A SOLUTION TO THE PROBLEM WITH ABSORBED DOSE

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In some situations, for example at very low doses, in microbeam irradiation experiments, or around high energy heavy ion tracks, use of the absorbed dose to describe the energy transferred to the irradiated target can be misleading. Since absorbed dose is the expected value of energy per mass it takes into account all of the targets which do not have any energy deposition. In many situations that results in numerical values, in Joules per kg, which are much less than the energy deposited in targets that have been crossed by a charged particle track. This can lead to confusion about the biochemical processes that lead to the consequences of irradiation. There are a few alternative approaches to describing radiation that avoid this potential confusion. Examples of specific situations that can lead to confusion are given. It is concluded that using the particle radiance spectrum and the exposure time, instead of absorbed dose, to describe these irradiations minimizes the potential for confusion about the actual nature of the energy deposition.

KEYWORDS : Low Dose, High LET, Fluence, Radiance

1. INTRODUCTION

The definition of absorbed dose, $d\bar{\varepsilon}/dm$, where $\bar{\varepsilon}$ is the average energy imparted in mass m [1], is the expected value of the energy imparted per mass. That is, it is the average value that is expected if the measurement at a point is repeated a large number of times. Due to the fact that energy is actually deposited by a discrete number of individual charged particle interactions with the target volumes it is unlikely that the actual energy imparted per mass, ε/m, will ever be exactly equal to $d\bar{\varepsilon}/dm$. In fact, in some situations the difference between ε/m and $d\bar{\varepsilon}/dm$ is very large. One way to visualize the difference is to consider the distribution of values of ε/m in small sites exposed to the same radiation. At small doses the relative variance of ε/m can be quite broad, with a large fraction of the sites having no charged particle track and therefore no energy deposited, some having 1 track, and a small fraction of the sites having 2 or more charged particle tracks resulting in a large amount of energy deposited. As the dose is increased the average number of charged particle tracks through a target increases and the relative variance of ε/m decreases, as you would expect from the general behavior of variance as the mean of the sample increases. At the doses and radiation qualities that are typically used in radiation therapy the average number of events in a cell nucleus is of the order of 10^3 and the relative variance of ε/m for cell nuclei in irradiated tissue is approximately 3.3%. Thus the use of the expected value $d\bar{\varepsilon}/dm$, the absorbed dose, does not cause any confusion with respect to the energy deposited in individual cells when the absorbed dose is large and the LET of the radiation is low.

Unfortunately, the large differences between $d\bar{\varepsilon}/dm$ and ε/m that can occur at low doses and in some specialized radiation exposures can be very confusing for people trying to understand the consequences of irradiation at the cellular or subcellular level. There is a natural tendency to assume that the low values of absorbed dose apply to all cells, but in fact the low absorbed dose occurs because a large fraction of the cells have no energy deposited in them. If the absorbed dose is supplemented with sufficient additional information about the type of radiation, its energy, and spatial homogeneity and about the size and shape of the target and its atomic composition, the details of the energy deposition can be deduced, but one has to be aware of when that additional information is needed.

It is reasonable to expect that progress toward understanding the biological effects of radiation would be expedited by a description of the interaction between radiation and biological targets that does not lead to confusion about the actual energy deposited. Such a system would not require the user to be aware of the subtleties of radiation actions or to know when answers to additional questions about the target and radiation field are needed in order to properly interpret the absorbed dose.

2. SOME EXAMPLES

In order to better understand the limitations of absorbed dose, and to illustrate the type of problems where a different description of the amount of radiation might provide a more meaningful connection to the biological consequences, three examples are described.

