Cellular Track Model for Study of Heavy Ion Beams

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Cellular Track Model for Study of Heavy Ion Beams

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Abstract

Track theory is combined with a realistic model of a heavy ion beam to study the effects of nuclear fragmentation on cell survival and biological effectiveness. The effects of secondary reaction products are studied as a function of depth in a water column. Good agreement is found with experimental results for the survival of human T-1 cells exposed to monoenergetic carbon, neon, and argon beams under aerobic and hypoxic conditions. The present calculation, which includes the effect of target fragmentation, is a significant improvement over an earlier calculation because of the use of a vastly improved beam model with no change in the track theory or cellular response parameters.

Introduction

The change in biological response behind the increasing amount of absorbing materials for various ion beams is of interest to the radiotherapeutic and space radiation communities whether one studies relative biological effectiveness (RBE) for some biological systems or average quality factors. The quality factor as defined in ICRP 26 (ref. 1) or in ICRU 40 (ref. 2) is now considered unsuitable for the risk assessment of human exposure to high-energy heavy ion (HZE) particles (ref. 3) as in deep space missions. Because no human data exist for cancer induction from the HZE particles, information on biological effectiveness is expected to be taken from experiments with animals and cultured cells (ref. 4). Experiments with cultured cells (refs. 5-7) indicate that the RBE of relativistic heavy ions is dependent on charge, energy, and level of fluence. Use of a single parameter, such as linear energy transfer (LET), to determine radiation quality therefore represents an oversimplification for risk assessment in the galactic cosmic ray environment.

The cellular track model of Katz et al. (refs. 8-10) has been successful for over 20 years in describing experiments with heavy ion exposures to mammalian cell cultures. Cellular damage at low fluence is described by the action cross section which is defined as the probability that a single ion will produce a specific biological end point. The cross section is calculated through the application of the response of cells to X-rays or y-rays as a function of dose to the radial dose from energetic electrons (5-rays) which are produced along the ion path and assumed to cause the damage. The cross section has been shown to depend on velocity and charge of the ions, but not on LET alone.

In their earlier work, Katz et al. (refs. 8 and 9) developed a theory of radiobiological response to energetic heavy ions and extracted a set of radiosensitivity parameters for human T-1 cells from Todd’s data (ref. 11), which were obtained with X-rays and ions of 6.5 MeV/amu up to argon. Subsequently, Blakely et al. (ref. 12) measured cell survival at several points along the beam paths of C, Ne, and Ar ions with initial energy approximately 400-500 MeV/amu as the ions came to rest in a water column. Katz proposed that the Blakely data could be calculated from track theory using the radiosensitivity parameters already determined provided that a beam model was available that properly described the particle-energy spectrum at all points along the beam line. With no other model available, an ad hoc beam model was generated by Roth and Katz (ref. 13) for this purpose. They compared their calculations with T-1 cell-survival data obtained at various locations (upstream and downstream of the Bragg peak) of water medium irradiated with heavy ion beams. Remarkable agreement was found except in the region behind the Bragg peak. They attributed the failure to the crudeness of the beam model. Curtis (ref. 14) used the 'HZESEC beam code to calculate the depth-dose curve for various heavy ions and obtained good agreement with the experimental data. He also characterized the radiation quality of the beam along the beam line in tissue by considering separate contributions from projectiles and fragments of different cell-kill modes in accordance with the Katz theory.

In this report, we reconsider the cell-survival data used in the previous analysis (ref. 13) by combining a realistic beam code LBLBEAM (ref. 15) developed at the Langley Research Center with the track theory of Katz. The uncertainties in many of the fragmentation cross sections still pose a problem in our analysis. Nevertheless, the problems encountered earlier (ref. 13) beyond the Bragg peak have largely been resolved.
Monoenergetic Beam Transport

In passing through a matter, heavy ions lose energy through interaction with atomic electrons along their trajectories. On occasion, they interact with nuclei of the matter and produce ion fragments moving in the forward direction and low-energy fragments of the struck target nucleus. The transport equations for the short-range target fragments can be solved separately in closed form (refs. 16 and 17). Hence, the transport of projectile fragments constitutes the main topic in the following discussion.

