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Formulation of Time-Dependent Cell Survival with Saturable Repairability of Radiation Damage

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This study aims to provide a model that compounds historically proposed ideas regarding cell survival irradiated with X rays or particles. The parameters used in this model have simple meanings and are closely related to cell death-related phenomena. The model is adaptable to a wide range of doses and dose rates and thus can consistently explain previously published cell survival data. The formulas of the model were derived by using five basic ideas: 1. "Poisson's law"; 2. "DNA affected damage"; 3. "repair"; 4. "clustered affected damage"; and 5. "saturation of reparability". The concept of affected damage is close to but not the same as the effect caused by the double-strand break (DSB). The parameters used in the formula are related to seven phenomena: 1. "linear coefficient of radiation dose"; 2. "probability of making affected damage"; 3. "cell-specific repairability", 4. "irreparable damage by adjacent affected damage"; 5. "recovery of temporally changed repairability"; 6. "recovery of simple damage which will make the affected damage"; 7. "cell division". By using the second parameter, this model includes cases where a single hit results in repairable–lethal and double-hit results in repairable–lethal. The fitting performance of the model for the experimental data was evaluated based on the Akaike information criterion, and practical results were obtained for the published experiments irradiated with a wide range of doses (up to several 10 Gy) and dose rates (0.17 Gy/h to 55.8 Gy/h). The direct association of parameters with cell death-related phenomena has made it possible to systematically fit survival data of different cell types and different radiation types by using crossover parameters.

INTRODUCTION

The first survival model of X-ray-irradiated cells was the target theory during the 1920s (*1*). In many studies, a simple model using linear-quadratic (LQ) equations significantly improved data fitting over the dose range clinically used in X-ray therapy (*2–4*), and extended to explain various phenomena (*5–7*). The characteristics and limitations of the LQ model were pointed out in previous works (*8–12*) and some works include the changing of relative biological effectiveness (RBE) (*13–16*) between different radiation types. The methods, which use simple equations, have evolved into methods that use numerical solutions of differential equations or the Monte Carlo simulation (*17–19*).

Models that explain radiation-induced cell death have been developed with various concepts since the early days, as shown in Fig. 1. The Appendix presents previous research on these models. The concepts are based on ideas that approach some of the essences that explain the elementary processes of cell death. The first idea is a formula derived from Poisson's law, which is involved in many models. In the formula, parameters are used that represent the probability of damage to the domain in a cell. A typical example is a relationship between this idea and the target theory model (*1*). The second is the idea that two or more simple damages are a major cause of contribution to cell death, which resembles the contribution to cell death by DNA double-strand breaks (DSBs) (*20, 21*). These damages will lead to cell death if they cannot be repaired. Research on DSB has been progressing recently, and new findings such as drift and pairing have been obtained (*22*). In our work, the amount of DSB is not suitable for use as an internal parameter for fitting the formulas because it can be estimated experimentally in many works (*20–22*). We use another phase, DNA-affected damage as a concept that is close but not the same as the effect caused by the DSB. Affected damage is a quantity defined only for fitting by using the present formulation. The third is the idea of repair. Of the damages that affect cell death, repairable damages return to their original state with a response determined by the repair time (*23*). Fourth is the idea of an adjacent or clustered affected damage, which means irreparable damage. The idea is incorporated in simulation methods, such as a local effects model (*19, 24*). The last is the saturation of reparability. If a lot of damage occurs in

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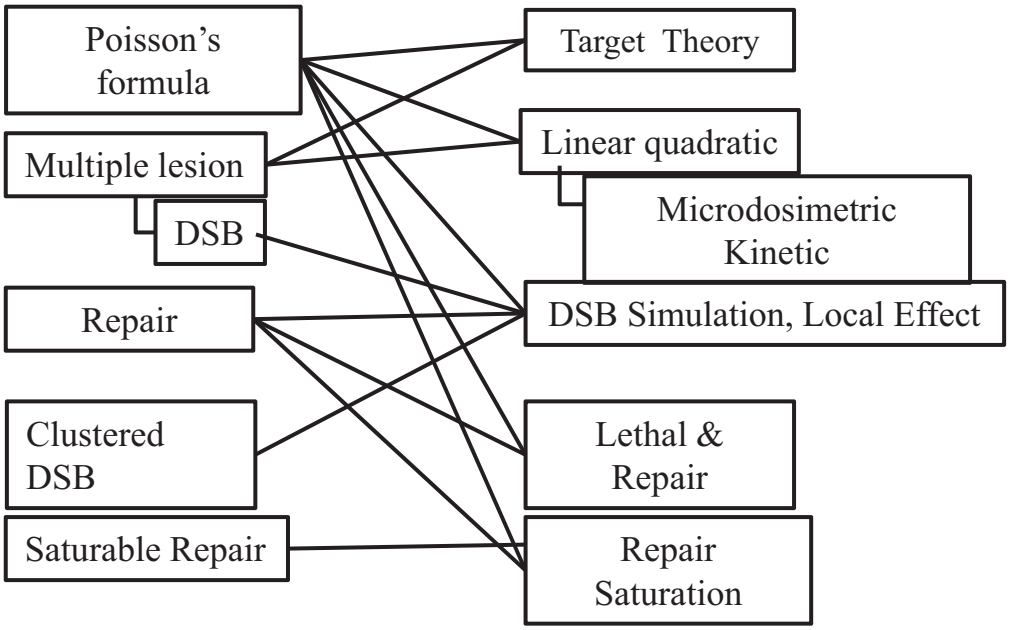