2.1 Low Dose of Gamma Rays

We are all exposed to low Linear Energy Transfer (primarily x and gamma ray) natural background radiation adding up to about 1 mGy/ year, slightly more than 0.01μGy/h. This radiation interacts with biological material primarily by producing Compton scattered electrons and photoelectric effect electrons. The stopping power of these electrons changes as they slow down and stop in tissue, but for simplicity we can assume that the mean stopping power is 1 keV/μm. Animals and humans are complex biological systems, but it is generally assumed that the consequences of irradiation are initiated by energy deposition in individual cell nuclei, and that the diameter of the typical cell nucleus is about 8μm. When one of these electrons interacts with a cell nucleus the value of ϵ/m will depend on the actual path of the electron through the nucleus, but the average value will be about 3 mGy. The energy deposited in each cell that is hit must be averaged with a large number of cells that are not hit during a one hour period in order to have an absorbed dose rate of 0.01 μGy/h. In this case the probability of a cell nucleus being hit during the hour is 3.3×10^{-6}. That is, one in every 300,000 cells in a tissue is hit by an electron each hour when the tissue is exposed to this natural background radiation. In the course of a year, about 1/3 of all of the cell locations will be hit by a charged particle event, but depending on the cell turnover rate in the tissue, that location may have been occupied by many different individual cells during the year.

The absorbed dose rate gives the impression that a very small amount of damage occurs in each cell every day, but the discreet nature of charged particle tracks actually results in a much larger amount of damage being done in a small fraction of the cells. On average it will be a very long time before a second charged particle track occurs in any individual cell or cell location. Although the individual charged particle tracks which deposit this energy are randomly distributed in space, the distribution of cells that are impacted by energy deposition is not entirely random. The secondary electrons produced by gamma ray radiation have ranges that are typically several times the diameter of the individual cell. Consequently the cells that have been hit by the charged particle are generally arranged in small clusters which mark the paths of the directly ionizing particles. The mean number of cells in these clusters depends on the range of the charged particles that produce them. Widely separated clusters of cells are expected to lead to different damage interactions than would be produced if cells which received energy deposition were randomly distributed or if all cells were hit within a few minutes, as is typically the case in low dose experiments with much higher dose rates.

2.2 Microbeam Irradiation

In recent years techniques have been developed to facilitate experimental investigation of biological response to ionizing radiation by controlling the physical location and number of charged particle tracks interacting with individual cells. Single particle microbeam irradiation [2-4] is one approach to this type of irradiation. Figure 1 illustrates the situation. By detecting individual particles as they pass through a cell and using that signal to control

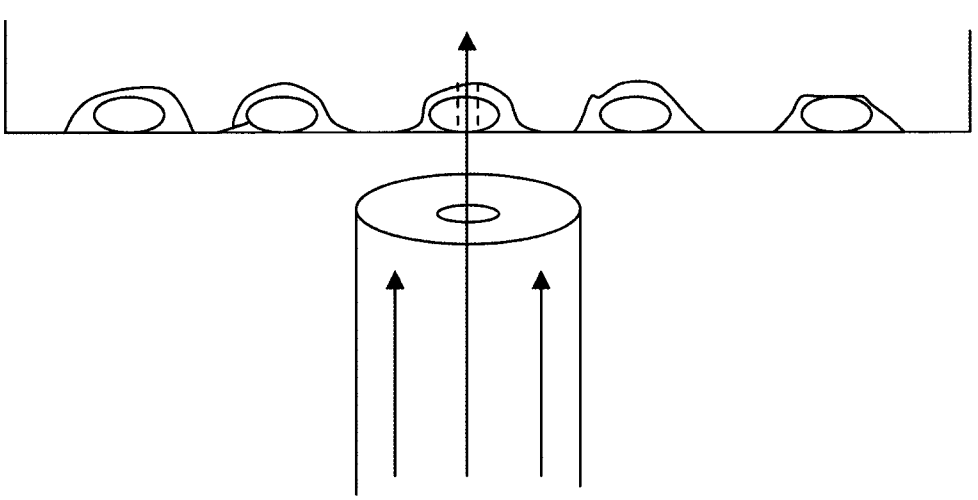

Fig. 1. Schematic Representation of Microbeam Irradiation and Alternatives for Calculating ϵ/m

