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- THE MODEL AND ITS APPROXIMATION -

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Computation of cell survival in heavy ion beams for therapy
- The model and its approximation -

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Abstract A simplified method for the calculation of mammalian cell survival after charged particle irradiation is presented that is based on the track structure model of Scholz and Kraft 1994 [1]and 1996 [2]. Utilizing a modified linear-quadratic relation for the x-ray survival curve, one finds that the model yields linear-quadratic relations also for heavy ion irradiations. If survival is calculated as a function of specific energy, z, in the cell nucleus - reducing, thus, the stochastic fluctuations of energy deposition - the increase of slope of the survival curve and thus the coefficient β_z can be estimated with sufficient accuracy from the initial slope, α_z. This permits the tabulation of the coefficients α_z for the particle types and energies of interest, and subsequent fast calculations of survival levels at any point in a mixed particle beam. The complexity of the calculations can thereby be reduced in a wide range of applications, which permits the rapid calculations that are required for treatment planning in heavy ion therapy. The validity of the modified computations is assessed by the comparison with explicit calculations in terms of the original model and with experimental results for track-segment conditions. The model is then used to analyze the influence of beam fragmentation on the biological effect of charged particle beams penetrating to different depths in tissue. In addition, cell-survival rates after neutron irradiation are computed from the slowing-down spectra of secondary charged particles, and are compared to experimental observations.

Introduction

Models that correlate the radial energy distribution of charged particle tracks with their biological effectiveness have been variously employed to fit charged particle inactivation cross sections over the entire LET range from 2-15000 *keV/μm* [3 - 5]. While the earlier models invoke separate formulations for the *intra-track* and the *inter-track* component of the radiation action, we have recently shown [1, 2] that survival curves after heavy ion irradiation can be deduced from x-ray survival curves through a formulation in terms of the radial dose distributions that does not require such separation. This recent, unified model does not invoke added parameters to account for radiation quality and is thus well suited to infer the effectiveness of complex radiation beams from radiobiological data obtained with x-rays.

The approach has been verified against a large set of experimental data for monoenergetic track segments with fixed LET, in which case the computations are comparatively simple. In charged particle tumor therapy, on the other hand, complex particle fields with very high energies and different atomic numbers need to be considered, and the computations - while straightforward, in principle - can then be too lengthy for fast optimization algorithms in treatment planning. A simplified approach will, therefore, be presented, that preserves, without the need for complicated computations, the basic features of the model and its agreement with radiobiological data.

Application of the model

Basic considerations

The subsequent calculations are based on the model developed by Scholz and Kraft [1, 2] which predicts heavy ion inactivation probabilities from three pieces of information:

- *The dose dependence of cell inactivation for x-rays*, expressed as logarithm, *ln(S)*, of cell survival, *S*. The survival curve is assumed to be shouldered with a purely exponential tail for doses greater than a threshold dose, D_t. In the region of the shoulder, the survival curve is described by the parameters α and β of the linear-quadratic model. Thus, the the survival curve is given by the equation:

$$-\ln(S) = \begin{cases} \alpha_x D + \beta_x D^2 & \text{for } D<D_t \\ \alpha_x D_t + \beta_x D_t^2 + s_{max}(D-D_t) & \text{for } D>=D_t \end{cases} \qquad (1)$$

$s_{max} = \alpha_x + 2\beta_x D_t$ being the maximum slope.

This formulation has been chosen as a convenient parametrisation of the x-ray survival curves which is well in accord with experimental data. It does not imply, that the model is principally restricted to a specific form of the survival curve or to the specific assumptions, on which the linear-quadratic model is based.

• *The radial distribution of dose* - we will here use the term *local dose, d,* - inside the charged particle track. The maximum radius, r_{max}, of the track is determined by the range of the most energetic δ-electrons. It increases with the projectile energy. A form of the radial dose distribution is invoked that corresponds - in line with the presumed diffusion of primary radiation products - to a certain displacement of the energy in the track center to the outer regions. Up to the radius 0.01 μm the local dose is taken to be constant, beyond this radius - and up to the maximum distance - it is assumed to decrease proportional to $1/r^2$; the dependence is normalized to the total collision stopping power.

• *The size of the critical target, i.e. the cell nucleus.* Disregarding changes of size and shape throughout the cell cycle, a constant, average nuclear volume is assumed as an approximation that disregards changes during the cell cycle. The nucleus is taken to be a cylinder of 5 μm radius. All particle trajectories are chosen parallel to the cylinder axis.

Let *d* denote the *local dose* at a given point in the nucleus; it is defined as the sum of the contributions of all ion tracks according to their radial dose distribution. *d* is a random variable; its distribution within the nucleus depends on the spatial pattern of particle traversals. The stochastic spatial configuration of particle traversals is simulated by Monte Carlo computations. For a given configuration of particles in a cell, the logarithm, *ln(S),* of the survival probability of this cell is obtained by an integration of the quantity $ln(S_x(d))$ which corresponds to the x-ray survival curve over the volume, *V,* of the nucleus [2]:

$$ln(S) = {}_V\!\int ln(S_x(d))\, dV / V \qquad (2)$$

Since it depends on the random variable *d*, i.e. on the stochastic distribution of particle traversals, *S* is itself a random variable. The survival probability, *S(D),* at a given dose *D* is, thus, derived as the average value of *S* from the simulation of a large number of irradiated cells.

The notion of *local dose, d,* raises conceptual questions that are here not treated. In the present context it suffices, to state that *d* is a *conditional absorbed dose*, i.e. an *absorbed dose* according to its usual definition, provided the location and energy of the heavy particle tracks - but not those of their δ-rays - are specified. The integration in Eq(2) is not trivial, since the spatial distribution of *d* is highly irregular on a submicroscopic level. However, one can utilize efficient sampling procedures as they have been developed earlier for the purpose of microdosimetric computations [6].

The model by Scholz and Kraft and the one that has been much earlier developed by Katz and coworkers [3, 4] have the common feature to relate the biological effectiveness of charged particle radiations to the *radial dose distribution*. However, there are substantial differences in the formalism that links this characteristic to cell survival. Different from our approach, the model of Katz refers to the average of the *local dose* in extended targets; furthermore, it invokes - as stated above - two different cell inactivation modes that dominate at low and high energy density.

Computational procedure

The numerical derivation of a survival curve for monoenergetic ions is comparatively simple. With the assumption of a cylindrical cell nucleus traversed by a uniform particle beam, parallel to its axis, the calculations reduce to a two-dimensional problem in a plane perpendicular to the axis. Nevertheless, the numerical evaluation becomes increasingly cumbersome in the case of highly energetic particles, because then, due to the large track diameters, very many particles contribute to the local dose at a given point. With a mixed particle spectrum it is thus difficult to achieve the rapidity of computations that is required in optimization algorithms for treatment planning in heavy ion therapy.

In the subsequent sections the exact computations will be considered first. Based on the results of these exact computations, an approximation is introduced that is suitable for quick exploratory computations relating to different tissues, i.e. to different parameters α_x ,β_x, and D_t.

Explicit computations

The initial slope:

For heavy ions of a specified type and energy, random traversals are considered through the reference region, i.e. the cylinder that represents the cell nucleus. The term *traversal* refers to all those particle passages that produce energy deposition in the nucleus, including those indirect events where a part of the track, but not the particle itself, intersects the reference region. For high energy particles the majority of traversals will be indirect.

