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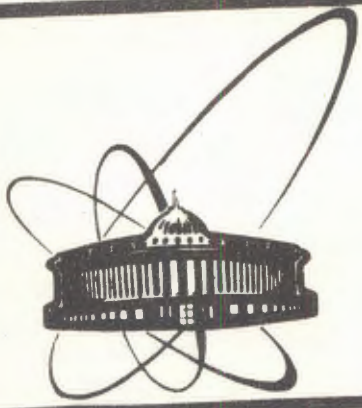

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THE SHAPE OF SURVIVAL CURVES FOR PIONS AND X-RAYS IN A LIVING TISSUE

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1. INTRODUCTION

The choice of a fractionation course in radiotherapy depends in a substantial degree on the shapes of survival curves for the corresponding cells. Their importance increases when some new kinds of ionizing radiations are to be introduced into clinical use. However, we have not yet understood the significance of all factors influencing the behaviour of living cells after irradiation. Consequently, the survival curves are being described mathematically by some simple phenomenological formulas, at the present the decisive preference being given to the so-called linear-quadratic one. Even if this formula describes their shapes in some cases to a sufficient approximation it has not any deeper substantiation; in many cases it can lead to misleading results and conclusions. The mistake can be even much greater if the simple linear-quadratic formula is applied to data obtained in fractionated irradiation.

In the following we would like to show a substantial difference between such an oversimplified model and a mathematical model being able to describe more detailed characteristics. We will start from the formula for survival-curves description shown in Ref.[1] and applied already to some experimental data (fractionated irradiation of pig lungs) in Ref.[2]. Some additional necessary generalization of this cumulative-effect model will be introduced here. This extended model will be applied to the experimental data taken from Ref.[3] giving an excellent basis for numerical analysis. Umfortunately, the similar analysis performed already in Ref.[3] is devalued by the application of the common simple linear-quadratic model as will be seen from the following.

2. FORMULA FOR DESCRIPTION OF SURVIVAL CURVES

An inactivation effect of ionizing particles on individual cells consists from two basic different processes acting one against another: radiation damages of important biomolecules and repair of these damages. It is known at the present that these damages are represented mainly by double-strand breaks (DSB) of chromosome DNA molecules or by their certain combinations (in diploid cells). A part of such damages can be lethal for a hit cell but a significant part of them can be removed by some repair processes (starting after the irradiation) before the given cell is passing to mitosis.

The shoulder on survival curves at smaller doses is connected closely with this repair. Mostly the already mentioned linear-quadratic formula is used for the description of their shapes. It is based on the assumption that the double action is needed if a lethal damage should be formed. However, such a picture is very simplified as it does not take into account the fact that practically all significant damages are formed in principle by a double action (see Ref.[4]). And the actual survival curves are a result of very complex processes. Thus, according to our experience instead of the linear-quadratic form a simply generalized formula seems to be much more appropriate:

$$s(d) = \exp\,[-\alpha d - (\beta d)^{\gamma}]\,; \tag{1}$$

both the parameter α and β are expressed in $[Gy^{-1}]$ and the value $1/\beta$ is equal to the approximate dose where the non-linear term starts to play a significant role (the given term giving the e^{-1} survival); the parameter γ is dimensionless. For a series of survival curves formula (1) represents a much better approximation than the linear-quadratic one.

Of course, when a living tissue is irradiated then some other term seems to be necessary to be added, mainly if greater fraction doses are applied to. As shown in Ref.[5] the analysis of fractionated data leads to the conclusion that a very small part (approximately 10^{-6}-10^{-7}) of cells exist in a tissue which are very radioresistent. Thus for an analysis of fractionation data the use of the following formula should be recommended:

$$s(d) = (1 - \delta)\exp\,[-\alpha d - (\beta d)^{\gamma}] + \delta \exp(-\alpha_r d), \tag{2}$$

where δ is a portion of radioresistent cells. The linear dependence of the other term seems to be fully sufficient as $\alpha_r \ll \alpha$. It plays a significant role for rather high doses only. The logarithmic survival is then expressed as

$$h(d) = -\log s(d). \tag{3}$$

For smaller doses (as δ is of 10^{-6} order) one can write

$$h(d) = \alpha d + (\beta d)^{\gamma}. \tag{4}$$

3. A MATHEMATICAL MODEL FOR THE DESCRIPTION OF FRACTIONATION DATA

As already mentioned the main characteristics of the semi-phenomenological formula used in Ref.[2] was described in Ref.[1]. The cell survival as the end of a fractionation course is expressed generally by