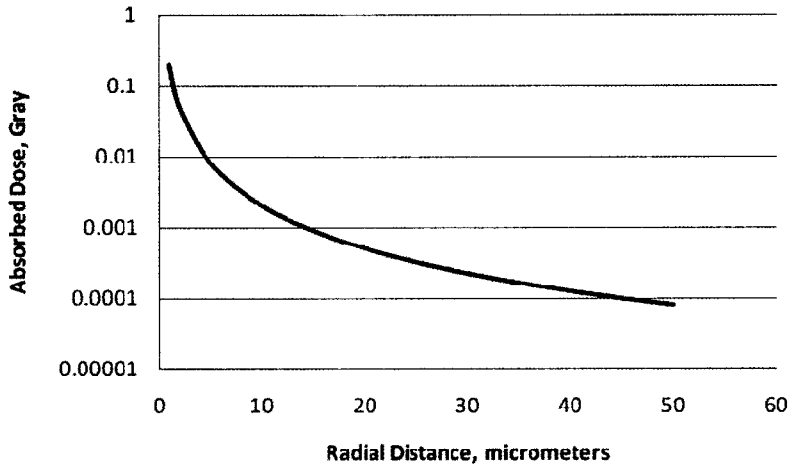

Fig. 2. Absorbed Dose as a Function of Radial Distance from a 600 MeV/u Fe Ion Track, Based on the Model by Chatterjee [7]

a beam shutter, the stochastic variation that is inherent in irradiation for a preset time can be eliminated. The distance between irradiated cells, or the time between charged particle tracks through a selected cell, can be controlled and repeated for a large number of trials. Since the exact number of particles delivered to the target is controlled by the experiment, and the particle energy is controlled by the charged particle accelerator, it is relatively easy to determine the energy imparted. However, in order to specify the absorbed dose it is necessary to also specify the mass that receives the energy. The fact that we have control over the positions of the tracks means that we no longer have a natural relationship between the number of tracks and the area irradiated. Consequently we can calculate the absorbed dose in any structure we want to emphasize. However, the results can vary dramatically depending on the target that is chosen. For example, if the radiation is alpha particles with a stopping power in water of 100 keV/μm, we can calculate the dose to a cell by determining its mass. If the cell is assumed to have the volume of an 8 μm diameter sphere, but to be flattened so that the path of the alpha particle through it is 4 μm the energy imparted is 400 keV or 6.40 x 10^{-14} Joules. The mass of the cell, assuming that the density is 1 g/cm^3, is 2.68 x 10^{-13} kg so the absorbed dose is 0.24 J/kg or .24 Gy. However, the dose is clearly not uniform throughout the cell. Perhaps we should be more concerned about the dose within a few nanometers of the charged particle path, the region where radiation induced chemical changes will occur. The dose in a 10 nm diameter cylinder around the particle track is 6.4 x 10^{-14} J divided by 3.14 x 10^{-19} kg, or 2 x 10^5 Gy. This is the approximate energy per mass in a 10 nm diameter region around any alpha particle track, but it is seldom considered because in a conventional irradiation we would not know where the track was relative to sensitive biological structures. Instead we use the absorbed dose which averages over the whole cell. However, we have also learned [5] that radiation passing through one cell on the dish will produce changes in cells all over the dish. This bystander cell effect may be responsible for much of the cytogenetic damage in some tissues when they are exposed to low doses of ionizing radiation. If this is the case perhaps we should consider the entire collection of cells when evaluate the dose. If the dish is 10 cm in diameter, the dose to the cells on the dish, resulting from a single particle track through one of them is 6.4 x 10^{-14} J divided by 3.14 x 10^{-5} kg or 2 x 10^{-9} Gy. It is clear that an attempt to apply the definition of absorbed dose to this nonrandom irradiation system gives results that are dependent upon the assumptions about the mechanism of the biological process being investigated.