The biological effect, $v_r = ln(S)$, produced by a single traversal with specified 'impact parameter', r, is computed according to Eq(2):

$$v_r = -\int_V ln(S_x(d))\, dV / V \qquad (3)$$

The survival probability of a cell traversed with this impact parameter is then $S_r = exp(-V_r)$. The expected survival for one random traversal is the weighted integral for all relevant impact parameters:

$$S_{T,E} = \int r\, S_r\, dr / (r_{max}^2 / 2) \qquad (4)$$

Let $N_{T,E}$ be the mean number of traversals per unit dose. In the limit of small doses, D, it is sufficient to consider the probabilities of no traversal and one traversal, which yields the survival relation:

$$S(D) = (1 - N_{T,E} D) + S_{T,E}\, N_{T,E} D \qquad (5)$$

The initial slope of the survival curve for a track segment exposure with this type of particle is, therefore:

$$\alpha_{T,E} = (1 - S_{T,E}) N_{T,E} \qquad (6)$$

For a mixed radiation at low dose levels, where *inter-track* effects can be neglected, the initial slope is obtained as a dose weighted integral over this parameter:

$$\alpha = \sum_T \int \alpha_{T,E} \cdot D_{T,E}\, dE \;/\; \sum_T \int D_{T,E}\, dE \qquad (7)$$

$D_{T,E}$ is the distribution of absorbed dose in particle type and differential in particle energy. $D_{T,E}$ is equal to the product of the fluence distribution, $\phi_{T,E}$, and the linear energy transfer, *LET(T,E)*.

Eq(7) has the convenient feature, that the values $\alpha_{T,E}$ can - according to Eqs(3), (4), and (6) - be precalculated, and tabulated for all relevant particle types, T, and energies, E. The parameter α in a mixed heavy ion beam is then rapidly obtained in terms of Eq(7) from the dose distribution, $D_{T,E}$, at this point. The solid lines in Fig.**1** give the parameters α that result for protons and carbon ions. The x-ray parameters are listed in the legend; the same parameters will be utilized in the subsequent numerical examples. The dotted lines are the result of the approximation to be discussed subsequently.

The increase of the slope with dose

To determine survival at higher doses, one needs to assess the increase of the slope with increasing dose. The explicit model permits this assessment, in terms of numerical simulations that generate configurations of Poisson distributed random traversals, and then evaluate Eq(2) in terms of a procedure that selects sampling points in such a way that their spatial density is proportional to the *local dose*, d. The details of this method sampling [6] are here not discussed.

It is not *a priori* apparent whether the explicit model calculations should provide survival curves that follow a linear-quadratic dependence for the dose range of relevance. However, the numerical results given in Fig. **2** for different ions and different energies show that this is, indeed, the case. The diagrams represent, as a function of dose, the logarithm of the survival probability divided by the dose, which has the advantage that the linear-quadratic dependence is readily recognizable as a linear relation which has the slope β, and intersects the ordinate at the value α:

$$-\ln(S)/D = \alpha + \beta \cdot D \qquad (8)$$

Although there are deviations from the linear-quadratic dependence at higher doses, which are here not shown, these deviations are not of interest in clinical applications where individual dose fractions are always considerably less than 10 Gy. Fig.**3** gives the values of β for protons and carbon ions in dependence on their energy.

Approximate calculations

The initial slope

Most of the energy of a heavy ion - and all of the energy that is associated with substantial local doses - is transferred in close proximity to the particle trajectory. It is, therefore, plausible that the integral in Eq(3) depends only weakly on the impact parameter, r, as long as r is smaller than the radius of the cell nucleus. This is, indeed, brought out in the calculations: if the calculations are performed merely for central traversals, i.e. zero impact parameter, values of α (dotted lines in Fig.**1**) are obtained that differ little from those obtained by exact calculations. The approximation employs, therefore, this simplified computation. For a mixed particle beam the over-all value α is readily obtained in terms of Eq(7).

The dependence at higher doses

While the derivation of the initial slope, α, is straightforward, the determination of β is somewhat more complex. It will here be described in terms of a rapid simulation method that has proved effective in a wide range of exploratory calculations. The accuracy to be achieved with this method and the comparison to even faster procedures for dose planning that do not require Monte Carlo calculations will be the subject of a separate treatment.

As seen from Figs.**1** and **3**, there is no unique relation between β and the parameter α. A clearer correlation between β and α results, if one disregards part of the randomness inherent in absorbed dose, D, and considers the relation of $ln(S)$ not to dose, but to the number of particles traversing the cell nucleus. To facilitate the comparison to the dose dependence, the microdosimetric variable specific energy, z, (see [8]) in the cell nucleus is used, rather than the number of particle traversals. The contributions, Δz, of all traversals to z are approximated in terms of total LET. Explicit computations show that linear-quadratic dependences result for $ln(S(z))$ over the relevant range of z:

$$ln(S) = \alpha_z z + \beta_z z^2 \qquad (9)$$

For a particle of specified type and energy one has:

$$\alpha_z = \nu_r / \Delta z \qquad (10)$$

Figure **4** gives, in the top panels, the relation between the slope $\alpha_z + 2\beta_z z$ of survival curves obtained by explicit calculations for protons and carbon ions. The diagrams suggest a fairly simple approximation with all curves reaching the maximum slope at approximately the same specific energy
$z_t = D_t$:

$$\beta_z = (s_{max} - \alpha_z) / 2 D_t \qquad (11)$$

which amounts to a linear increase of the slope of the relation $ln(S(z))$ versus z.

α_z and β_z are thus computed very rapidly for any particle type and energy and any set of x-ray parameters α_x, β_x and D_t. For a mixed field of particles a fast simulation procedure is then utilized. For a specified dose and particle spectrum random traversals are simulated according to Poisson statistics, and with every traversal $-ln(S)$ is incremented by the term $(\alpha_z + 2\beta_z)\,\Delta z$, where Δz is the increment of specific energy due to the traversal, Δz being approximated in terms of LET. For a simulated particle number, i.e. a random simulation of energy deposited in the nucleus, at the specified dose, a survival probability S results. The procedure is repeated, to obtain the mean, $S(D)$, of the various values S that are obtained in the simulation.

Figure **5** gives in terms of the exact computations and the approximation survival relations for protons and carbon ions.The agreement of the simplified approach with the explicit model is, of course, no proof of its radiobiological validity. But the broad range of validity of the model - established in terms of experimental data from track segment experiments with very widely varying LET-values - suggests its applicability also to mixed particle beams. In subsequent sections the computations will be compared to cell-survival data obtained at different penetration depths of ion beams and after neutron irradiations.

The above considerations and computational results permit a greatly simplified computational procedure: With the modified linear-quadratic survival relation for x-rays the explicit model yields linear-quadratic dependences for charged particle beams. The simplification is due to the fact that for a mixed radiation the parameters α_z need to be computed and tabulated only once for monoenergetic ions. The values can then be utilized to derive the corresponding parameters for any mixed ion beams of interest with significantly reduced computational effort compared to the explicit calculations.

Comparison to experimental data

Charged particle spectra

For heavy charged particle beams, fragment spectra as a function of atomic number and energy were obtained by a computer code simulating the penetration of charged particles through water. The code was developed by Th. Haberer [9]. The parameters were adjusted so that the calculations reproduce the experimental results obtained at GSI [10] and other laboratories [11]. The secondary particle spectra produced by neutron irradiation were taken from the literature [12, 13]

Charged particle exposures

Results from track segment experiments with monoenergetic carbon and oxygen beams are compared in Fig. **6** with computations according to the approach that has here been outlined. There is satisfactory agreement between the model calculations and the experimental data.