FIG. 1. Basic ideas and models of cell survival. The Appendix presents previous research on these models.

a short time, the substance used for repair (reparability) is temporarily depleted and additional repair becomes impossible (*25, 26*). The depleted reparability returns to the original amount with a response determined by the recovery time. This phenomenon is thought to be related to repair proteins that are supplemented from around the cell nucleus.

The five ideas are important as elementary processes for expressing the mechanism of cell death, but no studies have been conducted to make mathematical formulas in consideration of all of them. Incorporating these ideas into a formula is important from the perspective of clarifying the meaning of the parameters. In this paper, we expressed the properties of the ideas in differential equations and solved them to derive new formulas for cell survival. With this method, we aim to consistently explain cell survival data that includes a wide range of doses. Furthermore, by deriving a time-dependent difference sequence, we established a method to consider the effect of the dose rate and the interval time between irradiations.

FORMULATION AND FITTING METHOD

Model of Repairability

In this work, model parameters are the linear efficiency (a) of radiation dose to make simple damages, probability of making affected damage (c_1) in a track of chained damages as described below, cell-specific repairability (R), the proportion of repairable damages (f), recovery time constant of reduced repairability (τ_R), recovery time constant (τ_S) of simple damages and doubling time of cell division (T_d).

We assume that the amount of repair is determined by the product of damage and a variable of the remaining repairability $r(x)$. If repairability does not have sufficient time to recover, it is assumed that repair will be limited. This is the concept of "temporary depletion of repairability" which has been introduced in past models (*25, 26*).

Figure 2 gives an overview of the model of repairability. The variable $r(x)$ is consumed by the amount of damage produced. Parameters τ_R, τ_S, and T_d will be applied later. The recovery appears in a differential equation as a term of increased survival which is proportional to the amount of damage and the repairability,

$$\frac{dS}{S} = -A(x)\, dx(1 - fr(x)) \tag{1}$$

where S, $A(x)$, and dx are survival, a variable of damage (1/Gy) which is a function of dose in the consumption valance of repairability, and dose increment (Gy). $A(x)$ is calculated by the parameters a and c_1 as described below. From Poisson's law with linear coefficient a and probability c_1 of directly making affected damage, the probability of affected damage is approximated as a linear weighted sum,

$$\begin{aligned} AD &= c_1(1 - \exp(-ax)) + (1 - c_1)(1 - \exp(-ax))^2 \\ &= (1 - \exp(-ax))\{1 - (1 - c_1)\exp(-ax)\}. \end{aligned} \tag{2}$$

Here, c_1 is a parameter that probabilistically describes the process by which simple damage develops into affected damage. In other words, it is a parameter that separates the probabilistic case between "a single hit" that results in repairable-lethal damage and "double hits" that results in repairable-lethal damage. The tendency of low-linear energy transfer (LET) radiation can be expressed approximately by a small value of c_1 ($\cong 0.1$ or 0.15), high-LET radiation can be expressed approximately by a large value of $c_1 (\cong 0.9)$.