2.3 High Energy Charged Particle Beam

High energy heavy ions, protons through iron ions, present an interesting combination of high stopping power and relatively long range. They are a component of the natural background radiation in space and their well defined range, which leads to minimum exit dose, makes them attractive for some radiation therapy applications. A characteristic of high energy ions is the production of secondary electrons known as delta rays. The maximum energy, and therefore range, of the delta rays depends on the velocity of the primary ion, but can be large compared to the dimensions of mammalian cells. A general rule of thumb is that about half of the energy lost by a charged particle is transferred to secondary electrons, and if the range of those electrons is larger than the diameter of a cell, some of the energy will be deposited in cells that are not traversed by a primary ion. When this type of radiation is described in terms of absorbed dose it is natural to describe the dose as a

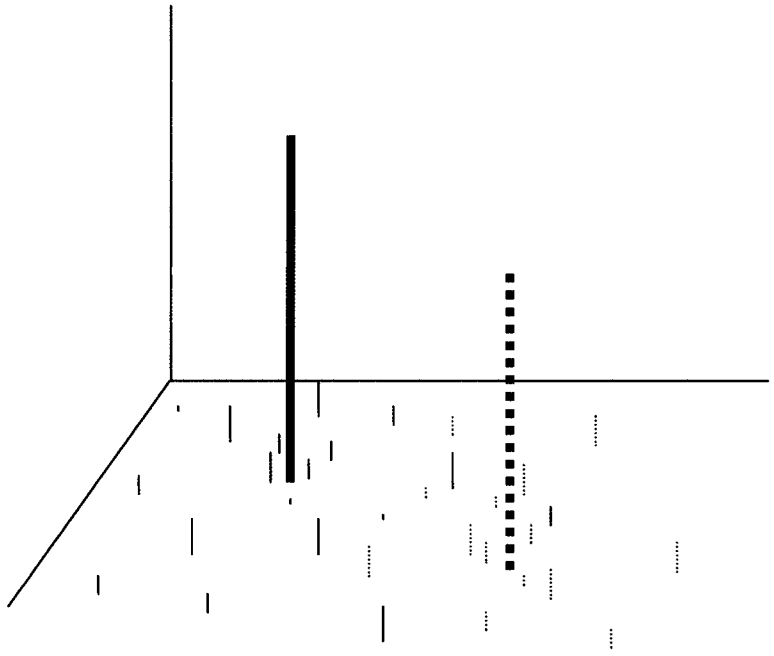

Fig. 3. Cartoon Representing the Energy Deposition in Small Sites within a Plane through a Tissue Irradiated by High Energy Heavy Particles. Energy Depositions by One Track and its Delta Rays are Represented by Solid Lines, a Second Track is Represented by Dashed lines. The Regions Influenced by Delta Rays Overlap but the Probability of Delta Rays from Two Primary Tracks Interacting in a Single Target is very Small

function of radial distance from the primary ion track. Experimental measurements [6] show the decrease in absorbed dose with the increased radial distance from the charged particle track, and several models have been developed to predict the radial dose distribution [7,8]. An example is shown in Figure 2. Recently it has been shown that for heavy ion irradiation at therapy doses there is substantial variation in the energy deposited in individual cells [9]. However, this approach overlooks the fact that the energy deposition in the volume surrounding the primary ion path is deposited by discreet secondary electron tracks. The experimental measurements [10] show that the energy deposited when a delta ray interacts with a cell is much more than the amount predicted by the absorbed dose as a function of radial distance from the track. Figure 3 illustrates the situation for two primary ion tracks. Delta rays deposit discrete amounts of energy in sites that they pass through, but as the radial distance from the primary particle path increases the probability that a specific target will be traversed by a delta ray decreases, both because the solid angle subtended by the target from the primary track decreases and because of the decrease in the fraction of delta rays with sufficient range to reach the target decreases. Energy depositions by delta rays from a second track, illustrated by dashed lines, can occur in the same region as those produced by the first primary ion, but the probability that delta rays from two separate primary ions will deposit energy in the same site is generally very small because the probability of a delta ray event in a specific target is low. In radiation therapy the exposures are given in a few minutes, and the consequences of delta rays in adjacent cellular volumes can be predicted from the response to low LET radiation at high dose rate. However, at lower dose rates, for example in exposure to cosmic ray radiation in space, the association of these delta ray events with the two primary ion events results in a temporal distribution of energy deposition that is very different from low dose rate low LET irradiation. Cells exposed to low LET irradiation at the dose rate that occurs in the space between high energy heavy ion tracks will experience energy deposition events that occur at random times as well as random positions, but all pairs of delta ray events produced by two primary ion tracks will have the same spacing in time. Additional primary ion tracks within delta ray range of a particular target will produce additional delta ray flashes, but all targets in the vicinity will receive delta ray events at the same time.

