Advancement of microdosimetric kinetic model in heavy-ion radiotherapy

T Inaniwa
Department of Accelerator and Medical Physics, National Institute of Radiological Sciences, QST, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan

E-mail: inaniwa.taku@qst.go.jp

Abstract. To date, more than 11,000 cancer patients have been treated with therapeutic carbon-ion beams at the National Institute of Radiological Sciences (NIRS). In the treatment planning system, the biological effectiveness of the therapeutic carbon-ion beams has been predicted based on the microdosimetric kinetic (MK) model. The MK model has a variety of applications. For instance, it can be used to predict the biological effectiveness of therapeutic carbon-ion beams under protracted irradiations as well as under hypoxic conditions. Recently, we have updated the MK model to a stochastic microdosimetric kinetic (SMK) model for a new research project about hypo-fractionated multi-ion radiotherapy, referred to as a “Quantum Scalpel”. This report overviews advancement of the MK model in heavy-ion radiotherapy.

1. Introduction
To date, more than 11,000 patients with various tumours have been treated with therapeutic carbon-ion beams at the National Institute of Radiological Sciences (NIRS). When carbon ions enter the patient body, some of them undergo inelastic nuclear interactions and light fragments are generated through these interactions [1]. Consequently, therapeutic carbon-ion beams have a complex radiation quality composed of various ion species with various kinetic energies. Since the in vitro and in vivo experimental data for these ion species are limited, the biological effectiveness of the therapeutic carbon-ion beams has to be predicted based on biological models. The microdosimetric kinetic (MK) model is one biological model used to predict cell-survival fractions from the specific energy absorbed by a microscopic subnuclear structure “domain” for any species of ions [2, 3]. Thus, the MK model has been integrated into the carbon-ion radiotherapy treatment planning system and has been used to predict the biological effectiveness of therapeutic carbon-ion beams for individual clinical cases at the NIRS [4, 5]. The MK model has a variety of applications. For instance, the model can be used to predict the biological effectiveness of the beams under protracted irradiations as well as under hypoxic conditions. Recently, we have updated the MK model to a stochastic microdosimetric kinetic (SMK) model for a new research project about hypo-fractionated multi-ion radiotherapy, referred to as a “Quantum Scalpel”. This report overviews advancement of the MK model in heavy-ion radiotherapy.

2. Microdosimetric kinetic model

2.1. Theory of the microdosimetric kinetic model [2]
The ion-species dependences observed in the relation between linear energy transfer (LET) and relative biological effectiveness (RBE) deduced from cell-survival data indicate that the LET is not an ideal index for expressing the biological effectiveness of heavy ions. Instead, microdosimetric quantities such as specific energy \( z_d \) may be better indices for this purpose, since they directly relate to ionizing density within microscopic sites. The MK model is one biological model used to predict the cell-survival fraction from the specific energy \( z_d \) absorbed by a microscopic subnuclear structure domain. When a population of cells is exposed to ionizing radiation of macroscopically measured dose \( D \), the dose absorbed by any individual domain, the specific energy \( z_d \), is a random variable that varies from domain to domain throughout the population of cells. Ionization radiation is assumed to cause two types of lesions in the domain, type I and type II lesions. Each lesion type is created with a probability proportional to \( z_d \) with the proportionality constants \( \lambda_d \) and \( k_d \), respectively. A type I lesion is lethal to the cell containing the domain. A type II lesion is non-lethal and may undergo one of four transformations:

- It may spontaneously convert to a lethal unrepairable lesion with first-order rate constant \( a \).
- It may undergo pairwise combination with another type II lesion in the same domain to form a lethal lesion with second-order rate constant \( b \).
- It may undergo spontaneous repair with the first-order rate constant \( c \).
- It may persist for a length of time \( t_r \), after which it becomes lethal and unrepairable.