With the straight-ahead approximation, the transport equation may be written as (ref. 18)

$$\frac{\partial}{\partial x} - \frac{\partial}{\partial E} \tilde{S}_j(E) + \sigma_j \left[ \phi_j(x, E) = \sum_{k>j} m_{jk} \sigma_k \phi_k(x, E) \right]$$

(1)

where $\phi_j(x, E)$ is the flux of ions of charge $Z_j$ with atomic mass $A_j$ at $x$ moving along the $x$-axis at energy $E$ in units of MeV/amu, $\sigma_j$ is the corresponding macroscopic nuclear absorption cross section, the stopping power $\tilde{S}_j(E)$ is the change in $E$ per unit distance, and $m_{jk}$ is the fragmentation parameter for ion $j$ produced in collision by ion $k$. The range of the ion is given as

$$R_j(E) = \int_0^E \frac{dE'}{\tilde{S}_j(E')}$$

(2)

The stopping powers used herein are based on Ziegler's fits to a large data base (refs. 19 and 20) with some necessary modifications as described elsewhere (ref. 21). The solution to equation (1) is found to be subject to boundary specification at $x = 0$ and arbitrary $E$ as

$$\phi_j(0, E) = F_j(E)$$

(3)

where $F_j(E)$ is called the incident beam spectrum.

From Bethe's theory we have

$$\tilde{S}_j(E) = \frac{A_p Z_j^2}{A_j Z_p^2} \tilde{S}_p(E)$$

(4)

for which

$$\frac{Z_j^2}{A_j} R_j(E) = \frac{Z_p^2}{A_p} R_p(E)$$

(5)

where the subscript $p$ refers to proton. Equation (5) is quite accurate at high energy but only approximately true at low energy because of electron capture by the ion that effectively reduces its charge, higher order Born corrections to Bethe's theory, and nuclear stopping at the lowest energies. Herein, the parameter $\nu_j$ is defined as

$$\nu_j = \frac{Z_j^2}{A_j}$$

(6)

so that

$$\nu_j R_j(E) = \nu_k R_k(E)$$

(7)

where the energy variation in $\nu_j$ is neglected.

By making use of the range-energy relation (eq. (2)) and the parameters defined previously, equation (1) can be transformed into characteristic coordinates. The transformed equation is then solved by considering a Neumann series expansion through complicated mathematical manipulation (ref. 15). For a monoenergetic beam if no energy spread is assumed, the boundary condition is taken as

$$F_j(E) = \delta_{jM} \delta(E - E_0)$$

(8)
where $\delta_j$ is the Kronecker delta, $\delta(\cdot)$ is the Dirac delta function, and $E_o$ is the incident beam energy. The final results for zeroth, first-, and second-order collision terms are as follows:

$$\phi_j^0(x, E) = \frac{1}{S_j(E)} \exp(-\sigma_j x) \delta_j \delta(x + R_j(E) - R_M(E_o))$$  \hspace{1cm} (9)$$

$$\phi_j^1(x, E) = \frac{1}{S_j(E)} \nu_j \frac{M_j}{M} \exp \left\{-\frac{1}{2} \sigma_j [x - R_j(E) - \eta'] \right\}$$  \hspace{1cm} (10)

as long as

$$\frac{\nu_M}{\nu_j} [R_M(E_o) - x] < R_j(E) < \frac{\nu_M}{\nu_j} R_M(E_o) - x$$  \hspace{1cm} (11)

Otherwise, $\phi_j^1(x, E) = 0$.

