BIOLOGICAL EFFECTIVENESS OF PROTON AND ION BEAM THERAPY: STUDIES USING G4-DNA

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Abstract

We have used the Geant4-DNA program to investigate on a radiobiological level the interaction of various types of particles within cells, to identify relationships between irradiation and damage to DNA, leading to cell death. Although the physical attributes of particle therapy clearly hold a benefit over conventional radiotherapy, the biological effects hold uncertainties, and modelling the way particles interact with tissue on a cellular level can reduce these. The understanding of the energy deposition pattern along the particle track and consequent probabilities of producing DNA cluster breaks enables us to predict the effects of a particle beam on a microscopic level, which can aid treatment planning.

INTRODUCTION

The mechanisms by which particles interact and lose energy are well understood, due to the full understanding needed for particle detectors for High Energy Physics [1, 2] and have been incorporated in the Geant4 simulation program [3].

This deposited energy is responsible for killing tumour (and healthy) cells in radiotherapy, but the mechanisms are much less well understood. Although considerable experience has been gained for x-ray therapy, there is much less data for proton therapy treatment, and even less for irradiation by heavier ions. This lack of data can lead to uncertainties in individual treatment planning, and in larger questions of the effectiveness of particular types of therapy. We therefore seek to explore ways of using our understanding of the physical processes to the radiobiological consequences proton and ion therapy.

This is a complex question: when particles pass through living cells, a wide variety of processes (physical, chemical, biological) take place. One cannot hope for a complete description, and generalisations are dangerous. And even if one could understand the mechanism of cell death, the death of a tumour involves much more. But increased understanding of *in vitro* cell death would be a good basis for understanding of *in vivo* processes.

LIMITATIONS OF RBE

The effect of proton therapy is often expressed in terms of the Radio-Biological Effectiveness (RBE): a factor by which the dose (in Grays) is multiplied to give an equivalent x-ray dose.

However this simple definition obscures the fact that the ratio is not just a constant. If a 10 Gy proton dose kills as many cells as an 11 Gy x-ray does, it does not follow that 20 Gy and 22 Gy are equivalent: when dose/survival curves are plotted for protons and x-rays, one is not just a multiple of the other. Hence a full definition needs to specify the fraction of cells killed, leading to quantities like RBE_{50} or RBE_{10}.

The x-ray dose also needs to be defined, as the effectiveness of an x-ray dose varies with the photon energy. If an electron HV source is used (as opposed to a radioactive isotope), the x-ray spectrum depends not only on the voltage but also on the target material and geometry. To simulate a proton RBE one would also have to simulate the specific x-ray source. Experimentally, protons and x-ray beams are generally very different (horizontal and vertical) which will produce systematic differences in the cell survival.

For these reasons it is better to work directly with the effectiveness of the protons: the fraction of cells killed by a particular dose, rather than expressing it as an ill-defined and complicated ratio.

EFFECTIVENESS AND LET

It is well established [4] that the effectiveness of a dose depends on the Linear Energy Transfer (LET), more familiar to physicists as $-\frac{dE}{dx}$. A dose spread over many cells does not pass the threshold for irreparable damage, and a very concentrated dose will 'overkill' the cell; peak effectiveness lies somewhere in between, in a way which depends on the effective target size and the spatial distribution of the LET which, at the microscopic level, occurs not continuously in discrete packets.

Further useful insight could be gained by experiments with beams of the same dose and LET but different patterns of energy deposit. To achieve this, consider the dependence of LET on charge and velocity with different ions.

For a particle of charge z travelling a distance x through material of density ρ and atomic mass and number A and Z, define

$$\xi = 2\pi N_A r_e^2 m_e c^2 \rho \frac{Z}{A}\frac{z^2}{\beta^2} x. \quad (1)$$

The mean energy loss at low energies is given by Eq. (2) [5]. We take I=13.5 Z eV. β and γ are the usual relativistic velocity quantities.

$$< LET >= 2\xi \left[\ln \frac{2m_e c^2 \beta^2 \gamma^2}{I} - \beta^2\right] \quad (2)$$

$< LET >$ thus depends on the charge z and the energy E of the particle. Particles of different charge and different energy, for example a slow proton and a fast α can have the same $< LET >$. This is shown in Fig. 1, where the results of G4DNA simulation are shown [3]. Combinations with

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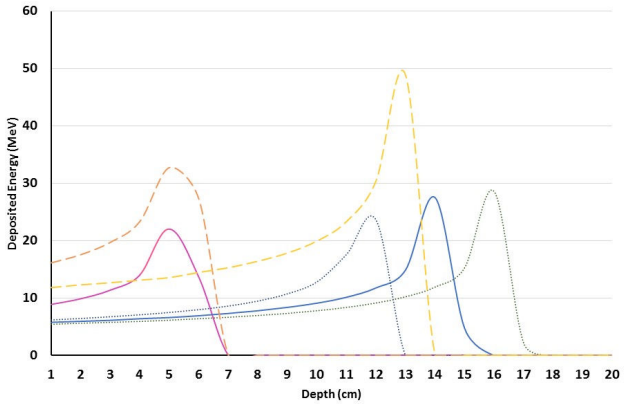

Figure 1: Energy loss in water for various ions and initial energies, as predicted by G4DNA.