$$S(D, N, T) = \exp(-C), \tag{5}$$

where

$$C = N\,h(d)\,f(t, T) \tag{6}$$

and D is a total dose, N — a number of dose fractions, and t — interval between individual fractions; T = N.T, D = N.d. The function h(d) is the logarithmic survival (as defined by Eq.(3)) corresponding to individual doses and f(t, T) is a modifying factor taking into account the influence of proliferation processes. If the total time T is not very long (as a rule less than 10 days) it is possible to put f(t, T) = 1.

Of course, it is not possible in fractionation experiments to measure the actual cell survival in a tissue but only a macroscopic effect. Thus, another relation must be introduced into the analysis of fractionation data. If this macroscopic effect is expressed by a value K determined in some suitable scale there will be one-to-one correpondence between K and C. One must expect the dependence of K on C to be expressed by a monotony rising function. In principle the following parametrization can be used.

$$K = K_{max}\,\{1 - \exp[-(aC)^{d}]\}/\,\{1 + b\exp[-(aC)^{d}]\} + K_{min} \tag{7}$$

enabling practically all possible monotone dependencies between K and C (at least in the case when no saddle point is present). The measured values will lie in the interval $(K_{min}, K_{min} + K_{max})$.

There is a series of free parameters in the model; one group determines the shape of the corresponding single-dose survival curve:

$\alpha,\ \beta,\ \gamma,\ \alpha_r,\ \delta$;

and the other one, the dependence of the tissue effect on the final cell survival:

a, b, d, K_{min}, K_{max}.

Some basic assumptions are included in the given mathematical model in addition to that the total time T is so short that the cumulative effect is not influenced by proliferation processes running between individual dose fractions (as they start with some delay): (i) The interval between individual fractions is long enough for the cell repair to be finished before the other fraction is applied to. (ii) The measurable macroscopic biological effect is given by the cell survival at the end of any fractionation course; there is not any dependence on the fractionation scheme.

4. COMPARISON WITH EXPERIMENTAL DATA

The proposed mathematical model will be now compared with experimental data taken from Ref.[3] and concerning the cumulative effect of pions and X rays on foot skin system of male $B_6C_3F_1$ hybrid mice. The cumulative effect for 5 different fractionation schemes was measured: N = 1, 2, 4, 10, 20. The total time T was always less then 10-20 days and intervals between individual fractions were greater than 12 hr. Thus we meet with the conditions under which it is possible to put $f(t, T) = 1$.

The results of the fits are shown in Fig.1. The lines represent the theoretical curves; the experimental values taken from Ref.[3] are represented by points (with corresponding error bars). The best fits (represented by dashed lines in Fig.1) were obtained with the following values of the free parameters:

a) pions (in peak — dose rate 15 cGy/m):
$\alpha = 0.300$, $\beta = 0.103$, $\gamma = 3.90$, $\alpha_r = 0.0317$, $\delta = 0.900\times10^{-6}$,
$a = 0.151$, $b = 212$, $d = 2.26$, $K_{min} = 8.83$, $K_{max} = 19.5$;

b) X-rays (270 kVp, HVL 3.0 mm Cu — dose rate 15 cGy/m):
$\alpha = 0.167$, $\beta = 0.100$, $\gamma = 2.05$, $\alpha_r = 7.0\times10^{-4}$, $\delta = 0.545\times10^{-6}$,
$a = 0.177$, $b = 166$, $d = 1.89$, $K_{min} = 7.49$, $K_{max} = 18.0$;

c) X-rays (270 kVp, HVL 3.0 mm Cu — dose rate 150 cGy/m):
$\alpha = 0.123$, $\beta = 0.146$, $\gamma = 1.79$, $\alpha_r = 0.0546$, $\delta = 0.483\times10^{-6}$,
$a = 0.171$, $b = 87.2$, $d = 1.83$, $K_{min} = 7.50$, $K_{max} = 17.5$.

It is evident from Fig.1 that especially the fit for pions must be regarded as fully insufficient. If the statistical errors (as indicated in Ref.[3]) are taken into account the given fits correpond to the following χ^2 values: 222/12, 154/29 and 310/30 degrees of freedom.