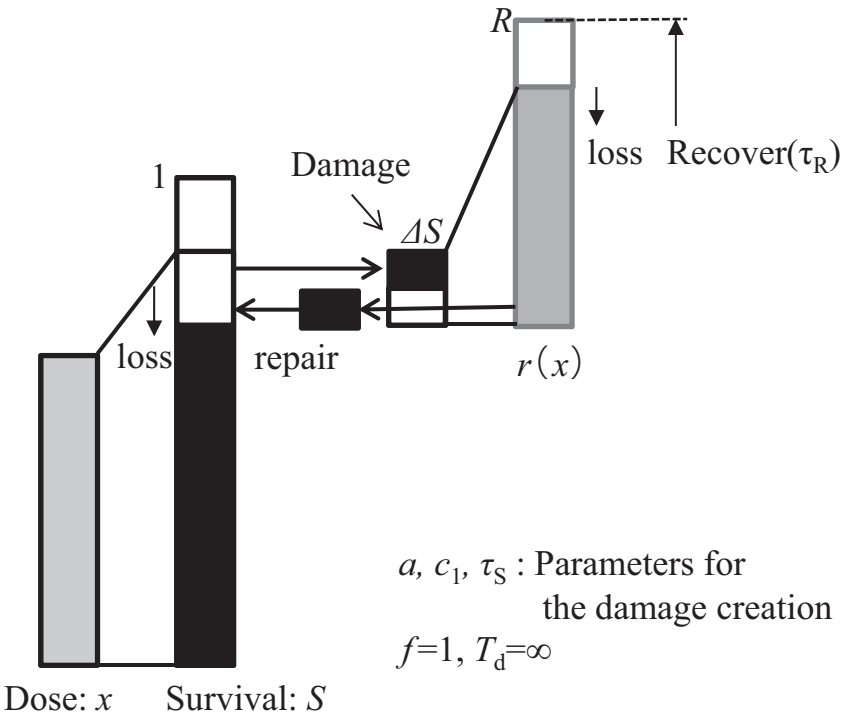

FIG. 2. Schematic diagram of the relation between parameters in the present model. Loss of survival ΔS is the product of dose, $A(x)$ and survival S. The loss is compensated by the repair which is the product of ΔS and variable of repairability $r(x)$. The loss of repairability is recovered with the time constant τ_R. R is the total amount of repairability.

Once the repair term (variable r(x)) is ignored, S is calculated from Eq. (2),

$S = 1 - AD = \exp(-ax)\{2 - c_1 - (1 - c_1)\exp(-ax)\}$

$\ln S = -ax + \ln(2 - c_1 - (1 - c_1)\exp(-ax))$.

The differential form is

$$\frac{dS}{S} = -adx + \frac{a(1 - c_1)\exp(-ax)}{2 - c_1 - (1 - c_1)\exp(-ax)}dx.$$

Therefore,

$$A(x) = a - \frac{a(1 - c_1)\exp(-ax)}{2 - c_1 - (1 - c_1)\exp(-ax)}. \qquad (3)$$

By the probability c_2 of forming a closely connected second affected damage near the first affected damage in one action of radiation incidence, the proportion of repairable damage can be calculated. The probability c_2 is a parameter determined by radiation type. The probability of creating a second affected damage simultaneously and adjacent to the first affected damage is $Adx \cdot Adx$, and the probability of creating a second affected damage in relation to the action that created the first affected damage is $Adx \cdot (1 - Adx)c_2$. The probability that two affected damages are adjacent is $Adx(Adx + (1 - \mathrm{Adx})c_2)$. The probability of repair is

$$f = \frac{Adx - Adx(Adx + (1 - Adx)c_2)}{Adx} = (1 - Adx)(1 - c_2) \cong 1 - c_2 \qquad (4)$$

In the case of low-LET radiation such as X ray and proton, f should be about 0.9.

Short-Time Irradiation with a Relatively High Dose Rate

For simplicity, we consider that the change in repairability depends on the amount of damage.

$$\frac{dr}{r(x)} = -kA(x)\,dx \qquad (5)$$

Here, k is a constant which means the loss of $r(x)$ is proportional to $r(x)$ and the cell damage. Assuming that the integral of $A(x)r(x)\mathrm{d}x$ is the total repair capability R, k should be $1/R$. R is the constant that determines the finite value of repair capacity, or the maximum amount of damage that can be repaired in a short time. The remaining $r(x)$ after irradiation x is

$$r(x) = \exp\left(-\frac{K(x)}{R}\right), K(x) = ax - \ln(2 - c_1 - (1 - c_1)\exp(-ax)), \qquad (6)$$