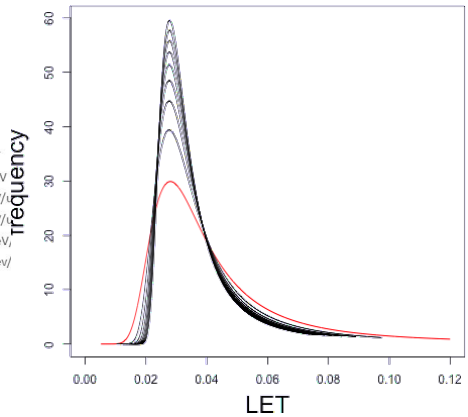

Figure 2: Landau distributions with the same peak LET for protons (in red) and ions of higher charge.

the same $< LET >$ can be read off these curves, or obtained by solving Eq. (2).

However the energy distribution is not the same. According to Landau [6, 7] the probability density for an energy loss Δ in a distance x is

$$P(\Delta) = \frac{1}{\xi}\phi(\lambda) \tag{3}$$

where ϕ is the Landau function:
$\phi(\lambda) = \frac{1}{\pi}\int_0^\infty e^{-ulnu-\lambda u} sin(\pi u)du$, and

$$\lambda = \frac{\Delta}{\xi} - ln\frac{2mc^2\beta^2\gamma^2\xi}{I^2} - 1 + \beta^2 + \gamma_E \tag{4}$$

The probability distribution for Δ is thus the universal Landau function, shifted and scaled.

The peak occurs at [5]

$$\Delta_p = \xi\left[\ln\frac{2mc^2\beta^2\gamma^2}{I} + \ln\frac{\xi}{I} + 0.200 - \beta^2\right] \tag{3}$$

and the Landau distribution predicts that a high z high energy particle has a narrower distribution in deposited energy, over a particular distance, than a slow low z particle with the same mean energy loss.

Figure 2 shows the distributions for protons and ions up to Flourine, with increasing β chosen to ensure that $< LET >$ is constant. The width of the Landau distribution falls as charge increases.

The Landau approximation is simple as it neglects complex details, however Geant4 confirms (Fig. 3) that the energy deposition patterns for ions with similar $< LET >$ is different, at the scale relevant for the cell size.

This is interesting because it can enables the study of the dependence of effectiveness on the energy deposited in a particular cell. This must be sigmoid in form - in the limit of small LET there is no damage, and saturation occurs at high LET as the cell can only die once. Thus if one particle type always delivers the same LET whereas another sometimes delivers more and sometimes less, the measurement of whether this is more or less effective for killing cells will reveal a great deal about the fundamental process.

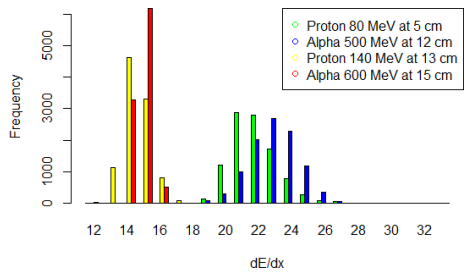

Figure 3: Energy loss distributions predicted by Geant4.

STATUS OF THE LQ MODEL

Models may be *prescriptive*, based on a mechanism of the underlying process, or *descriptive*, adopting a form suggested by the data. A (prescriptive) single-target model in which the energy deposited in a dose D has a probability of killing a cell leads to the prediction $S(D) = e^{-\alpha D}$, but this is not supported by the data.

The Linear-Quadratic (LQ)model $S(D) = e^{-\alpha D-\beta D^2}$, is widely used (some data compilations just quote values of α and β). It was introduced in a descriptive way ("the cell survival curve derived here was well fitted by an equation of the form...") but subsequent authors have ascribed a mechanism to it [8], saying the probability of two breaks is proportional to the square of the dose. But with some probability $p \propto D$ for breakage, the probability of 2 (or more) breaks is $1-e^{-p}-pe^{-p}$ (assuming a Poisson process: strictly it is a multinomial for the 46 chromosomes) which is indeed a power series for which the quadratic is an approximation..

The validity of the LQ model thus rests on the experimental data. But the experiments are hard to do, with large statistical and systematic errors. We therefore propose a simple *in silico* Markov Chain model to investigate the range of validity of the LQ model.