The presented results indicate that the survival curves have much more complex shapes than allowed by formula (2). We have obtained much better fits (quite satisfying for pions) if the shapes of corresponding survival curves have been represented by the formula

$$\bar{s}(d) = (1 - \bar{\delta})\, s(d) + \bar{\delta} \exp[-(\bar{\beta} d)^{\bar{\gamma}}]. \qquad (8)$$

These fits are represented by full lines in Fig.1. They were obtained with the following values of free parameters:

a) pions:
$\alpha = 0.304$, $\beta = 0.116$, $\gamma = 4.76$, $\alpha_r = 7.1\times10^{-5}$, $\delta = 0.425\times10^{-6}$,
$\bar{\beta} = 0.0734$, $\bar{\gamma} = 3.61$, $\bar{\delta} = 0.00727$,
$a = 0.151$, $b = 232$, $d = 2.26$, $K_{min} = 9.07$, $K_{max} = 19.5$;

b) X rays (15 cGy/m):
$\alpha = 0.191$, $\beta = 0.0929$, $\gamma = 2.62$, $\alpha_r = 0.061$, $\delta = 18.0\times10^{-6}$,
$\bar{\beta} = 0.0460$, $\bar{\gamma} = 9.50$, $\bar{\delta} = 0.0137$,
$a = 0.154$, $b = 242$, $d = 2.34$, $K_{min} = 8.00$, $K_{max} = 24.2$;