These specifications can be expressed in the following rate equations:

\[
\frac{dx_{II}}{dt} = k_d x_{II} - (a + c) x_{II} - 2b x_{II}^2 ,
\]

\[
\frac{dx_1}{dt} = \lambda_d x_{II} + ax_{II} + bx_{II}^2 ,
\]

where \( x_{II} \) is the mean number of type II lesions per domain that has absorbed \( z_d \), and \( x_1 \) is the mean number of type I lesions per domain. By solving the rate equations (1) and (2) for a given irradiation condition, the cell-survival fraction \( S \) under this condition is determined as the probability that there are no domains containing the type I lethal lesions within the cell nucleus at \( t \rightarrow \infty \). For a single instantaneous irradiation of a macroscopic dose \( D \), the natural log of the cell-survival fraction is given by

\[
\ln S = -(\alpha_0 + z_{d,D} \beta)D - \beta D^2 ,
\]

where \( \alpha_0 \) and \( \beta \) are cell-type dependent and radiation-type independent parameters, and the variable \( z_{d,D} \) is the dose-averaged specific energy absorbed by a domain in a single event.

2.2. Microdosimetric kinetic model in carbon-ion radiotherapy

In carbon-ion radiotherapy, the dose is imparted to a domain by a passage of high energy particles through, or near, it. Thus, \( z_d \) can occasionally be very high, up to a few hundred Gy, while the macroscopic dose \( D \) is low, e.g., 1 Gy. The RBE of the radiations with very high specific energies may decrease due to the overkill effect. Kase et al [3] introduced the dose-averaged saturation-corrected specific energy \( z_{d,D} \) to express this effect. By substituting \( z_{d,D} \) in \( z_{d,D} \) of equation (3), the cell-survival fractions for the radiations with high specific energy, e.g., carbon ions, can be predicted based on the MK model.

Inaniwa et al [4] developed a computation method to calculate the biological effectiveness in mixed radiation fields of therapeutic carbon-ion beams based on the MK model. They determined the MK model parameters, i.e., \( \alpha_0, \beta \), and radii of domain and cell nucleus \( r_d \) and \( R_n \), so that the predicted
survival fractions with the MK model reproduced the experimental survival fractions reported by Furusawa et al [6] for human salivary gland (HSG) tumour cells. They are $a_0 = 0.172 \text{ Gy}^{-1}$, $\beta = 0.0615 \text{ Gy}^{-2}$, $r_d = 0.32 \mu m$, and $R_n = 3.9 \mu m$. $z_{d,D^*}$ of the mixed radiation fields was calculated using the particle-energy spectrum of therapeutic carbon-ion beams derived with Monte Carlo simulations, and assuming that a cylindrical sensitive volume domain with a radius $r_d$ and a length $2r_d$ is irradiated by the particles with the microscopic radial dose distribution given by the Kiefer-Chatterjee amorphous track structure model. The MK model was integrated into the treatment planning system and validated through the cell irradiation experiments. Figure 1 shows some experimental results, where the depth–survival curve of a therapeutic carbon-ion beam predicted with the MK model was compared with the experimental measurements for HSG tumour cells.

![Figure 1. Measured survivals for HSG tumour cells (symbols) are compared with the predicted survivals (solid curve) based on the MK model.](image)

3. Applications of microdosimetric kinetic model

3.1. Application for protracted irradiations

By solving the rate equations (1) and (2) for a continuous irradiation over a time period $T$, the cell-survival fraction under protracted irradiations can be predicted with equation (3) just replacing the quadratic coefficient $\beta$ by $\beta'$ given by

$$\beta' = \frac{2\beta}{(a+c)^2T^2} \left[ (a+c)T \left( 1 + e^{-2(a+c)r_d} \right) - 1 + \frac{e^{-(a+c)r_d}}{1 - e^{-2(a+c)r_d}} \left( 1 - e^{-(a+c)T} \right) \right].$$  (4)