In a next step the same type of calculations are applied to exposures with an ion beam for therapy that - due to fragmentation processes - contains a mixture of charged particles. A comparison between the dependence on penetration depth of absorbed dose and of the

biological effect of a 195 MeV/u carbon beam is shown in Fig. 7. With regard to fragmentation the characteristic mean free path of the carbon beam is approximatly 200mm in tissue, so that the fraction of primary particles is reduced to 75 % and 55 % of the incoming particle fluence for a penetration depth of 60mm and 120mm, respectively. Survival fractions were determined for CHO Chinese hamster cells, which were grown as monolayers in culture flasks. The penetration of tissue was simulated by a water layer of variable thickness.

Within the first few centimeters of penetration depth, survival remains nearly constant, followed by a sharp decrease of survival in the region of the Bragg peak. These features are reproduced quantitatively by the model. This is demonstrated more clearly in Fig. **8**, where complete survival curves are compared with the calculations for different penetration depths. Up to approximatly 6cm; the increase of LET and the correspondingly increased biological efficiency of the primary particles is compensated by their decreasing number due to fragmentation. The lighter fragments have reduced LET and a greater range than the primary particles, they cause most of their biological effect beyond the Bragg peak of the primary beam. The calculations reproduce the experimental data well. They can, therefore, be taken to represent equally well the relative effect of the primary particles and of the secondary fragments at different penetration depth; this is shown in Fig.**9**. The dashed lines indicate the reduction in survival that is solely due to the primary particles, whereas the full lines indicate the total biological effect, including that of the fragments. It is concluded, that the fragments contribute only about 10-20 % to the biological effect. Thus, the biological effect is predominantly determined by the number of primary particles. The reduction of the primary particles is - in the case of a 270 MeV/u carbon beam - only slightly compensated compensated by the effect of the fragments.

Neutron exposures

To test their range of applicability, the calculations have been applied also to cell inactivation studies with neutrons. These calculations were based on the equilibrium slowing-down spectra for secondary charged recoil particles. Fig.**10** compares the calculations with experimental data for neutron irradiations obtained by Eguchi-Kasai et al. [14]. Three cell lines were irradiated with neutrons from the d-Be reaction with 30 MeV deuterons . As the average neutron energy in this reaction is approximately half of the deuteron energy, the computations are based on the secondary charged particle spectra for 14 MeV neutrons, as given by Caswell and Coyne [12]. The parameters for the x-ray survival curves of different cell lines are obtained from experimental data which were concurrently determined in the experiments of Eguchi-Kasai. Although the three cell lines exhibit considerable differences in their sensitivity to x-rays, there is good agreement between the calculations and the experimental results.

Discussion and conclusions

A modification of a recently developed track structure model for mammalian cell survival after charged particle irradiation has here been introduced, and its agreement with radiobiological data has been assessed. The objective of the modification has been, to facilitate computations of the biological efficiency of mixed charged particle fields, so that sufficient calculational rapidity can be achieved for dose planning purposes in heavy ion therapy.

The simplified approach makes use of the fact that - in agreement with a broad range of radiobiological data from cell inactivation studies - the explicit model calculations provide linear-quadratic dose relations for charged particle beams, when the survival curve for x-rays follows the linear-quadratic dependence. The dose coefficients α and β of the linear and the quadratic terms in dose can be determined through explicit calculations, and they can be checked against experimental cell-inactivation data. The approximations presented here are based on tabulated values of the coefficients α_z, which have to be calculated only once for all energies and particle types involved. The calculation of the coefficients α_z is very fast, because only single particle effects need to be considered, and *inter-track* effects can be disregarded. Comparison with the explicit calculations reveal, that β_z can be estimated with sufficient accuracy from the difference between the initial slope, α_z, and the final slope, s_{max}. The practical value of the result is the facility of computations for mixed radiations that is achieved, once the parameters α_z have been precalculated for the component radiations.

A comparison with track-segment experiments and with ion beams that include the fragments of primary projectiles has shown that the calculations predict survival in complex charged particle fields with good accuracy. There is also good agreement between the computated the depth dependence in water of the efficiency of a carbon beam of initial energy 260MeV/u and the observed dependence of cell inactivation - or of entire survival curves - with this beam. The calculations for the carbon beam show, that the primary projectiles dominate the biological effect, and that secondary fragments contribute to the effect only at the 10-20 % level. Further calculations were performed for the charged recoil spectra of energetic neutrons; they, too, demonstrate good agreement of the computational procedure with the experimental cell inactivation data. In line with the predominance of protons in the slowing-down spectra, the high RBE of the neutrons is found to be mainly attributable to the low energy protons. That the heavier particles play only a minor role, is consistent with the observation of very high RBE of low energy protons in track segment experiments [15, 16].

A clinical program of heavy ion tumor therapy is in preparation at the Gesellschaft für Schwerionenforschung (GSI) in Darmstadt. The exposures will utilize a raster scan dose delivery system that provides complex superpositions of carbon beams with different energies, in order to obtain a uniform biological effect in the tumor and to minimize the dose outside the target region. Different from the situation in conventional radiation therapy, the treatment planning needs to refer to biologically weighted dose, rather than unmodified absorbed dose. The weighting factor depends on the spectrum of particle types and energies and must be computed for each volume element of interest, therefore it is essential that it can be computed rapidly. The model that has here been presented permits such rapid computations and ensures good agreement with experimental cell-inactivation data. It is an essential feature that the computations are based on the parameters α_x and β_x which describe the x-ray sensitivity of specific tissues, and they account thereby equally for the sensitivity of the specific tissues to other radiation qualities. Effects on the tumor and on different normal tissues can thus be described with the same type of calculations [17], which makes the approach a flexible tool for treatment planning in heavy ion therapy.

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Figure legends

Figure 1
Initial slope, α, of survival curves for protons and carbon ions as a function of the particle energy. The solid lines represent the exact calculation according to Eq(2), the dashed lines the approximation, where the effect is calculated only for central traversals through the nucleus (see section *'Approximate calculations'*). x-ray parameters for CHO-cells: a_x=0.18, b_x=0.028 and D_t =30Gy; diameter of the nucleus: 10 mm, are employed here and in the subsequent computations.

Figure 2
Computed survival curves in a representation of *ln(S)/D* vs. *D*, as proposed by Douglas and Fowler [7]. Straight lines correspond to survival curves that are linear-quadratic in the usual semi-logarithmic representation.

Figure 3
Parameters *b* of the survival curves for protons and carbon ions from explicit model caculations as a function of the particle energy.

Figure 4
Slope of survival curves as a function of the microdosimetric variable specific energy, *z*, in the nucleus for protons (top) and carbon ions (bottom). The left panels represent the results of the exact calculation according to Eq.(2), but with the increments of specific energy approximated in terms of LET. The right panels show the values chosen as approximation.

Figure 5
Survival curves according to the exact calculation and the approximation. The numbers that are inserted give the particle energies in MeV/u.

Figure 6
Comparison of measured survival curves (symbols) and model calculations (lines) for carbon beams (upper panel) and oxygen beams (lower panel). The experiments were performed with CHO cells grown as monolayers in culture flasks under track segment conditions at different beam energies (Kraft-Weyrather et al., unpublished)

Figure 7
Comparison of the depth dependence of absorbed dose, D, and the biological effect of a 195 MeV/u carbon beam represented in terms of the logarithm, *ln(S)*, of cell survival.
CHO cells were irradiated in monolayers at different depths in a water phantom to simulate penetration of the beam through tissue. An entrance particle fluence of $2 \cdot 10^7/cm^2$ was used, which corresponds to an entrance dose of 0.52 Gy.