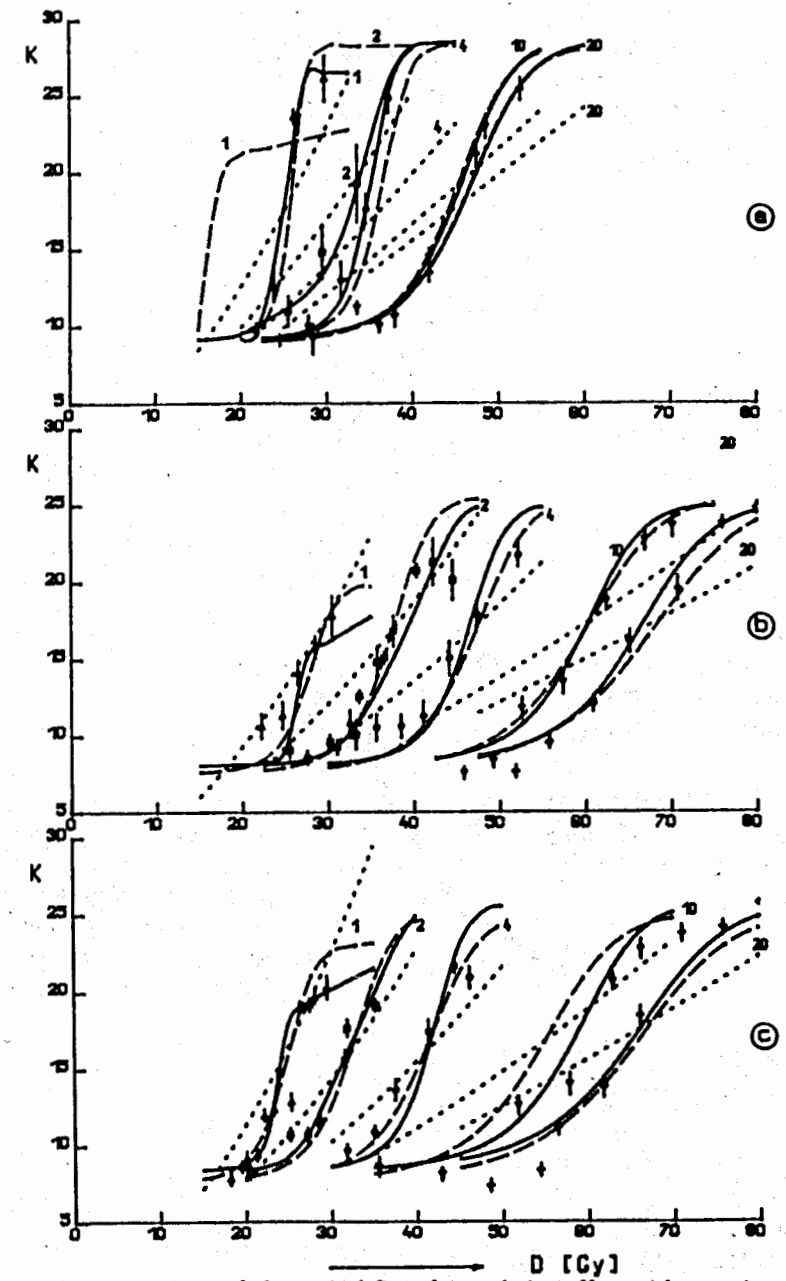

Fig.1. The comparison of theoretical fits of cumulative effect with experimental data; th individual curves and experimental points correspond to fraction numbers N = 1 2,3,10,20 (a) pions (dose rate 15 cGy/m), (b) X-rays (dose rate 15 cGy/m), (c) X-rays (dose rat 150 cGy/m). The interpretation of lines of different kinds is given in the text.

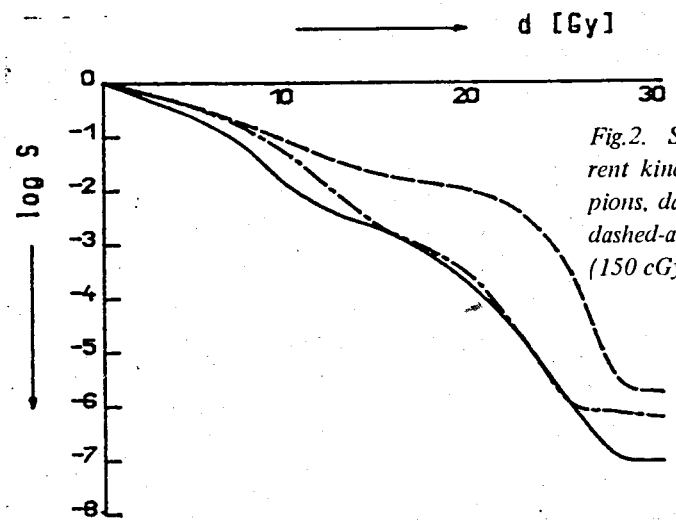

Fig.2. Survival curves for different kinds of radiation: full line – pions, dashed line – X (15 cGy/m), dashed-and-dotted line – X (150 cGy/m).

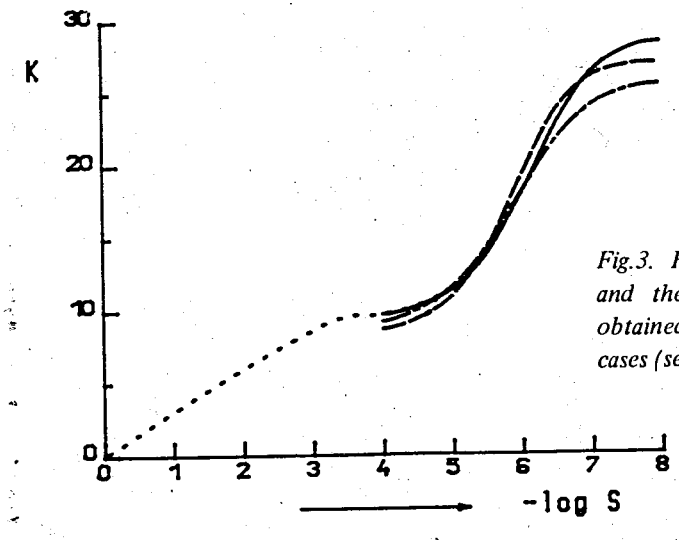

Fig.3. Relations between K-values and the logarithmic survival (C') obtained in the three different cases (see Fig.2).

c) X rays (150 cGy/m):

$\alpha = 0.199$, $\beta = 0.105$, $\gamma = 3.36$, $\alpha_r = 0.096$, $\delta = 9.63 \times 10^{-6}$,

$\bar{\beta} = 0.0574$, $\bar{\gamma} = 6.19$, $\bar{\delta} = 0.0021$,;

$a = 0.164$, $b = 167$, $d = 2.06$, $K_{min} = 8.24$, $K_{max} = 17.4$;

the corresponding χ^2 values are now 17/9, 110/26 and 244/27 degrees of freedom; the rather great values for X rays seem to be related to systematic deviations in individual measurement series being not taken into account.

