the breaks produced by two independent particles. The effect, averaged with the multievent density, will be Linear-Quadratic with *D*.

microscopic aspects will much help to develop better compounds and delivery strategies.

In the radiobiology of BNCT, the term "Compound Biological Effectiveness" (CBE)[22,23] of the ^{10}B dose component is used to distinguish the ratio of doses experimentally obtained when looking at a given level of effect relative to photons, from the traditional Relative Biological Effectiveness (RBE) factor, which should only depend on radiation quality. This departure from a "pure" RBE factor can be explained considering that, for a non-uniform boron microdistribution (and in consequence, a non-uniform production of boron reactions), the calculated KERMA differs from the actual average dose deposited on cells, thereby under or overestimating the "true" value. This microdistribution depends on the particular ^{10}B compound used, specific cell types or tissues and biological end-points.

3.2.1. *Stochastic aspects*

If we consider a microscopic spherical site approximately 10 μm in size, the mean specific energy, z_F, deposited in it by a single ^{10}B reaction for a uniform distribution of ^{10}B is approximately 0.27 Gy. Just about 4 reactions are needed to produce 1 Gy of absorbed dose, on the average, and large fluctuations among identical sites are produced. Fig. 2 reveals the importance of these stochastic fluctuations, important even for therapeutic doses. In this figure, typical values achieved in the clinic of BNCT for thermal neutron flux and boron in tumor are used for calculating the average dose, for different irradiation times.

3.2.2. *Biological aspects*

It can be demonstrated that, for a situation where different boron concentrations inside and outside the cell exist, the mean microscopic dose rate for a population of cells is the product of the KERMA rate, calculated based on the maximum of both concentrations, and a form factor that contains the information of the cell size and shape and the relative concentration ratio.[19] Therefore, that correction can be used to better calculate the actual average boron dose in cells under non-CPE conditions. In that case, the CBE factor can be expressed as the product of a "physical factor", –that contains the information about the microdistribution, size and shape of the sensitive target–, a relative radiosensitivity factor, that accounts for possible differences in the intrinsic radiosensitivity of cells to different microdistributions, and a reference RBE obtained from an experiment designed to assure microscopic dose uniformity on such target:

$$\mathrm{CBE} = \eta(a)\frac{\alpha_B}{\alpha_{CPE}}\mathrm{RBE}_{CPE}, \tag{4}$$

where a is the ratio of inside vs. outside boron concentrations, RBE_{CPE} is the "reference" RBE factor for boron, measured assuring CPE conditions. The coefficients α_B and α_{CPE} are the initial slopes of the boron survival curves for a given microdistribution and for CPE conditions, respectively, and

$$\eta(a) = \xi_a\left[1 + (a-1)\rho V_S\frac{z_F^I}{\bar{\varepsilon}}\right]; \quad \xi_a = \begin{cases} 1 & a < 1 \\ 1/a & a > 1 \end{cases}, \tag{5}$$

where ρ and V_S are the density and the sensitive target volume, z_F^I is the mean specific energy for an intrasite distribution (when boron reactions occur only inside the site) and $\bar{\varepsilon} = 2.34$ MeV, the average sum of the kinetic energies of the alpha and ^7Li particles. For example, for an isolated tumor cell within normal tissue, considering a tumor-to-normal boron ratio of 3.7 as it can be achieved using one of the clinically accepted boron compounds, the boronated aminoacid boronophenylalanine or BPA, and assuming that the slopes of the boron survival curves are identical, the CBE factor for BPA will be approximately 2.7 instead of 3.8. This results in a biologically weighted boron dose of about 71% of the calculated value for the gross tumor mass. Therefore, isolated tumor cells or islands of tumor cells within normal tissue or poorly perfused tumor regions can receive appreciably lower doses than the KERMA-calculated average macroscopic dose.[19] The standard approach for calculating biologically weighted doses in BNCT treatment planning is to use fixed CBE or RBE factors, e.g., 3.8 for BPA and melanoma, and 1.3 for BSH (sodium borocaptate, another compound used in the clinic) and brain tumor. A more

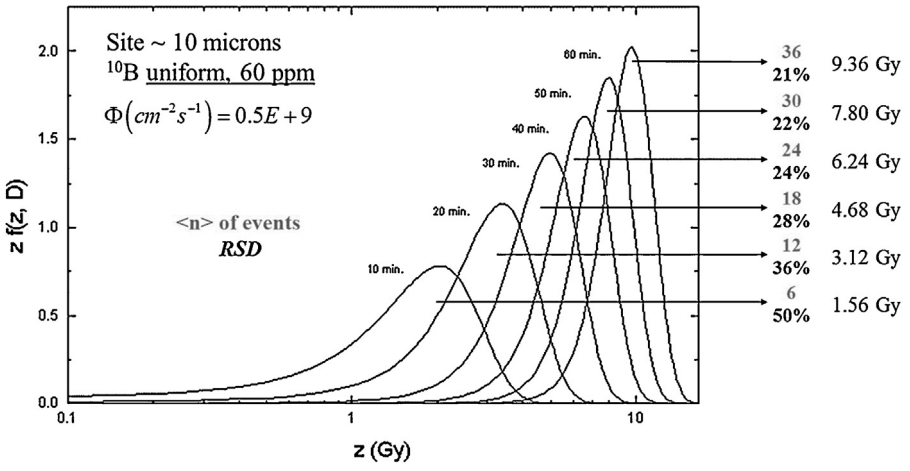

Fig. 2 – Multievent specific energy densities for a 10 μm spherical site, exposed to a uniform distribution of reactions, produced by thermal neutron flux of 0.5 x 10^9 cm^{-2} s^{-1} and different irradiation times, from 10 to 60 min. The numbers at the right correspond to the mean number of events ⟨n⟩, the relative standard deviation, RSD and the average absorbed dose. The assumed average boron concentration is 60 ppm (60 μg per gram of tissue).