Figure 8
Comparison of survival curves obtained behind a water column with variable thickness to simulate different penetration depths. The energy of the primary beam was 270 MeV/u. The survival is plotted vs. entrance particle fluence.

Figure 9
Cell survival computed for the primary particles alone (dashed lines) and for the primaries and their fragments (full lines) for different penetration depths in water. All particles fluences refer to zero penetration depth.

Figure 10
Comparison of the computations for neutron irradiation with experimental results obtained by Eguchi-Kasai et al. (1996) (30 MeV d→Be). The calculations are approximated in terms of a neutron energy of 14 MeV. The x-ray survival curves that are used as input for the calculation are given as dotted lines (cell lines: AT and MRC (human origin); irs1SF (Chinese hamster)).

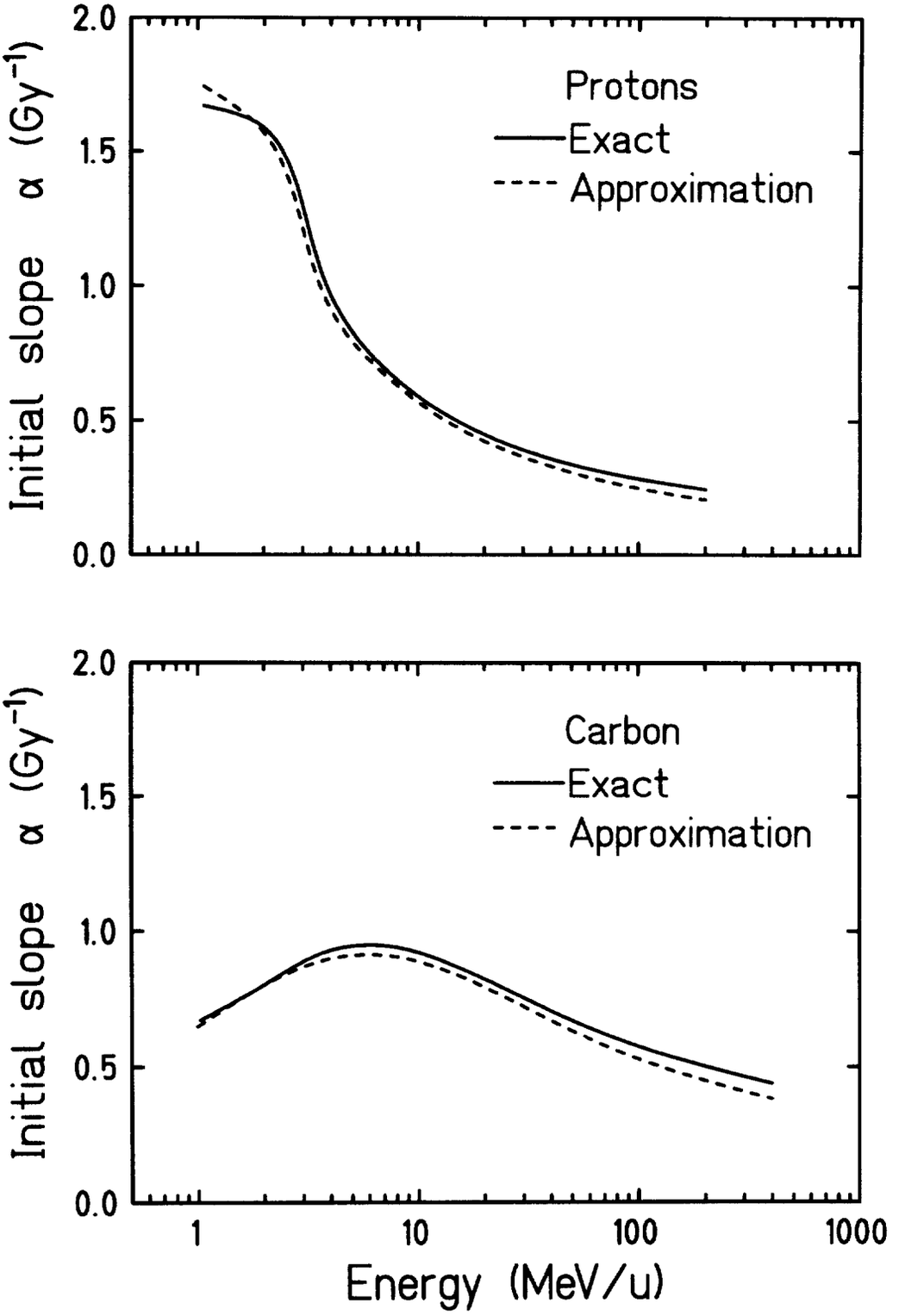

Figure 1

Scholz et al., Calculation of mammalian cell survival in complex charged particle fields

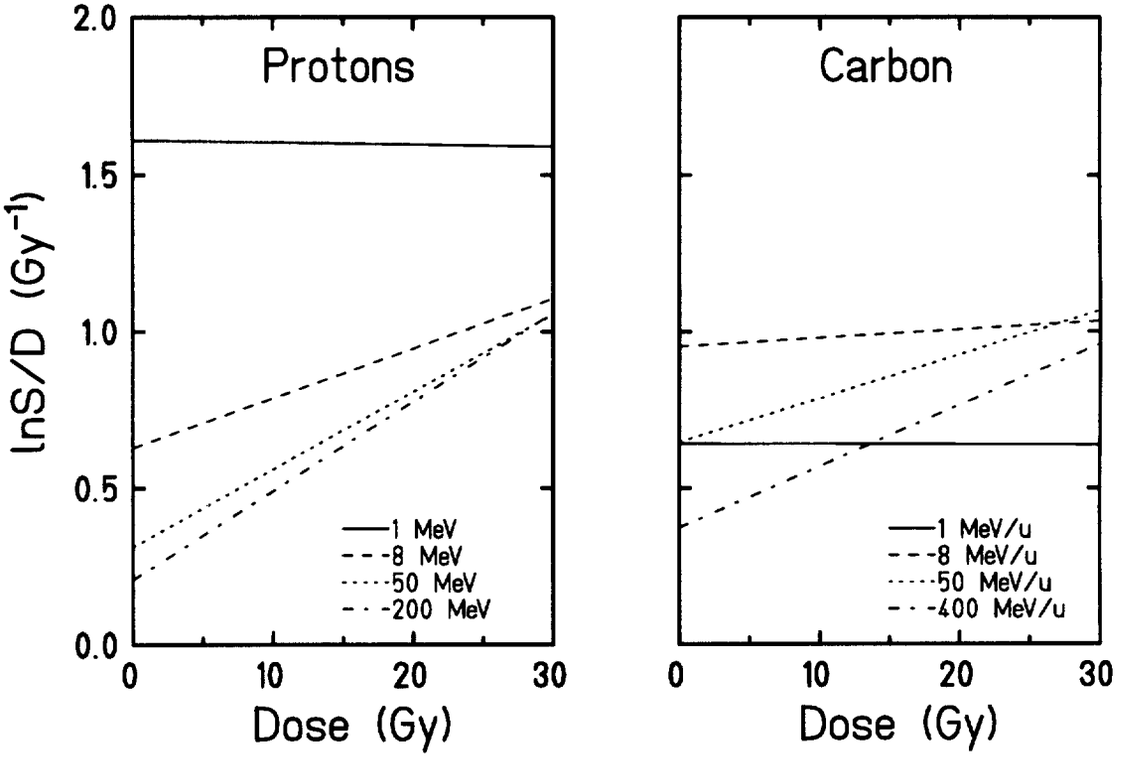

Figure 2

Scholz et al., Calculation of mammalian cell survival in complex charged particle fields

