



Microdosimetric event distributions in sub-cellular volumes with a general purpose Monte Carlo code

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Abstract

The general purpose Monte Carlo code PENELOPE is used to calculate microdosimetric quantities including dose-weighted lineal energy spectra, which can be used to predict relative biological effect (RBE), for binary radiation therapies that utilise the photoabsorption of X-ray of high- Z materials. Spectra are calculated for Gd homogeneously distributed at a concentration of 10 mg/ml in water and irradiated by 70 keV monoenergetic photons, around 20 keV above the k -edge of Gd (50.239 keV), which has been shown to give optimal dose enhancement, and for a metallic Gd surface in close proximity (within 2 μ m) to a sensitive component of the nucleosome, modelled as a sphere of water of 1 μ m diameter, for 60 and 70 keV monoenergetic X-rays. X-ray interactions with homogeneously distributed Gd lead to a greater population of high lineal energy electrons than in liquid water, probably due to the creation of short range Auger electrons and photoelectrons, whereas interactions with Gd outside of the sensitive volume are longer ranged increasing the population of low lineal energy electrons. The data does not support increased therapeutic advantage through increased RBE in the case of Gd bearing contrast systems where little cellular absorption of Gd occurs. Homogeneously distributed Gd leads to higher lineal energies than pure water, probably due to the creation of short range, high LET Auger and photoelectrons, whereas photoelectrons that originate in Gd that are outside the sensitive volume tend to have relatively higher energies and long ranges increasing the population of low LET electrons.

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1. Introduction

Future progress in the treatment and management of cancer is likely to depend on radiation therapy that offers increased treatment specificity; through better tumour targeting, likely utilising binary techniques that are a synergistic combination of radiation and biological targeting, and exploiting aspects of tumour pathology.

Several binary therapies have been shown to offer life extension in the case of cancers with severely poor prognoses and resistance to conventional therapies such

as glioblastoma. One example is boron neutron capture therapy (BNCT) which requires specialised dosimetry techniques for the characterisation of a mixed radiation field [1] and planning procedures that incorporate information about the microdistribution of boron and the radiation weighting factors (RBEs) of the separate components [2]. Although lacking clinical demonstration, survival of glioma bearing rats following synchrotron X-rays applied in combination with the cytotoxic chemotherapy drug cisplatin, was shown to substantially exceed that of separate applications of cisplatin or X-rays, and of BNCT [3].

High Z materials when irradiated with above threshold X-rays become a source of high-LET Auger electrons and photoelectrons which, depending on the biological context,

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are generated in the vasculature, in the vicinity of the target cell, inside the cell or even incorporated in the nucleosome, as is suggested in the case of the enhancement brought about by Pt-based cytotoxic chemotherapy agents. It is probable that atomic models will not suffice in this latter circumstance. The flexibility of an all atom system in this context is desirable but it is unclear how such a general-purpose Monte Carlo code can be adapted to model the wide range of biologically relevant molecules and newly observed processes such as electron attachment disassociation [4] that may need to be considered in order to model radiation transport at the length scale of the DNA.

Binary therapies that utilise photoionisation are considered in this work. Some theoretical and experimental studies have been forthcoming in this area including the comparison of Monte Carlo and measured dose distributions in the vicinity of high- Z materials. The work shows a complex picture, including the prediction that for intermediate Z materials, such as the elements I and Gd typically used in contrast media, the energy of maximum dose enhancement occurs somewhat above edge (10's of keV) [5,6]. Indeed the production of photoelectrons with sufficient energy and range to generate damage must inevitably occur somewhat above edge, where, relatively long-range, fluorescent photons serve to redistribute the majority of the incoming photon energy at threshold. For high Z materials such as Au and Pt, however, enhancement does not continue to increase above edge due to the increasing dominance of the Compton process in the low- Z medium at such energies, although studies show that the degree of dose enhancement could be of the order of 100 for cells in close proximity to a metal surface [7]. In all cases, the precise enhancement depends on the distribution of the activating compound. In fact the presence of the compound outside of the tumour is doubly counter-productive in that it enhances the attenuation of the flux of the radiation field reaching the tumour as well as enhancing the toxicity of the treatment.