$$\phi_j^2(x, E) = \sum_k \frac{x_{jk} \sigma_{jkl}}{S_j(E)} \exp \left\{-\sigma_M x_{Ml} - \sigma_k x_{kl} - \sigma_j x_{jl} \right\}$$  \hspace{1cm} (12)

where

$$\Delta_{jkl} = \sigma_j + \frac{(\nu_k - \nu_j)}{(\nu_M - \nu_k)} \sigma_M - \frac{(\nu_M - \nu_j)}{(\nu_M - \nu_k)} \sigma_k$$  \hspace{1cm} (13)

and $x_{Ml}$, $x_{kl}$, $x_{Ml}$, and $x_{kl}$ are the values of the following equations evaluated at the corresponding upper and lower limits of $x_j$:

$$x_{Ml} = \frac{\nu_M R_M(E_o) - \nu_k [R_k(E) + x] + (\nu_k - \nu_j)x_j}{\nu_M - \nu_k}$$  \hspace{1cm} (14)

$$x_{kl} = \frac{\nu_M [R_M(E) + x] - \nu_M R_M(E_o) - (\nu_M - \nu_j)x_j}{\nu_M - \nu_k}$$  \hspace{1cm} (15)

As has been shown in reference 15, total flux summing up to the secondary collision term is sufficiently accurate in most cases.

Similar results have been derived (ref. 15) for a more realistic situation where the energy spread in the incident beam is considered by modifying equation (8). In this report, however, we are assuming no energy spread in the beam for simplicity.

The variation in the secondary spectra with depth in a water column as predicted in reference 15 by LBLBEAM (eqs. (9)-(15)) is presented in figure 1 where the flux of all secondaries with charges from 3 to 10 ions is plotted versus energy for a 396-MeV/amu Ne beam at three positions in the Bragg curve. The secondary spectrum at 10 g/cm\(^2\) before reaching the Bragg peak is shown in figure 1(a). Ions close to the beam in charge are seen to dominate with a rather narrow energy spectra centered close to the beam energy. In figures 1(b) and 1(c) at 4 g/cm\(^2\) before and 2 g/cm\(^2\) beyond the Bragg peak, respectively, many ion types are seen to be important with broad energy distributions. Not shown are the charges of 1 and 2 ions that are found to make only a small contribution to biological effects in the present study. In reference 22, theoretical results using LBLBEAM are compared with experimental measurements for secondary spectra from a 670-MeV/amu beam.

**Cellular Track Model**

Biological damage from heavy ions is principally caused by $\delta$-ray production. In the Katz model (ref. 8), cellular damage proceeds through two modes of response. In the ion-kill mode, damage occurs through the
action of single ions, whereas in the gamma-kill mode, cells not inactivated in the ion-kill mode can be sublethally damaged from a passing ion and then inactivated by the cumulative addition of sublethal damage due to δ-rays from other passing ions. The response of the cell is described by four cellular response parameters, two of which (m, the number of targets that must be inactivated per cell, and $D_0$, the characteristic X-ray dose) are extracted from the response of the system to X-ray or γ-ray irradiation. The other two parameters ($\sigma_0$, interpreted as the cross-sectional area of the cell nucleus, within which the damage sites are located, and $\kappa$, a measure of the size of the damage site) are found from survival measurements with a set of track segment irradiations by energetic charged particles. The surviving fraction of a cellular population ($N_0$), after irradiation by a fluence of particles ($F$), is written as (ref. 8)

$$\frac{N}{N_0} = \pi_i \times \pi_\gamma \quad (16)$$

where the ion-kill survivability is

$$\pi_i = e^{-\sigma F} \quad (17)$$

and the gamma-kill survivability is

$$\pi_\gamma = 1 - \left(1 - e^{-D_\gamma/D_0}\right)^m \quad (18)$$

The gamma-kill dose fraction is defined by

$$D_\gamma = (1 - P)D \quad (19)$$

where $D$ is the absorbed dose and $P$ is the fraction of cells damaged in the ion-kill mode given by

$$P = \frac{\sigma}{\sigma_0} \quad (20)$$

where $\sigma$ is the single-particle inactivation cross section. The ion-kill cross section is found from

$$\sigma(E) = \sigma_0 \left(1 - e^{-Z^2/\kappa^2}\right)^m \quad (21)$$

where the effective charge number is $Z = Z(1 - e^{-125\beta/Z^{2/3}})$. For the mixed-radiation fields of projectile fragments produced in a water medium, the ion-kill term is written as (ref. 23)

$$\sigma F = \sum_j \int_0^\infty dE_j \phi_j(x, E_j) \sigma(E_j) \quad (22)$$

where $E_j$ is the energy of ion $j$ in MeV, the subscripts $j$ and $\alpha$ label the projectile fragment and target fragment, respectively, and $\phi$ is the fluence of particles of a particular type with energy $E$ at position $x$. Then, on the right-hand side of equation (22), the first term corresponds to the contributions from projectile and projectile-fragment particles, and the second term to the contributions from target fragments.