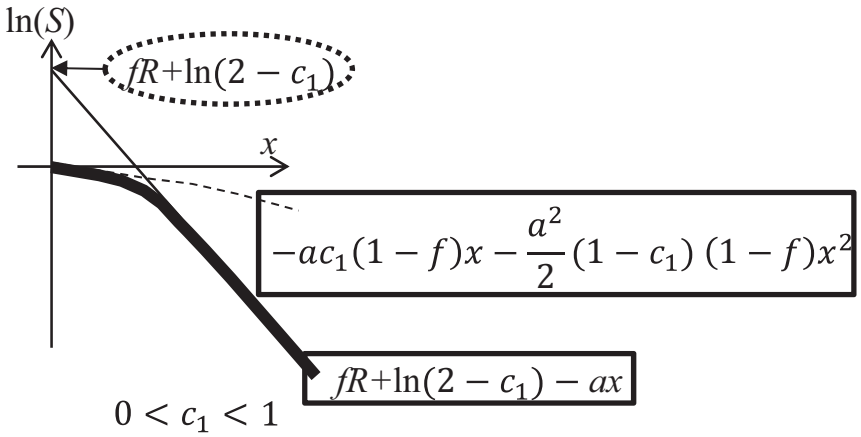

FIG. 3. Schematic shape of survival curve for the present model which has high dose asymptote not passing through the origin. The dose rate is assumed to be not small and the irradiation time negligibly short. Asymptotic lines for small dose and large dose are shown as formula in figures by solid square. The intersection of the extrapolated line to the survival axis is indicated by a dotted circle.

Where

$$\frac{dK(x)}{dx} = A(x). \tag{7}$$

Eq. (1) is,

$$\frac{dS}{S} = -A(x)\,dx + fA(x)\,dx\,\exp\left(-\frac{K(x)}{R}\right). \tag{8}$$

From integration and the initial condition ($x = 0$, $\ln S = 0$), the effect of the irradiation is expressed by the following equation.

$$\ln S(x) = -K(x) + fR\left(1 - \exp\left(-\frac{K(x)}{R}\right)\right) \tag{9}$$

For the case $c_1 = 0$ where a track made by radiation incidence cannot make affected damage directly, survival can be expressed,

$$\ln S(x) = -ax + \ln(2 - \exp(-ax)) + fR\left(1 - \exp\left(-\frac{1}{R}(ax - \ln(2 - \exp(-ax)))\right)\right). \tag{10}$$

For the case $c_1 = 1$ where a track made by radiation incidence makes affected damage directly, survival can be expressed,

$$\ln S(x) = -ax + fR\left(1 - \exp\left(-\frac{ax}{R}\right)\right). \tag{11}$$

Parameter c_1 can represent the state between Eqs. (10) and (11). The values 0 and 1 for c_1 are not realistic. In the case of X rays, which have a low probability of making strong damage at the same time, it is considered that c_1 has a small value near 0.1 or 0.15. For high-LET radiation that easily creates affected damage, c_1 is close to 1. These equations contain three essential quantities − the amount of simple damages (ax), total repairability (R), and the proportion of repairable damage ($f = 1 - c_2$).

The schematic shape of the proposed model is shown in Fig. 3 as the survival curve of Eq. (9). This curve does not include time dependence. The formulas of asymptotic lines for small doses and large doses are indicated in solid squares. The intersection of the extrapolated line with the survival axis is indicated in dotted circles. The intersection shows the total repair components which means a shift of survival in the large dose region (*27, 28*). As one of the features of this model, the shift of radiation effect ($fR + \ln(2 - c_1)$) is independent of the linear coefficient, and fR shows the maximum value of repairable damage including repair efficiency f. The asymptotic curve for low doses is a linear quadratic curve $-ac_1(1-f)x - \frac{a^2}{2}(1-c_1)(1-f)x^2$. It means that the new model has an affinity with the LQ model at low doses, with the condition that c_1 has a value between 0 and 1.

Variable RBE and Equivalent Dose in 2 Gy Fractions (EQD2)

Recent studies treat RBE as a variable that depends on the endpoint of cell death (*6, 13–16*). Instead of expressing RBE as a function of endpoint, it is expressed here as a function of fractionated dose (d). It is assumed that the interval time of fractionated irradiation is sufficiently longer than the recovery time of repairability. Based on the cell survival irradiated by X ray, RBE is expressed by the following equation.

$$S_{\mathrm{X}}(d_{\mathrm{eq}}) = S(d), \mathrm{RBE}(d) = \frac{d_{\mathrm{eq}}}{d} \tag{12}$$

Where S_{X} is the cell survival irradiated by the reference radiation and d_{eq} is the equivalent dose by the reference radiation. To find d_{eq} from d, it is necessary to solve Eq. (12) numerically, because this is not the quadratic equation such as the LQ model. As Eqs. (9–11) shows, the asymptotic value of RBE is the ratio of parameter a when the fractionated dose is large enough.

$$\mathrm{RBE}(d \to \infty) = \frac{a}{a_{\mathrm{X}}} \tag{13}$$

Here, a_{X} is a coefficient of the amount of simple damages caused by the reference radiation. One of the features of this model is that the RBE is asymptotic to the constant value at high doses.