Microdosimetry calculations have been performed [8] using TRION [9], considering the circumstance of homogeneously infused I contrast media. These calculations show only a small change in lineal energy spectra due to the presence of I in the tissue, but fail to account for the microdistribution of the contrast media may be limited to the vasculature and therefore the exterior of the cell.

In essence, new methods of Monte Carlo radiation transport need to be developed for use in the planning of photoionisation-based binary therapies where, as with BNCT, the applied radiation field needs to be enfolded with the microdistribution of the activating agent. The thermal neutron capture reaction with boron leads to alpha and Li ion products which, due to experience with light ion therapies, have well-known radiobiological properties.

The radiobiological characteristics of the photoelectrons and Auger electrons generated in the photoionisation process are not well known, in addition the physics required to transport low-energy (below 10 keV) electrons at cellular

dimensions has not generally been incorporated in general purpose Monte Carlo codes. This is due to the poor quality of cross-section data for many elements as well as the emergence of molecular processes at low energies.

PENELOPE is a general purpose Monte Carlo code which offers photon and electron transport down to 50 eV where microscopic cross-section has been computed according to the independent particle approximation for a wide range of elements $Z = 1-92$. The current version of PENELOPE enables microdosimetric quantities, such as lineal energy, to be calculated in the sub-micron range [10]. The lineal energy quantity is used to model radiation risk including late effects in conventional radiotherapies. Recent work [11] has shown how PENELOPE can use molecular data for simple molecular systems such as liquid water. An advantage of this code over-specialised microdosimetry codes, using either liquid water or water vapour cross-sections, is access to a wider variety of materials which offers the potential to accurately benchmark the code against microdosimetry measurements including gas-filled tissue equivalent proportional counters (TEPC) and emergent solid-state microdosimeter systems.

2. Methods

A user-code incorporating the PENELOPE libraries (version 2005) has been written to calculate lineal energy microdosimetric spectra at sub-cellular dimensions. For the synchrotron radiation beams considered in this study, the field size is typically several mm; however, cellular length scales are of the order of microns presenting a target cross-section that is smaller than the radiation field by a factor of 10^6 . In order for the calculation to run in a feasible time frame, it is necessary to take one of several possible approaches. In microdosimetry codes, such as TRION, equilibrium electron slowing-down spectra are determined before the microdosimetry calculation. This approach enables electrons to be started from a point and the scored quantity becomes that of a cell volume fluctuating in position about the starting point; however, there are circumstances where photoelectrons have a non-uniform distribution close to the cell. Such a circumstance, where electronic equilibrium cannot be assumed, is the focus of this study.

As the cell volume in which the statistical picture of the profile of radiation events is being scored is just one of many equivalent sites, it is possible to use a geometrical layout with a large number of adjacent sites and at the end of the history sum the spectra together. The approach used in this study is to use just one cell volume but move it in an unbiased fashion to a position that coincides with the radiation track. The cell position will be unbiased if a randomly selected point in the cell is placed on a randomly selected segment of track; however, the selection of the track segment will depend on which particular spectral quantity is being scored. In this work, dose-weighted lineal energy spectra are calculated so the determination of the

track segment has been made according to the dose-weighted distribution of the segments.

3. Results and discussion

The PENELOPE code enables the calculation of microdosimetry spectra in non-equilibrium conditions and the two situations we have considered are the modelling of gas filled proportional counters where large density variations occur and for a complex microdistribution of radiation emitter or activating agent.

Discrepancies beyond 5% statistical precision achieved in calculation of spectra in Fig. 1 may be important in the determination of energy deposition at sub-cellular length scales, due to the atomic data used by PENELOPE. Tilly et al. [11] have shown how PENELOPE can use energy loss distributions that are specific to the molecule under consideration, for example, water, rather than a combination of elemental cross-sections.

The variation in lineal energy spectra moving from water to a gadolinium loaded solution (Fig. 1a) confirms previous work [8] showing an upward shift in the position of the maximum which translates to enhancement of the biological

effect of the radiation in the range 10–30% depending on the biological model used.

