Revealing the underlying mechanism of microbeam radiation therapy with low energy Monte Carlo simulations

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Abstract. Microbeam radiation therapy (MRT) is a new experimental oncological modality, intended for the treatment of inoperable brain tumours, particularly in difficult cases where conventional radiation therapy can cause irreversible damage. MRT consists of an array of highly collimated, quasi-parallel x-ray microbeams aimed at the tumour tissue, delivering high dose within the beam path and low doses in regions between the beams. For reasons still not fully understood, healthy tissue exposed to the microbeam array is able to regenerate while tumour volumes are significantly reduced. Low energy Monte Carlo radiative transport simulations provide new insight into understanding the underlying mechanisms of MRT. In particular, predicting the ionisation cluster distribution, which is a significant cause of lethal damage to cells, would provide insight into the biological responses. Geant4-DNA was used to model an x-ray microbeam of width 20 µm in liquid water. Secondary electrons, predominately responsible for ionisation clustering, were tracked to predict damage to cells within and adjacent to the beams. We find that higher energy beams (100 keV) produce less secondary electrons in the regions outside the beam than low energy beams (30-50 keV).

1. Introduction

A new innovative radiation modality called Microbeam Radiation Therapy (MRT) could potentially revolutionise brain malignancy radiotherapy in paediatric cases. In MRT nominally supralethal doses (> 100 Gy/s) are delivered to the patient in micron-sized beams, based on the observation that healthy tissue is exceptionally resistant to high dose in small volumes, while cancerous tissue is not [1, 2, 3]. Despite promising results in tumour-bearing animals, MRT is yet to be applied to human oncological treatment since the underlying biological mechanism for preferential tumour damage is not known.

MRT consists of an array of intense, parallel synchrotron x-ray beams, each with a typical width of 20 – 50 µm and with a 200 – 400 µm centre-to-centre distance [1, 2]. The microbeam array is aimed at the tumour volume, delivering high radiation dose in the beam paths (peaks) and low dose in the regions in between the beams (valleys). The success of the treatment in animal studies has been shown to be highly dependent on the microbeam width and beam-to-beam spacing as well as the peak-to-valley dose ratio [4, 5, 6, 7].

Computational modelling of ionising particles down to very low energies (~ few eV), where biological damage predominantly occurs, has advanced our understanding of the interaction of...
ionising radiation with living cells [8, 9]. To date, both *in silico* and *in vivo* studies have mostly focused on the effect of radiation on the DNA molecule because of its central role to continuing cell viability [10, 11]. Although DNA strand breaks as a direct result of ionising radiation can be used to measure the efficacy of damage, it is well known that *indirect* damage caused by free radicals produced in the immediate surroundings of DNA is considerably more prevalent than direct radiation in causing damage to the DNA molecule itself [12]. Furthermore, there is mounting evidence to suggest that free radical production and damage in other regions of the cell (e.g. cytoplasm, mitochondria) are also important for understanding inexplicit biological responses e.g. bystander non-targeted effects [13, 14, 15]. Indeed, non-DNA focused models [16, 17] could be particularly important for understanding the success of MRT.

In this investigation, the distribution of secondary electrons is investigated in the peak and valley regions for MRT. The low-energy secondary electrons, produced through the interaction of ionising radiation with matter, play a key role in the production of biological damaging ionising events, particularly electrons with energies less than $\sim 1$ keV. Predicting the number of ionisation and excitation events occurring within molecular sized volumes can infer information about the biological effectiveness of the primary ionising particle. Monte Carlo simulations have shown that ionisation clustering can be correlated with the biological effectiveness of radiation on the nanometre scale [8] and may be a more pertinent quantity than the absorbed dose, currently used to determine radiation damage.

2. Monte Carlo Simulation

An x-ray microbeam of width $20 \times 20 \mu m^2$ incident on a liquid water cube of dimension $40 \times 40 \times 40 \mu m^3$ was simulated using the Monte Carlo simulation toolkit Geant4 (version 9.6.p01). X-rays were modelled using the Low Energy Electromagnetic Physics models, including the following processes: Compton scatter, Rayleigh scatter, pair production and the photoelectric effect. Secondary electrons were modelled with the Geant4-DNA physics models [18, 19] including the following processes: elastic scattering, electronic excitation, ionisation, vibrational excitation and attachment. Monoenergetic microbeams with 30, 50 and 100 keV energies were investigated and in each case $10^6$ incident photons were simulated.