suitable approach considers using all the information available from survival experiments, since the use of fixed factors always lead to gross overestimations of tumor dose.[24] Nevertheless, differences between the effectiveness of the different compounds can only be explained by considering their specific distribution at microscopic scale.

4. Conclusions

Microdosimetry is an invaluable tool to understand and explain results that apparently have no suitable explanation by considering only average quantities, like absorbed dose or LET. It also provides an appropriate framework and measuring techniques useful for performing quality control tests of radiation beams, where differences in the acquired microdosimetric spectra are almost always associated with variations in radiobiological properties of the beams.

Conflict of interest

There is no conflict of interest.

Financial disclosure

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REFERENCES

1. Dessauer F. Übereinige Wirkungen von Strahlen. *Z Physik* 1922;**12**:38–47.
2. Crowther JA. Some considerations relative to the action of X-rays on tissue cells. *Proc Royal Soc Lond B* 1924;**96**: 207–11.
3. Lea DE. *Actions of radiations on living cells*. University Press; 1962.
4. Zirkle RE, Marchbank DF, Kuck KD. Exponential and sigmoid survival curves resulting from alpha and x-irradiation of Aspergillus spores. *J Cell Comp Physiol* 1952;**39**(1):75.
5. Kellerer AM. Microdosimetry: reflections on Harald Rossi. *Radiat Prot Dosim* 2002;**99**(1–4):17–22.
6. Rossi HH, Rosenzweig W. A device for the measurement of dose as a function of specific ionization. *Radiology* 1955;**64**:404.
7. Rossi HH. Specification of radiation quality. *Radiat Res* 1959;**10**:522.
8. Rossi HH. Spatial distribution of energy deposition by ionizing radiation. *Radiat Res Suppl* 1960;**2**:290.
9. Rossi HH. The role of microdosimetry in radiobiology and radiation protection. In: Ebert HG, editor. *Proceedings of the third symposium on microdosimetry. Rep. No. EUR 4810*. Luxemburg: Commission of the European Communities; 1972.
10. ICRU. *Microdosimetry. Report 36*. Bethesda, MD: International Commission on Radiation Units and Measurements; 1983.
11. Rossi HH, Zaider M. *Microdosimetry and its Applications*. Berlin, Heidelberg/New York: Springer; 1996.
12. Solomon H. *Geometric Probability*. Philadelphia, PA: Society for Industrial and Applied Mathematics; 1978.
13. Santaló LA. *Encyclopedia of Mathematics and its Applications, Vol. 1, Integral Geometry and Geometric Probability*. Reading, MA: Addison-Wesley; 1976.
14. Kellerer AM, Rossi HH. The theory of dual radiation action. *Curr Top Radiat Res Q* 1972;**8**:85–158.
15. Kellerer AM, Rossi HH. A generalized formulation of dual radiation action. *Radiat Res* 1978;**75**:471–88.
16. Rossi HH, Zaider M. Compound dual radiation action. I. General aspects. *Radiat Res* 1992;**132**:178–83.
17. Kobayashi T, Kanda K. Analytical calculation of boron-10 dosage in cell nucleus for neutron capture therapy. *Radiat Res* 1982;**91**(1):77–94.
18. vanVliet-Vroegindeweij C, Wheeler F, Stecher-Rasmussen F, Moss R, Huiskamp R. Microdosimetry model for boron neutron capture therapy: I. Determination of microscopic quantities of heavy particles on a cellular scale. *Radiat Res* 2001;**155**(3):490–7.
19. Santa Cruz GA, Zamenhof RG. The microdosimetry of the (10)B reaction in boron neutron capture therapy: a new generalized theory. *Radiat Res* 2004;**162**(6):702–10.
20. Nichols TL, Miller LF, Kabalka GW. The microdosimetry of boron neutron capture therapy in a randomised ellipsoidal cell geometry. *Radiat Prot Dosim* 2005;**116**(1–4 Pt 2):466–9.
21. Lu XQ, Kiger WS. Application of a novel microdosimetry analysis and its radiobiological implication for high-LET radiation. *Radiat Res* 2009;**171**(6):646–56.
22. Gahbauer R, Fairchild RG, Goodman JH, Blue TE. RBE in normal tissue studies. In: Gabel D, Moss RL, editors. *Towards clinical trials of glioma treatment*. New York: Plenum Press; 1992. p. 123–8.
23. Morris GM, Coderre JA, Hopewell J, Micca PL, Rezvani M. Response of rat skin to boron neutron capture therapy with p-boronophenylalanine or borocaptate sodium. *Radiother Oncol* 1994;**32**:144–53.
24. González SJ, Santa Cruz GA. The photon-isoeffective dose in boron neutron capture therapy. *Radiat Res* 2012;**178**(6):609–21.