For Gd particles that have not penetrated the cell nucleosome (Fig. 1b), there is enhancement at lower values of lineal energies which would typically lead to a decrease in the biological response. If the synchrotron energy is reduced to 60 keV, with an associated reduction in dose enhancement, contributions from lower energy photoelectrons appear to lead to a slightly increased biological response as long as the photon energy is above the k -edge threshold.

Several important aspects of the physics are not modelled in this work including the polarisation of the synchrotron X-rays and its influence on scattering as well as the direction of the photoelectron. As an example, similar lineal energy spectra were obtained whether photoelectrons were being forward- or back-scattered from the Gd.

4. Conclusion

The general purpose Monte Carlo code, PENELOPE, has proved to be valuable in providing calculations relating to photoionisation enhanced X-ray radiation therapies. Standard microdosimetry codes tend only to have a limited range of materials such as liquid water and usually demand the electron field at the point of interest is in equilibrium. We consider the non-equilibrium condition of a Gd-based binary photoionisation therapy where Gd particles do not infuse into the nucleosome showing that this displacement leads to a therapeutic disadvantage at higher energies above threshold that have shown to lead to conditions of maximum dose.

Microdosimetry measurements with devices such as tissue equivalent gas-filled proportion counter (TEPC) and emerging solid-state microdosimetric systems present complex combinations of materials and non-equilibrium conditions are a further candidate for analysis with a general purpose code Monte Code and will offer a valuable benchmark of the calculation not accessible with standard microdosimetry codes.

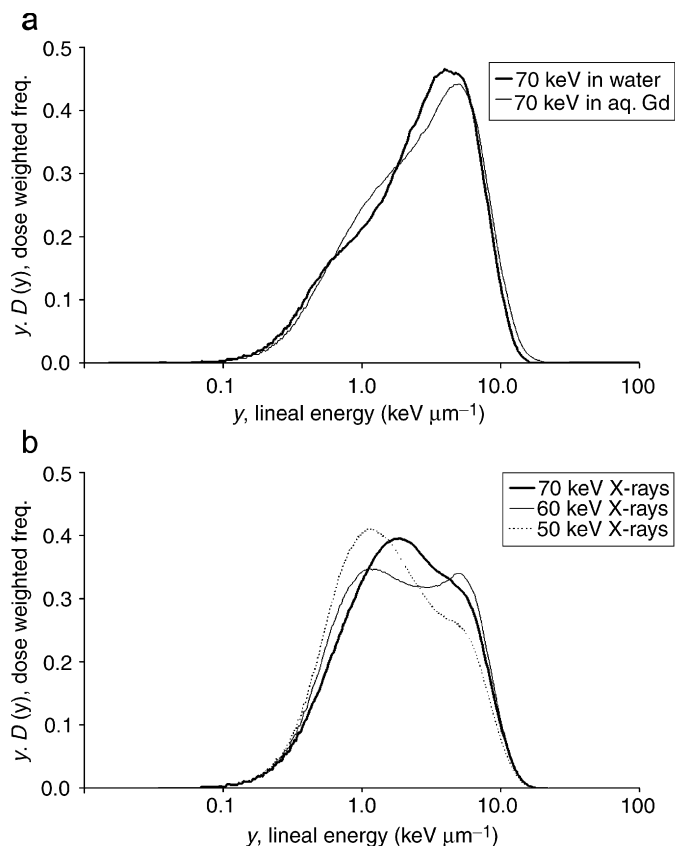


Fig. 1. Lineal energy event spectra calculated for a Gd-based photoactivation therapy with monoenergetic synchrotron X-rays. Spectra are calculated for (a) water (solid line) and Gd loaded solution 10 mg/ml (broken line) irradiated at the optimal energy for dose enhancement (70 keV) and for (b) 1 μ m diameter volumes in the vicinity of 100 μ m thick metallic Gd surface irradiated with 70 keV (solid line) and 60 keV (thin line) and 50 keV (broken line) where the k -edge of Gd is 50.239 keV.

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