The gamma-kill dose fraction becomes

$$D_\gamma = \sum_j \int dE_j \phi_j(x, E_j) \left[1 - P_j(E_j)\right] S_j(E_j) \quad (23)$$

+ \sum_j \sum_\alpha \int dE_j \phi_\alpha(x, E_\alpha; E_j) \sigma_\alpha(E_\alpha) \times \left[1 - P_\alpha(E_\alpha)\right] S_\alpha(E_\alpha) \quad (23)$$
where $S_j$ is the stopping power of ion $j$. Equations (22) and (23) are used in equations (17) and (18), respectively. The summations over all particle types in equations (22) and (23) represent the addition of probabilities from all ions in the radiation field that contribute to the end point under study.

The RBE at a given survival level is given by

$$RBE = \frac{D_x}{D}$$

(24)

where

$$D_x = -D_o \ln \left[ 1 - \left( 1 - \frac{N}{N_o} \right)^{1/m} \right]$$

(25)

is the X-ray dose at which this level is obtained. At low doses in which intertrack effects are negligible, the RBE reduces to (ref. 24)

$$RBE = D_o \left( \frac{\sigma}{L ET} \right)^{1/m} D^{(1/m-1)}$$

(26)

**Results and Discussion**

Survival curves for aerobically and hypoxically irradiated human T-1 kidney cells have been calculated for several locations in a water column for carbon, neon, and argon beams which represent a wide range of LET. These curves are compared with the experimental data of Blakely et al. (ref. 12) for various doses, as shown in figures 2–4 where $x$ represents the distance from the Bragg peak with positive values indicating upstream locations and negative values indicating downstream locations. The cellular response parameters used in the calculation were obtained from experiments of Todd (ref. 11) as given in table 1 where the values enclosed in parentheses were suggested by Roth and Katz (ref. 13) for a higher degree of hypoxia achieved in Blakely’s experiment. Better agreement is obtained with the suggested new parameters. Also, the discrepancy is lessened when compared with the results obtained by Roth and Katz (ref. 13) for the locations beyond the Bragg peak. Some remaining slight discrepancy is justifiable if one considers the large uncertainties that exist in the knowledge of nuclear fragmentation parameters, the assumption of energy-independent cross sections, and the negligence of straggling and multiple scattering in the beam model. Trial calculations made with the addition of tertiary fragments or the inclusion of beam energy spread did not improve the situation.

The fragmentation cross sections used in the present beam model are from Silberberg, Tsao, and Shapiro (ref. 25) for the heavy ions and from Bertini (ref. 26) for the light ions. A previous study (ref. 27) showed that Silberberg, Tsao, and Shapiro underpredicted the heavier fragments. In calculating the depth-dose curve for an argon beam, some correction factors were used to compensate for the underprediction, and these correction factors are given in table 2. In figure 5, two separate depth-dose calculations with and without correction factors are compared with the experimental results. Better agreement is obtained with the correction factor included. (Note that the calculated Bragg peak is higher than the data because no energy spread was assumed.)

**Table 1.** Cellular Response Parameters$^a$ for Human T-1 Cells

<table>
<thead>
<tr>
<th>Cell-death type</th>
<th>$m$</th>
<th>$D_o$, cGy (b)</th>
<th>$\sigma_o$, cm$^2$</th>
<th>$\kappa$, (b)</th>
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</thead>
<tbody>
<tr>
<td>Aerobic</td>
<td>2.5</td>
<td>170</td>
<td>$6.7 \times 10^{-7}$</td>
<td>1000</td>
</tr>
<tr>
<td>Hypoxic</td>
<td>2.5</td>
<td>460</td>
<td>$6.7 \times 10^{-7}$</td>
<td>1300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(520)</td>
<td>(1450)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$These parameters were originally obtained by Katz et al. (ref. 8) from the data of Todd (ref. 11).