Suppose that a cell may be healthy, dead, or injured, and we write the probability of these as a 3 element vector. If an incremental dose has a probability p of killing a health cell, p' of injuring it, and an additional probability p'' of killing an injured cell, then the effect is expressed through the transition matrix

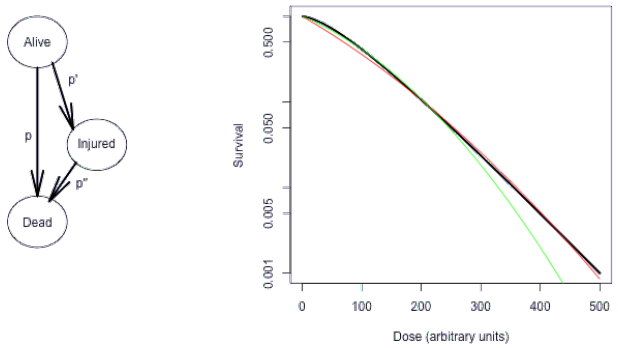

Figure 4: (a) A Markov Chain model, and (b) its predicted survival curve (black), with LQ model fits to the whole range (red) and the lower half (green).

$$M = \begin{pmatrix} 1-p-p' & 0 & 0 \\ p & 1 & p+p'' \\ p' & 0 & 1-p-p'' \end{pmatrix} \quad (5)$$

A survey of the literature suggests survival probabilities are relevant over 3 orders of magnitude, down to 0.001, so we study this range, adjusting p to give the desired fall of 1000 over 500 increments. Figure 4 shows a predicted survival curve with $p'/p = 6$ and $p''/p = 8$. The (least squares) best fit LQ model is shown in red. It provides a fair description, but the shoulder at small doses is not well described. This can be remedied by fitting only the lower half of the curve (green) but then the uncontrolled high dose fit is poor.

Scanning a range of values of p'/p and p''/p, with p scaled as above, shows the maximum absolute deviation between the Markov chain model and the LQ fit, is typically several percent. We conclude that the LQ model does not do a very good job of describing even a simple Markov process.

Of course cell death may not be a simple Markov process. However a general model would not look very different. A full model would contain cells which had been injured in different ways (and 'injured' includes 'resource-depleted') each with its of p' and p'', and there would also be transitions between different cell injury states. Nevertheless one can group all these together under the 'injured' label, and the only difference from the simple model is that p'', the additional probability for killing an injured cell, would vary as the dose increased, as the population changed. This could be explored through simple models of this time dependence. One can also test whether an alternative two parameter model can be found giving better fits than the LQ model.

DIRECT AND INDIRECT DAMAGE

Damage is classified into *direct* damage, where the energy deposited ionises the DNA molecule, and *indirect* damage, where the energy deposited produces radicals, typically (OH), which then damage the DNA. Damage by x ray photons is mostly indirect, whereas protons produce more direct damage, and higher LET particles such as αs even more.

We hypothesize that direct radicals produced by charged particles have the same effects as radicals produced by x-rays, and that direct damage is similarly independent of the particle producing it. This means that differences in effectiveness for different particles can be expressed as differences in the amount of direct and indirect damage.

Furthermore Geant4 can predict the amounts of direct DNA breaks and indirect ion production for different particles So from observed survival curves of, say, x-rays and αs we can deduce the effects of direct and indirect damage. (Direct will be close to the effect of αs and indirect close to the effect of x rays). We can then, using their direct and indirect quantities from Geant4, use these to predict the effect due to other particles. The hypothesis can be tested: if true it will clarify future models of particle therapy.

THE IMPORTANCE OF THE CELL CYCLE

Tumour cells, like normal cells, cycle through 4 stages: G_1, S, G_2 and M. The time spent in each phase varies with cell type, but is of the order of some hours. Data from x-rays suggests that the cell susceptibility varies greatly during the cycle, being much more vulnerable in the M and G_2 phase than in the G_1 and S phase [4].

This is the second of the '4Rs of radiotherapy' (Repair, Redistribution, Repopulation, and Reoxygenation). It is especially important for proton therapy as proton doses may be given in large fractions, and a simple Lea-Catcheside [10] modification to the LQ model, replacing β by $G\beta$, may not be sufficient; one needs to know the stages the surviving cells will be in, and understand their sensitivity.

The cell-killing power of radiation, expressed in terms of SSBs and DSBs, depend on the size of the DNA molecule. This can be studied using G4DNA simulations [11]. It is important to understand the way the DNA configuration (extended or coiled-up) effects the sensitivity, though the change is also due to repair mechanisms. Simple arguments about target size suggest a sensitivity variation opposite to that observed by experiments.

CONCLUSIONS

Geant4, and G4DNA, provide a powerful tool in helping our understanding of how cell damage and cell death occur, embodying the knowledge the physics community has acquired over more than half a century. Four topics are listed here as suggestions to explore: progress will be reported in future publications.

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