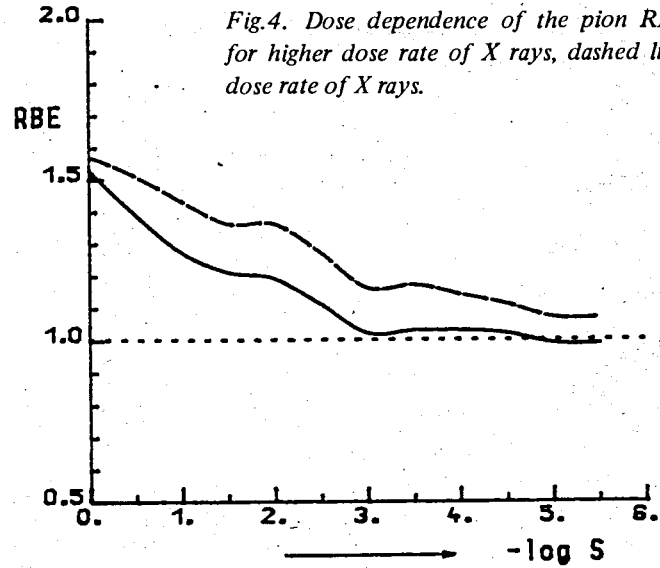

Fig.4. Dose dependence of the pion RBE: full line – for higher dose rate of X rays, dashed line – for lower dose rate of X rays.

The corresponding survival curves are then shown in Fig.2. And the dependence of the macroscopic effect on the logarithmic survival C' is represented in Fig.3; C = C.loge. All fits are limited by the condition taken from Ref.[6] (see also Ref.[3]), i.e. K = 17 for $S = 1.3 \times 10^{-6}$.

The survival curves for pions and X rays shown in Fig.2 allow also to derive the dose dependence of the pion RBE. This dependence is indicated in Fig.4; the pion effect is compared to X rays at the higher dose rate as well as at the lower one.

5. DISCUSSION

The analysis of the given data was performed already with the help of a very simple mathematical model in Ref.[3]. However, the model based on a mere linear-quadratic formula cannot provide a corresponding picture of the mechanism lying under the cumulative fractionation effect; especially when an additional assumption has been involved tacitly in the model used, being represented by the condition

$$K = k.C, \tag{9}$$

where $C = -\lg S$ (see Eq. (5)) and k is a constant. By the normalization condition taken from Ref.[6] this constant was fixed to a $k \doteq 1.25$. The corres-

ponding fits are represented by dotted lines in Fig.1, manifesting the insufficiency of the mathematical model used in Ref.[3].

Our results show quite convincingly that the survival curves have a very complex shape and that they cannot be described by a simple linear-quadratic formula even in the region of radioterapeuthic doses. Their curvature is much greater in this region; it is only the existence of the other shoulder at greater doses which makes the global characteristics so as to be possible to describe them approximately by such a formula.

In evaluating the fractionation data measured in vivo the second term in Eq.(2) seems to be also indispensable. It describes the influence of a very small portion of resistant cells which seems to be always present in living tissues, corresponding probably to a short interval in the mitotic cycle. The corresponding term plays a significant role for rather high single doses. It cannot be omitted if the cumulative effect of fractionated irradiation should be compared to the effect of a single dose.

However, let us return to the additional term in Eq. (8). It represents undoubtedly a very complex distribution of energy over the whole cell population after the impact of radiation of any type. Such a situation is strongly expressed especially in the case of pions. It is evident that after the absorption of a negative pion by an atomic nucleus photons and electrons are emitted together with heavy fragments. The range of these light particles is rather great and they hit a significant part of cells relatively distant from an original place of the pion absorption. The additional term corresponds then to a divers inactivation mechanism in which probably the effects of several different pions are combined in forming potentially lethal and lethal damages. This mechanism is effective in a smaller part of cells at higher doses, being characterized by a smaller value of β. In the mechanism represented by the first term in Eq. (2) the individual potentially lethal damages are supposed to be formed already by one beam particle, the non-linear term being a result of their combined effect (leading to lethal damages) and of the repair processes running in cells and removing the damages being lethal if not repaired before mitosis.

The second shoulder exists on the survival curves for X rays, too. It seems to exhibit a dose-rate dependence being more expressed in the case of the higher dose-rate. Its existence may be related to the fact that there is a great difference between ionization densities in different parts of electron tracks. A major biological effectiveness is exhibited by the densely ionizing track ends while the cell damages caused by other parts are much smaller. Thus, a situation seems to occur being very similar to that for pions, even if shifted to higher doses.