Inaniwa et al [7] investigated the effect of the irradiation time $T$ on biological effectiveness of therapeutic carbon-ion beam using this formula. They revealed that the longer the period of dose delivery $T$ and the higher the fractionated dose, the more significant is the reduction of biological effectiveness of the beam, due to the sublethal damage repair (SLDR) during the dose delivery time. Single-fractionated treatment used against non-small cell lung cancer (NSCLC), where the treatment is administered by sequential delivery of two sets of vertical and horizontal fields, separated by a change in patient roll angle and patient repositioning, may allow the damaged malignant cells to undergo a significant degree of SLDR. Inaniwa et al [7] investigated the effects of the period of dose delivery, particularly the interruption time $\tau$ due to patient repositioning, on the tumour control probability (TCP) of NSCLC by applying the rate equations defined in the MK model to the protracted/interrupted irradiations. The single-fractionated treatment was modelled as an interrupted irradiation composed of
two continuous irradiations of $T_1 = T_2 = 7.5$ min with a beam interruption over a period of time $\tau$ between them. Figure 2 shows the TCP curves of the planned and recalculated dose distributions for various interruption times $\tau$ ranging from 0 to 120 minutes. The TCP of NSCLC decreased with prolongation of the interruption time compared to the planned TCP due to the repair of non-lethal lesions. The curative dose that was defined to result in a TCP of 90% increased from 34.5 Gy (RBE) under the planning condition with $T_1 = T_2 = \tau = 0$ to 43.4 Gy (RBE) for the irradiation with $T_1 = T_2 = 7.5$ min and $\tau = 60$ min.

Figure 2. TCP curves of the planned (black) and recalculated dose distributions on NSCLC for interruption time $\tau$ from 0 to 120 minutes.

3.2. Application for hypoxia

Heavy-ion beams present a potential advantage in treating tumours under hypoxic conditions. In order to optimally use this potential, it is important to accurately model the cell-survival fraction of oxic cells as well as hypoxic cells. Bopp et al. [8] adapted the MK model making it able to account for cell hypoxia. The adaptation relies on the modification of damage quality due to radiation, and the MK model parameters are determined through the fitting procedure of experimental survival data under oxic and hypoxic conditions. The experimental data behaviour of the oxygen enhancement ratio (OER) can be reproduced with the approach, including dependence on particle type at the same LET.

4. Update to a stochastic microdosimetric kinetic model

In the derivation of equation (3), the stochastic nature of the specific energy within the domain $z_d$ was considered, while that within the cell nucleus $z_n$ was neglected by assuming a constant value $z_n = D$. Sato and Furusawa [9] indicated that this approximation was valid only for radiations with LET < 150 keV/µm and fractionated dose of < 10 Gy. For this, they numerically determined the cell-survival fractions by considering the stochastic natures of specific energies both in a domain $z_d$ and a cell nucleus $z_n$, namely a stochastic microdosimetric kinetic (SMK) model. With the SMK model, the cell-survival fractions can be predicted accurately for radiations with wide LET and dose ranges. However, this was computationally intensive both in time and memory space requirements to deal with the stochastic natures in $z_d$ and $z_n$, making the model difficult to use in daily clinical practice. We developed a computational method with a shorter computation time and a reduced memory space to calculate the biological effectiveness of charged particle beams based on the SMK model in treatment planning software [10]. With the method, the SMK model is applicable to treatment planning of the Quantum Scalpel, i.e., the hypo-fractionated multi-ion radiotherapy.

5. References

[1] Inaniwa T, Kanematsu N, Hara Y and Furukawa T 2015 Phys. Med. Biol. 60 421-35
[2] Hawkins RB 1996 Int. J. Radiat. Biol. 69 739-55
[3] Kase Y 2006 Radiat. Res. 166 629-38
[4] Inaniwa T et al 2010 Phys. Med. Biol. 55 6721-37
[5] Inaniwa T et al 2015 Phys. Med. Biol. 60 3271-86
[6] Furusawa Y et al 2000 Radiat. Res. 154 485-96
[7] Inaniwa T et al 2015 Phys. Med. Biol. 60 4105-21
[8] Bopp C et al 2016 Phys. Med. Biol. 61 7586-99
[9] Sato T and Furusawa Y 2012 Radiat. Res. 178 341-56
[10] Inaniwa T and Kanematsu N 2018 Phys. Med. Biol. 63 095011