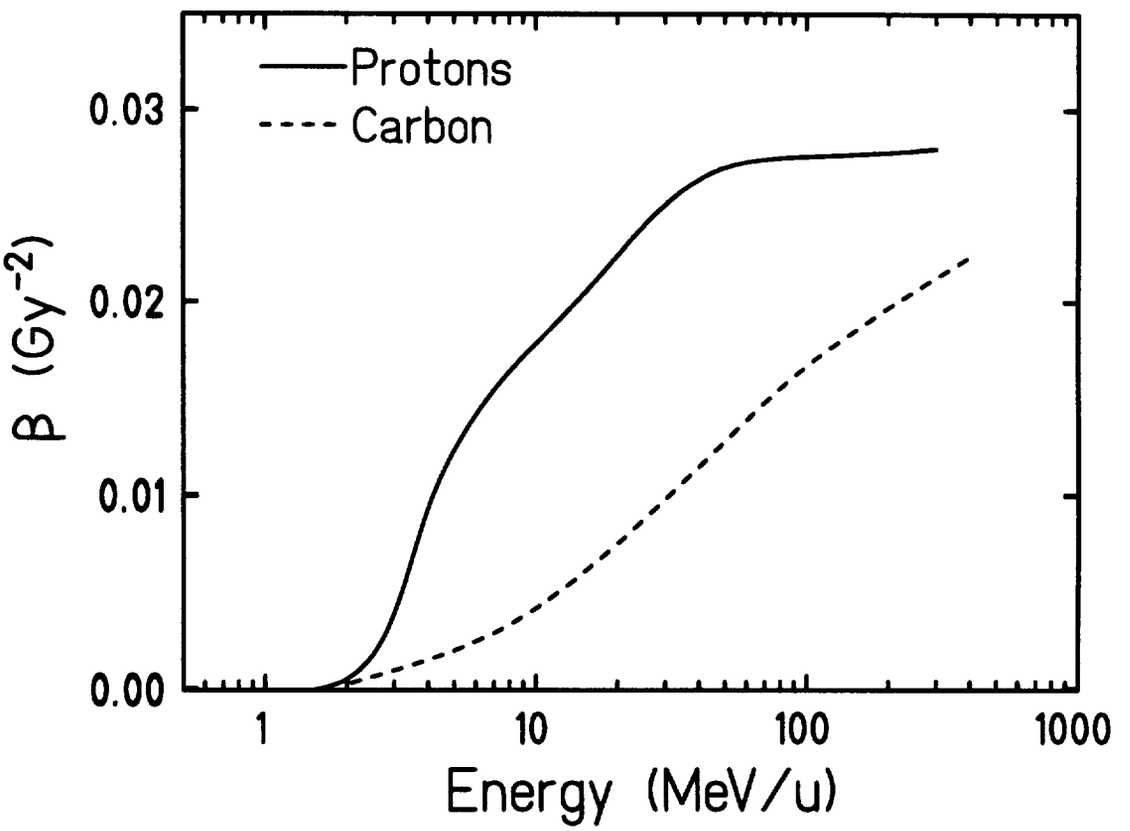

Figure 3

Scholz et al., Calculation of mammalian cell survival in complex charged particle fields

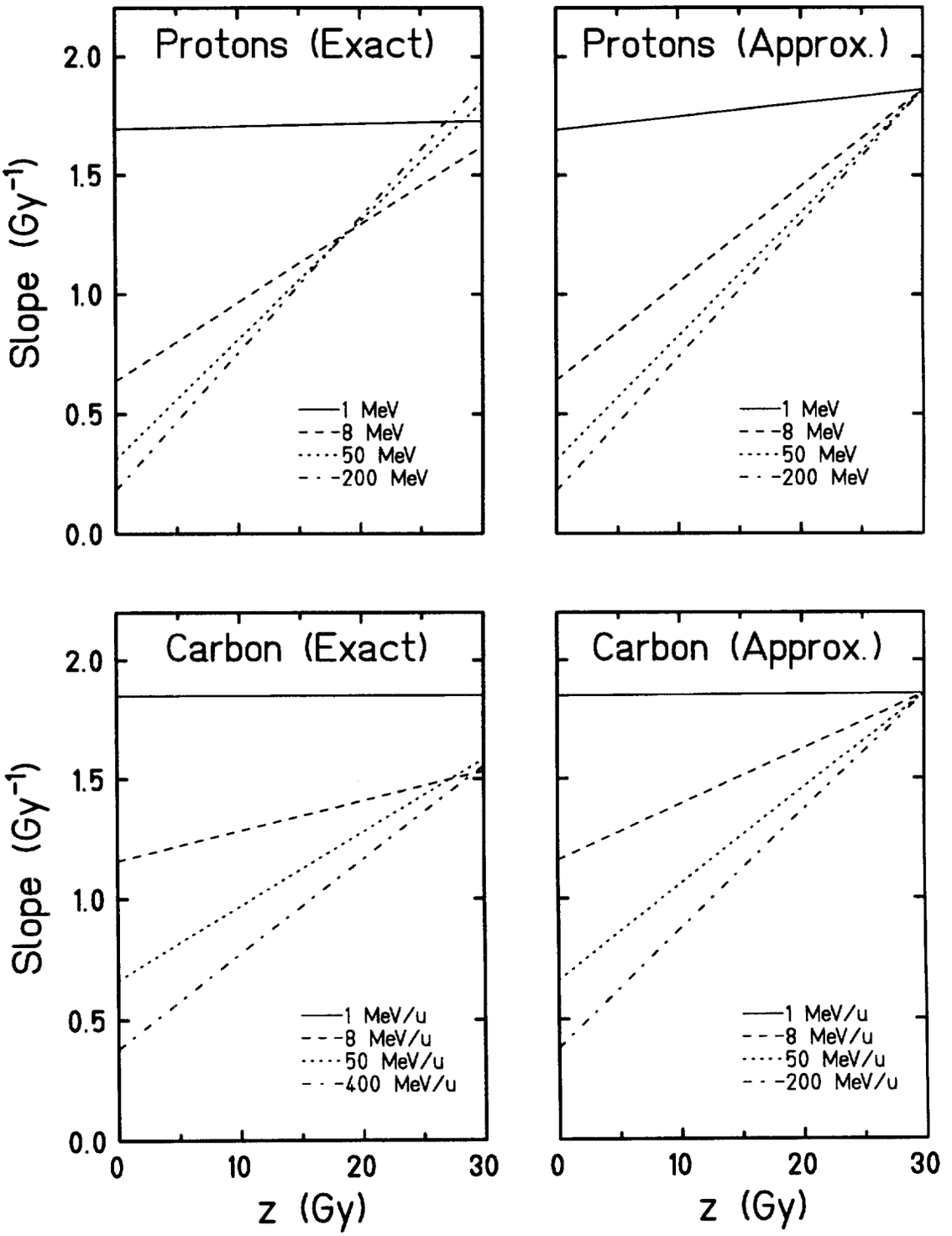

Figure 4

Scholz et al., Calculation of mammalian cell survival in complex charged particle fields