Our analysis has also enabled to attribute corresponding survival values to different degrees of macroscopic damages if a basic relation for $K = 17$ was taken from Ref.[6]. This relation is shown to be practically independent

of the radiation kind as only very small differences have been found for X-radiation and pions. We could derive, of course, the given dependence in the range of experimental values only. The supposed dependence for lower values of K and C is indicated by the dotted line in Fig.3.

It follows from our analysis that there are several different kinds of inactivation mechanism (if the influence of a small portion of resistant cells is left aside) which can contribute to the final effect of any cell inactivation in the dependence on the radiation type. One can divide them into three categories characterized by the values of the parameters γ and β:

(i) $\gamma \doteq 4{,}75$, $1/\beta \doteq 8$ Gy;

(ii) $\gamma \doteq 3.0$, $1/\beta \doteq 10$ Gy;

(iii) $\gamma > 6$, $1/\beta \doteq 22$ Gy.

The first one may be related to heavier nuclear fragments where the inactivation effect is given not only by the DSB formation but also by some damages of the whole cell which makes it unable to repair even a smaller number of chromosome DSB. The other category may be related to the effect to densely ionizing electron track ends and one can assume that only the proper chromosome damages are responsible for an inactivation effect. And finally, the last category corresponds to other rarely ionizing track parts when a greater number of particle tracks must be combined to form potentially lethal damages. Here the cell repair capability must be assumed to play a maximum role. In the first two categories one must admit that a part of cells is damaged lethally immediately after being hit by one beam particle, which is characterized by the already given values of the α parameter. The individual shoulders will be more or less distinct according to the quality and energy of the primary beam. Measured microdosimetric characteritics might be made use of for some predictions of survival-curve shapes under different conditions (including geometrical arrangements).

It follows from our results that the shape of survival curves deviates rather significantly also in the region of the first shoulder from that being accepted commonly. Its curvature seems to be much greater than that given by the term of the second order, which might influence arguments concerning the choice of fractionation regimes in radioterapeuthic tumour treatments. The linear-quadratic formula may represent an acceptable approximation in describing a global behaviour of the whole survival curves but it can hardly describe all necessary characteristics in the dose region important for radiotherapy.

The complex situation in this region was already mentioned in Ref.[7] where for some doses pions were found to be less biologically effective than X rays. Such a behaviour was related to the greater damages of cell repair systems in the case of pions. However, such an explanation seems to be rather simplified and does not seem to take into account all needed characteristics of the whole radiobiological mechanism in cells. It is not clear, either, what role is played in this respect by the biological system (or by the primary energy of X beam) as our results indicate that for mouse skin the RBE of pions is greater practically than 1 at all dose values (see Fig.4). There is not any doubt that the repair rates are fundamentally influenced already by the distribution of primary damages in individual cells. To solve the problem of survival-curve shapes in a more reliable way a detailed analysis of all processes running in cells of a given type after radiation impact and of their influence on these shapes seems to be necessary, which cannot be done without the help of suitable mathematical models (see, e.g., Ref.[4]).

6. CONCLUSION

The analysis performed shows quite convincingly the insufficiency of the linear-quadratic formula for the description of survival curves. All analyses of radioterapeuthic treatment courses should be reevaluated in the light of the presented results as the survival curves exhibit much stronger curvature in the range of corresponding doses than usually assumed. At the same time the necessity of suitable mathematical models for the study of inactivation mechanism has been demonstrated. It has been also shown that in the corresponding analysis it is not possible to limit the number of free parameters under a level required by the complexity of an actual phenomenon. However, it is important for any parameter used (or at least for a partial phenomenological function) to have a concrete interpretation corresponding to a process running in a cell after radiation impact.

The proposed model is fundamentally based on the combination of two different mathematical functions: one describing the survival curve for a given radiation kind and the other one determining the connection between a macroscopic damage and the fraction of cells surviving at the end of a fractionation course. The available data (taken from Ref.[3]) have allowed to determine both these dependencies to a sufficient degree. The fact that sufficiently good fits have been obtained for all kinds of radiations should be regarded as a strong validation of the presented model.

The given model does not include any dependence on the total time T. Thus it can be applied to the total times less than approximately 10 days. For greater times some correction terms should be introduced enabling to take into account the influence of proliferation processes, too (see Ref.[7]).

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