3. Results and Discussion

The left panel in figures 1, 2 and 3 show the 3D electron track structure for 30, 50 and 100 keV x-ray microbeams of width $20 \mu m$ centred at 0 on the $yz$ plane, respectively. The right panels show the total amount of elastic scattering (process number 11 on x-axis), excitation (12), ionisation (13) and excitation vibrational (15) processes occurring in the entire phantom volume. In each case, the number of excitation and ionisation process counts are significantly high, however the distribution of the secondary electrons differ for each energy case. Ionisation and excitation processes are primarily caused by low energy secondary electrons and are predominately responsible for inducing direct and indirect (free radical) biological damage. In the 30 and 50 keV cases (fig. 1 and 2), a large amount of electrons are found both in the peak and valley regions, indicating damage may occur in both regions. In the 100 keV case however, the electrons are mostly confined to the peak region. Animal studies have indicated that the success of MRT is somewhat dependent on confining cell death to the peak regions [1], if this is the case, our results indicate that high energy beams would be most suitable for successful MRT.

These preliminary results are limited by the size of the phantom volume. The high energy case is more indicative of an entrance dose, while the lower energy beams would represent the beam at a greater depth within a realistic phantom, most likely closer to a deep-seated tumour volume. In a future study, a phantom of realistic dimension, corresponding to a human head, will be modelled.
Figure 1. The left panel shows the 3D electron track structure for a 30 keV monoenergetic X-ray microbeam of width 20 µm incident at the centre of the $yz$ plane of the $40 \times 40 \times 40$ µm liquid water phantom, centred at the origin. The right panel shows the total number of each physical process (elastic scatter - green (11), excitation - orange (12), ionisation - blue (13) and vibration excitation - red (15)) occurring within the entire phantom volume. $10^6$ incident photons was simulated.

Figure 2. The left panel shows the 3D electron track structure for a 50 keV monoenergetic X-ray microbeam of width 20 µm incident at the centre of the $yz$ plane of the $40 \times 40 \times 40$ µm liquid water phantom, centred at the origin. The right panel shows the total number of each physical process (elastic scatter - green (11), excitation - orange (12), ionisation - blue (13) and vibration excitation - red (15)) occurring within the entire phantom volume. $10^6$ incident photons was simulated.

4. Conclusion
The success of MRT in eliminating cancerous tissue, while preserving surrounding healthy tissue has been experimentally shown to be dependent on the beam width, spacing between the beams and the peak-to-valley dose ratio. The underlying biological mechanism for the success of the treatment is however still unknown. Investigating the effect of ionising radiation on a nanometer/molecular level could provide more insight into MRT.

Three different energy x-ray microbeams, incident on a $40 \times 40 \times 40$ µm phantom, were investigated: 30, 50 and 100 keV. Large numbers of ionisation and excitation processes, mostly responsible for biological damage, occurred in each case. However the distribution of the secondary electrons responsible for these processes, differed with incident photon microbeam energy. Electrons in the 100 keV case were mostly confined to the beam (peak) region while
Counts
Elastic (11)
Excitation (12)
Ionisation (13)
Vibration Excitation (15)

Figure 3. The left panel shows the 3D electron track structure for a 100 keV monoenergetic X-ray microbeam of width 20 µm incident at the centre of the yz plane of the 40 × 40 × 40 µm liquid water phantom, centred at the origin. The right panel shows the total number of each physical process (elastic scatter - green (11), excitation - orange (12), ionisation - blue (13) and vibration excitation - red (15)) occurring within the entire phantom volume. 10⁶ incident photons was simulated.

in the 30 and 50 keV cases, large numbers of electrons were found in both the peak and valley regions. Results in animals studies have indicated that the therapy is most successful in cases where cells are killed only in the peak regions. From these preliminary results, higher energy beams will result in cell death in the peak regions and possibly less biological damage in the valley regions. In a future investigation, a realistic phantom will be modelled to further investigate the spread of electrons in a larger volume.

4.1. Acknowledgments
The authors acknowledge the Cancer Institute of NSW for funding the Advanced Computing Facility for Cancer Research which was used in this study.

5. References
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