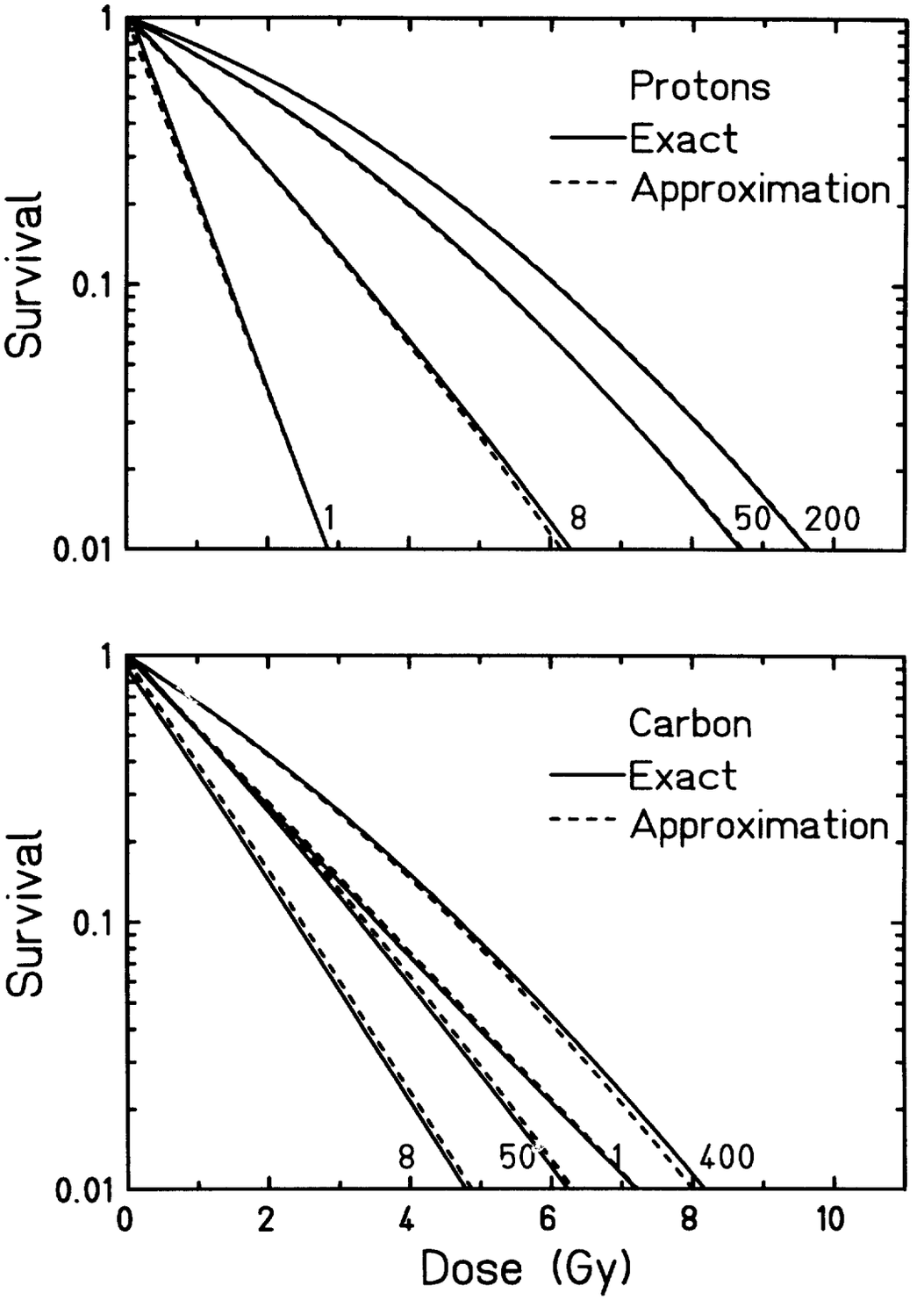

Figure 5

Scholz et al., Calculation of mammalian cell survival in complex charged particle fields

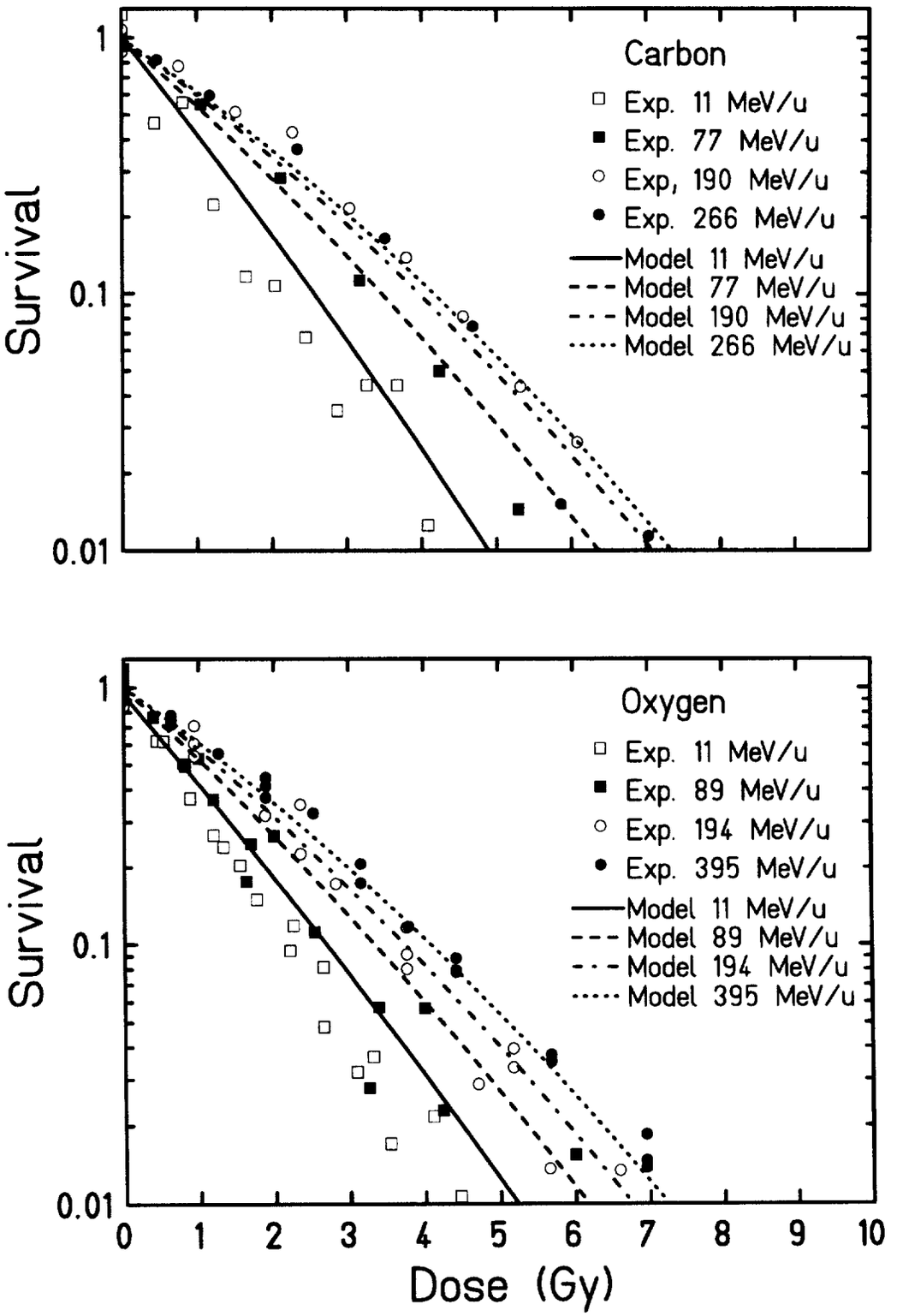

Figure 6

Scholz et al., Calculation of mammalian cell survival in complex charged particle fields