$^b$The values enclosed in parentheses were suggested by Roth and Katz (ref. 13).

The RBE as a function of survival level has also been calculated for aerobically and hypoxically irradiated T-1 cells in a water column exposed to a neon beam. These results are compared in figure 6 with the data of Blakely et al. (ref. 12) for three locations (the distances from the Bragg peak ($x$) of 16.1, 1.2, and 0.14 cm, with positive values indicating upstream locations). The agreement is excellent except for the hypoxic cell at 1.2 cm upstream of the Bragg peak where the data are uniformly lower than the
theory. The ion beam is seen to be more biologically damaging at locations closer to the Bragg peak. The steep rise in RBE near the zero-dose region for the location near the Bragg peak is due to the dominance of the ion-kill mode for the neon beam and the sigmoid behavior of the X-ray as described by equation (26). On the other hand, the sigmoid behavior of the survival curve for neon at the most upstream location counteracts that of the X-ray, and therefore it results in a flatter slope of RBE near the zero-dose region. This sigmoid shape is due to the effect of overlapping δ-rays which is dominant over the ion-kill mode.

Table 2. Correction Factors to Nuclear Fragmentation Model of Reference 25

<table>
<thead>
<tr>
<th>ΔA (a)</th>
<th>Correction factor</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1.3</td>
</tr>
<tr>
<td>1</td>
<td>1.2</td>
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<td>3</td>
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<tr>
<td>4</td>
<td>1.1</td>
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<td>5</td>
<td></td>
</tr>
</tbody>
</table>

*ΔA denotes the number of nucleons removed.

Concluding Remarks

Using a realistic transport model, we can successfully predict cell-survival levels for several locations along the heavy ion beam line within a water column. Theoretical relative biological effectiveness (RBE) curves as a function of survival level are also in excellent agreement with the data. Further improvement in the depth-dose curve calculation can be made when fragmentation parameters that are more accurate become available. The breadth of the Bragg peak can be predicted if we consider the energy spread of the primary beam and the effect of straggling. The results support the claim of track theory that knowledge of radiosensitivity parameters for cell survival coupled with knowledge of the particle-energy spectrum of a complex radiation field make it possible to predict cell survival and RBE in that field. We have done so here over a wide range of linear energy transfer (LET) for various doses.

References


Figure 1. Energy spectra with charges \((Z)\) from 3 to 10 ions produced by 396-MeV/amu neon beam at three positions in water column. Results are derived from LBLBEAM (ref. 15).
Figure 2. Survival level as a function of dose for aerobically and hypoxically irradiated human T-1 cells in water column exposed to 381-MeV/amu carbon beam. $x$ denotes distance from Bragg peak, with positive values indicating upstream locations.
Figure 3. Survival level as a function of dose for aerobically and hypoxically irradiated human T-1 cells in water column exposed to 396-MeV/amu neon beam. $x$ denotes distance from Bragg peak, with positive values indicating upstream locations.
Figure 4. Survival level as a function of dose for aerobically and hypoxically irradiated human T-1 cells in water column exposed to 514-MeV/amu argon beam. $x$ denotes distance from Bragg peak, with positive values indicating upstream locations.
Figure 5. Relative ionization ratio as a function of depth in water column exposed to 514-MeV/amu argon beam. We show contributions from primaries, from sums of primaries, from secondaries and tertiaries without use of correction factors of table 2, and the total ionization using these correction factors.

Figure 6. Relative biological effectiveness as a function of survival level for aerobically and hypoxically irradiated human T-1 cells in water column exposed to 396-MeV/amu neon beam.
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### Abstract
Track theory is combined with a realistic model of a heavy ion beam to study the effects of nuclear fragmentation on cell survival and biological effectiveness. The effects of secondary reaction products are studied as a function of depth in a water column. Good agreement is found with experimental results for the survival of human T-1 cells exposed to monoenergetic carbon, neon, and argon beams under aerobic and hypoxic conditions. The present calculation, which includes the effect of target fragmentation, is a significant improvement over an earlier calculation because of the use of a vastly improved beam model with no change in the track theory or cellular response parameters.