3. SOME ALTERNATIVES

Several alternatives to current system using absorbed dose have been suggested. Perhaps the simplest approach,

at least conceptually, is to retain absorbed dose rate as the primary quantity but add substantially to the additional information used to describe the radiation and the target. The additional information required would depend on the specific irradiation circumstances but would generally include detailed information on the charged particle spectrum, the fluence distribution to different areas of the target, and the size and geometry of the target. Proper application of this system requires that the user to actively monitor radiation quality and evaluate the circumstances of each irradiation.

Another approach is to emphasize the energy deposited in individual cellular or molecular targets. This leads to the concepts of microdosimetry [11] which emphasize the probability of specific energies being deposited in specified sites and the rate at which those events occur. The limitation of this approach is that one or more specific site sizes have to be chosen to describe the irradiation, and there is no clear biochemical reason for selecting any specific site size. One advantage of this approach is that the microdosimetric quantities can be evaluated experimentally once the site size has been specified. Another advantage of this approach is the close relationship between quantity measured and the energy imparted which is often assumed to be directly related to biological changes in individual targets.

The third, and most basic approach is to describe the particle fluence rate as a function of particle type, energy, and direction at the point of interest. This quantity is designated radiance spectrum, $\dot{\Phi}_{\Omega,E}$, by the ICRU [1].

4. ADVANTAGES OF RADIANCE SPECTRUM

The consequences of energy deposition by small numbers of charged particle tracks per target cannot easily be assessed based on the absorbed dose. The description in terms of absorbed dose implies a uniformity of radiation induced changes in time and space which does not occur in reality. The radiation induced changes actually occur along the tracks of individual charged particles which are separated in time and space. The most direct way to describe irradiation is in terms of the energy spectrum of the incident radiation, the particle direction, and the number of particles per area per time, the particle radiance spectrum, $\dot{\Phi}_{\Omega,E}$. This is a complete specification of the radiation field, and, given sufficient information about the cross sections for the interactions of radiation with mater, any other description of the radiation or its interaction with the target can be calculated from $\dot{\Phi}_{\Omega,E}$. Consequently, radiance spectrum, accompanied by the exposure duration and a description of the target, provides all of the information about physical nature of the energy deposition. In the case of background radiation it provides the number of particles interacting with any target, the amount of energy deposited, and the distribution of energy deposition events in time and space. In the case of microbeam irradiation $\dot{\Phi}_{\Omega,E}$, with the beam diameter and location, provides the number of interactions and the amount of energy deposited. This approach avoids the need to specify the size or mass of the target. In this way it avoids the confusion that results from trying to specify a site size to describe different processes, involving different biochemical mechanisms, occurring simultaneously. The use of particle radiance spectrum also solves the problem with heavy ion irradiation since there is no implication of a radial dose distribution. The physics of high energy charged particle tracks implies the random production of secondary electrons of different energies, and the events produced by these electrons are easily estimated.

As illustrated by these examples $\dot{\Phi}_{\Omega,E}$ provides a convenient way to describe irradiation in situations where absorbed dose does not represent the energy imparted in individual targets. When the radiance is high the relative variance of energy deposited in individual sites is small and absorbed dose is an effective way to describe the radiation exposure. However, when the radiance is low it is important to use this, more basic, quantity.

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