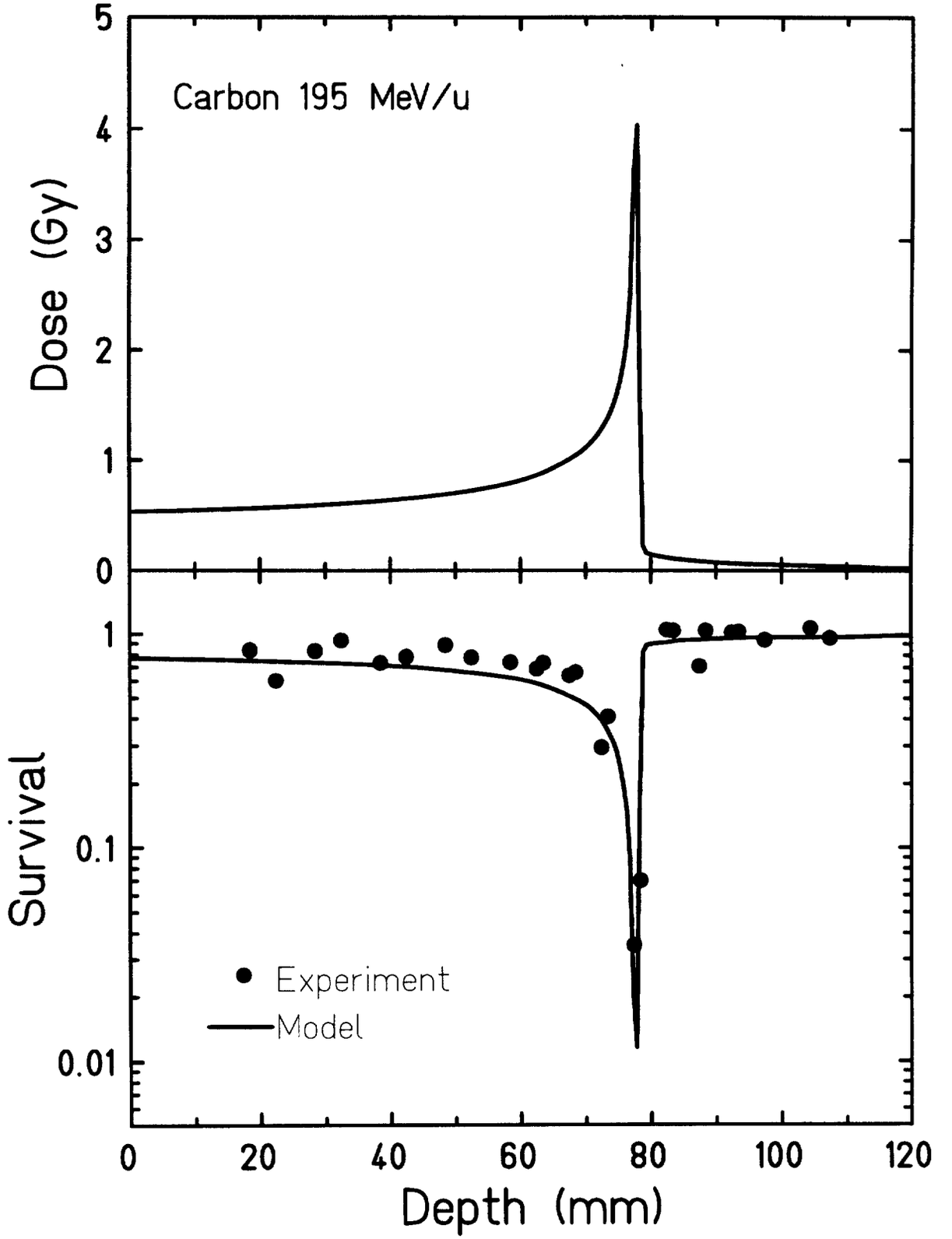
Carbon 195 MeV/u
Dose (Gy)
5
4
3
2
1
0
Survival
1
0.1
0.01
Experiment
Model
0
20
40
60
80
100
120
Depth (mm)

Figure 7

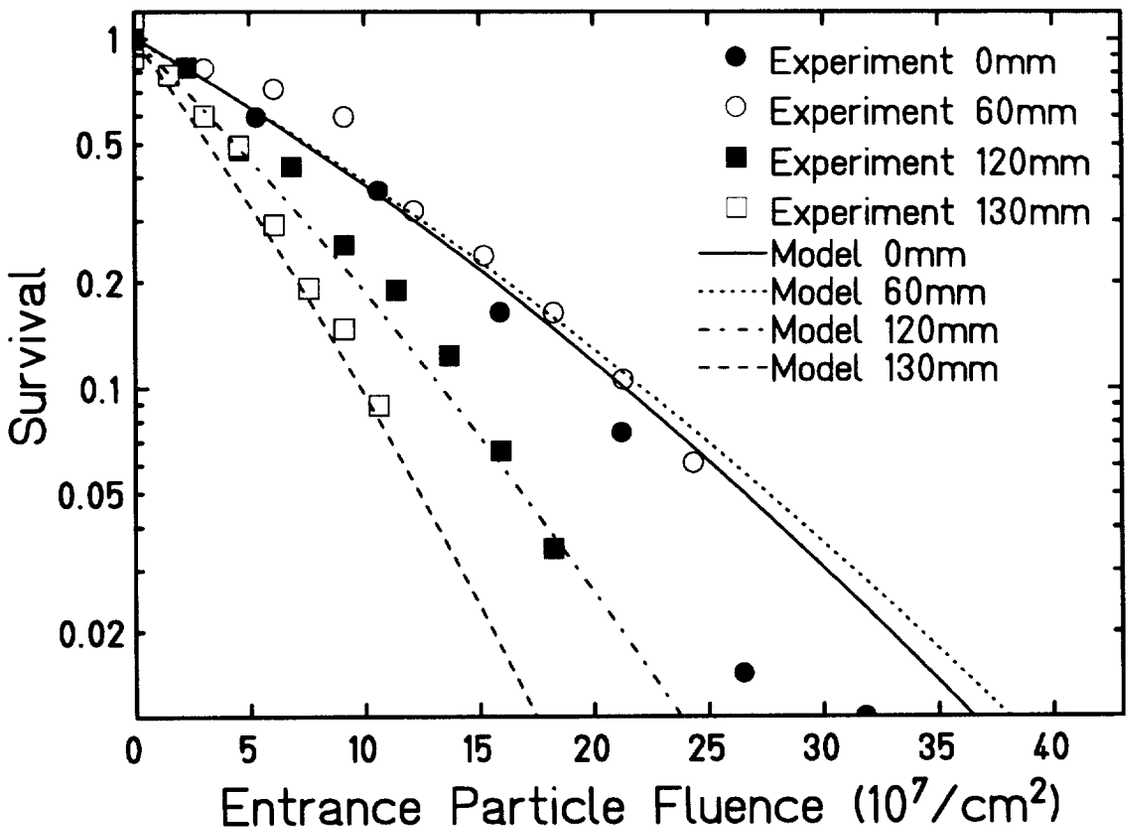

Figure 8

Scholz et al., Calculation of mammalian cell survival in complex charged particle fields

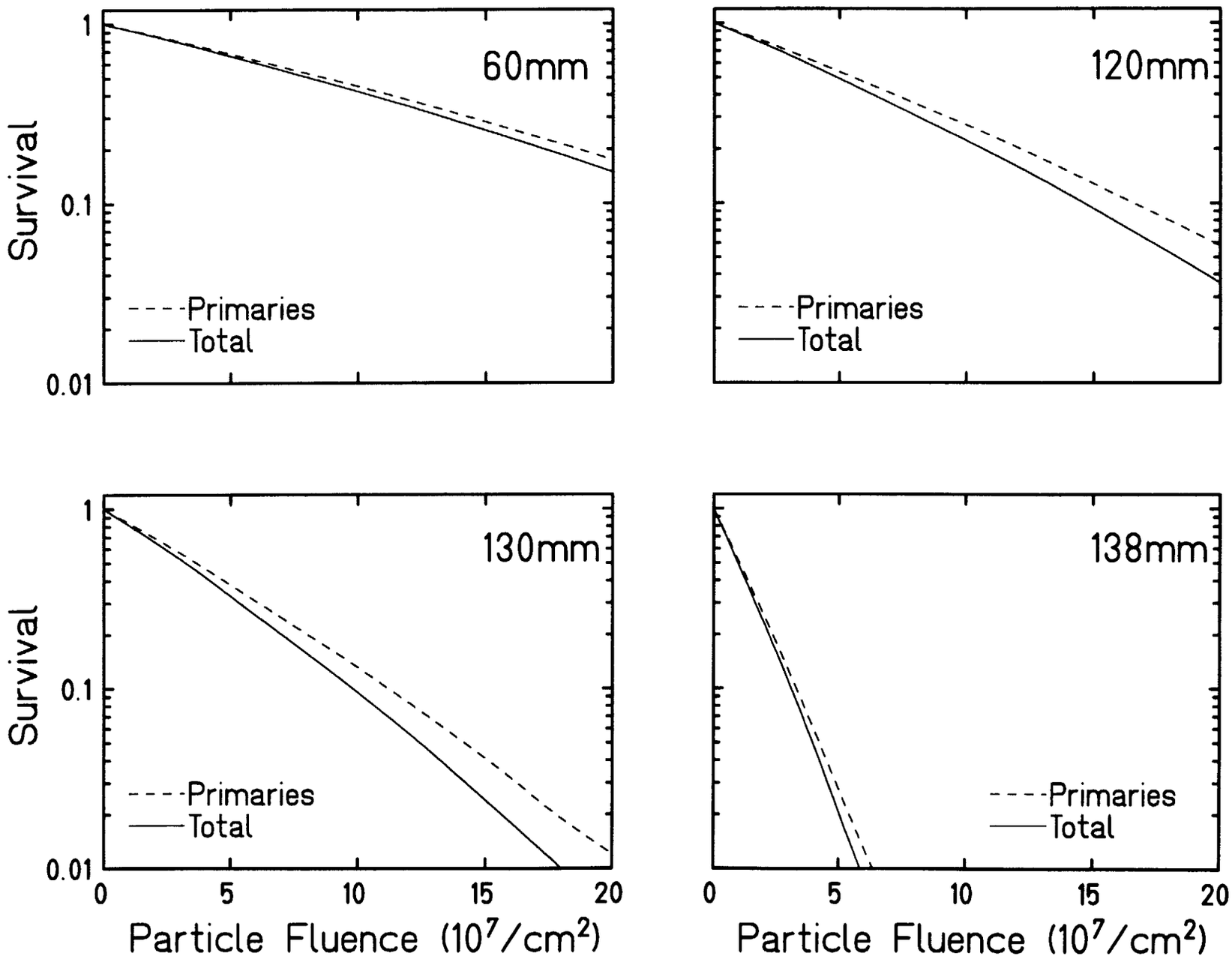
60mm
120mm
130mm
138mm
Survival
1
0.1
0.01
Primaries
Total
0
5
10
15
20
Particle Fluence (10^7/cm^2)

Figure 9

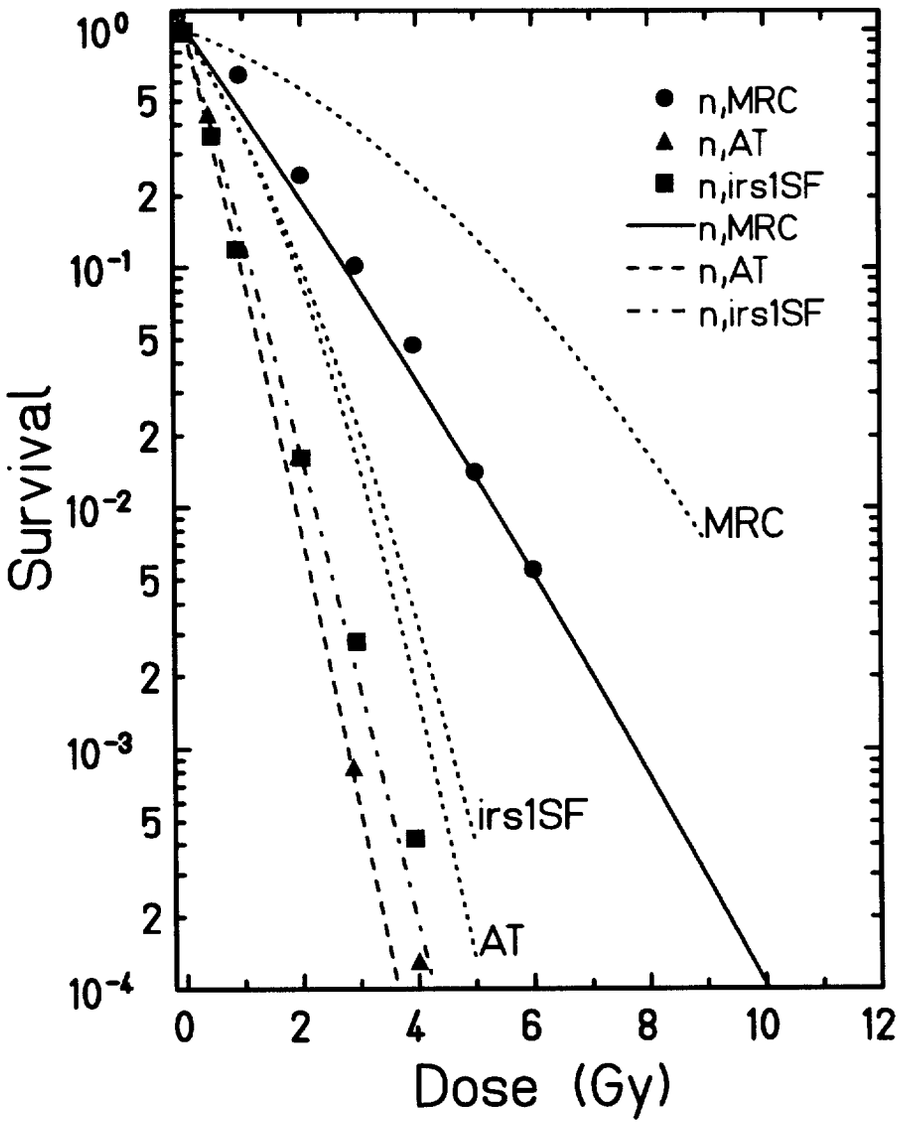

Figure 10

Scholz et al., Calculation of mammalian cell survival in complex charged particle fields