The formula of the EQD2 is given by the general definition.

$$\mathrm{EQD2} = \frac{\ln S_{\mathrm{X}}(d_{\mathrm{eq}})}{\ln S_{\mathrm{X}}(2)} 2n_f, \tag{14}$$

Where n_f is the number of radiation fractions. Suppose that EQD2 calculated by the LQ model is close to the correct value between 2 Gy and 4 or 5 Gy. If R is determined so that EQD2 becomes the same as the LQ model at 4 or 5 Gy in case using fixed values of f and a, the obtained EQD2 by Eq. (14) becomes smaller than that of LQ at a large dose region. This is consistent with the results obtained in the study of the LQL and other models (*8, 27, 29, 30*).

Case of Low Dose Rate and Fractionated Irradiations

The time-dependent formula of the survival for low dose rate and low LET radiation is not simple to be solved, except for $c_1 = 1$. Here, it is expressed as a difference sequence using many fractions of small dose irradiation and time intervals $(x_1, t_1), (x_2, t_2), \cdots (x_{\mathrm{i}}, t_{\mathrm{i}}), \cdots$.

In the case of the constant dose rate $\left(\frac{dx}{dt} = x'\right)$, the divided dose is

$$x_{\mathrm{i}} = x' t_{\mathrm{i}}. \tag{15}$$

As a phenomenon in which recovery of cell death occurs due to interval time, repair of simple damages and recovery of repairability can be considered. Especially in the case of low-LET radiation, since the formation of affected damage depends on the combination of simple damages, the probability of affected damage decreases when simple damages repair occurs. The difference sequence can be derived from a principle similar to how to calculate time factor G in the LQ model (*28*) which is represented by an integral formula.

$$\ln S_i - \ln S_{i-1} = \frac{t_i}{T_d} \ln 2 - \left\{K\left(X_{\mathrm{S,i-1}} + x_i\right) - K\left(X_{\mathrm{S,i-1}}\right)\right\} + fR\left\{\exp\left(-\frac{K\left(X_{\mathrm{R,i-1}}\right)}{R}\right) - \exp\left(-\frac{K\left(X_{\mathrm{R,i-1}} + x_i\right)}{R}\right)\right\} \tag{16}$$

$$X_{\mathrm{S,i}} = \left(X_{\mathrm{S,i-1}} + x_i\right)\exp\left(-\frac{t_i}{\tau_{\mathrm{S}}}\right) \tag{17}$$

$$X_{\mathrm{R,i}} = \left(X_{\mathrm{R,i-1}} + x_i\right)\exp\left(-\frac{\tau_{\mathrm{S}} + \tau_{\mathrm{R}}}{\tau_{\mathrm{S}}\tau_{\mathrm{R}}} t_i\right). \tag{18}$$

As defined before, τ_{S}, τ_{R}, and T_{d} are a time constant of simple damages repair, a time constant of recovery of repairability, and a doubling time of cell division.

The accumulation of Eq. (16) including the term of cell division $\left(\frac{t_i}{T_d} \ln 2\right)$ gives the log scale survival. By setting t_{i} to zero, changing survival by continuous plural irradiations can be obtained. By setting x_{i} to zero, it makes a simple interval. Using Eq. (16), the effect of the fractionated irradiation is expressed as a curve of survival in Fig. 4. Here, 4 cases of survival curves are calculated by using daily fractionated doses from Monday to Friday. To show the continuous change in survival, one fractionated dose is divided into small doses without interval time. The irradiations started on Monday. Interval of the weekend and of a 9-day break (arrows) by an accidental stop of the irradiation system are included in the case of the 2 Gy fraction where the doubling time of cell division is set to 10 days as an example. Both of the recovery time constant τ_{S} and τ_{R} are set to 1 h. Here the parameters are set as $a = 1.0, f = 0.95, R = 1.6$ and $c_1 = 0.1$ (solid curve) and 0.15 (dotted curve). To know the influence of changing a parameter, all calculations were performed using two values of c_1. Changes in this range do not have a large effect.

Fitting Method

In comparison to the LQ model, which shows stable fitting performance, the fitting of this model has instability due to the correlation between R and a. Only if this instability exists, to achieve stable fitting, we propose a method with two steps of calculation. For simplicity, we assume that c_1 is kept at a fixed value close to zero. (i) Fitting of R and a is performed using only data at a large dose. At this time, f is fixed at 1. Let R obtained is fR for the next step. As shown in Fig. 3, a and fR are the slope and intercept of the straight line, so if only high-dose data are used, a stable solution can be easily obtained by fitting in step (i). In particular, fR and a are parameters that represent the characteristics of the shape of the survival curve, so

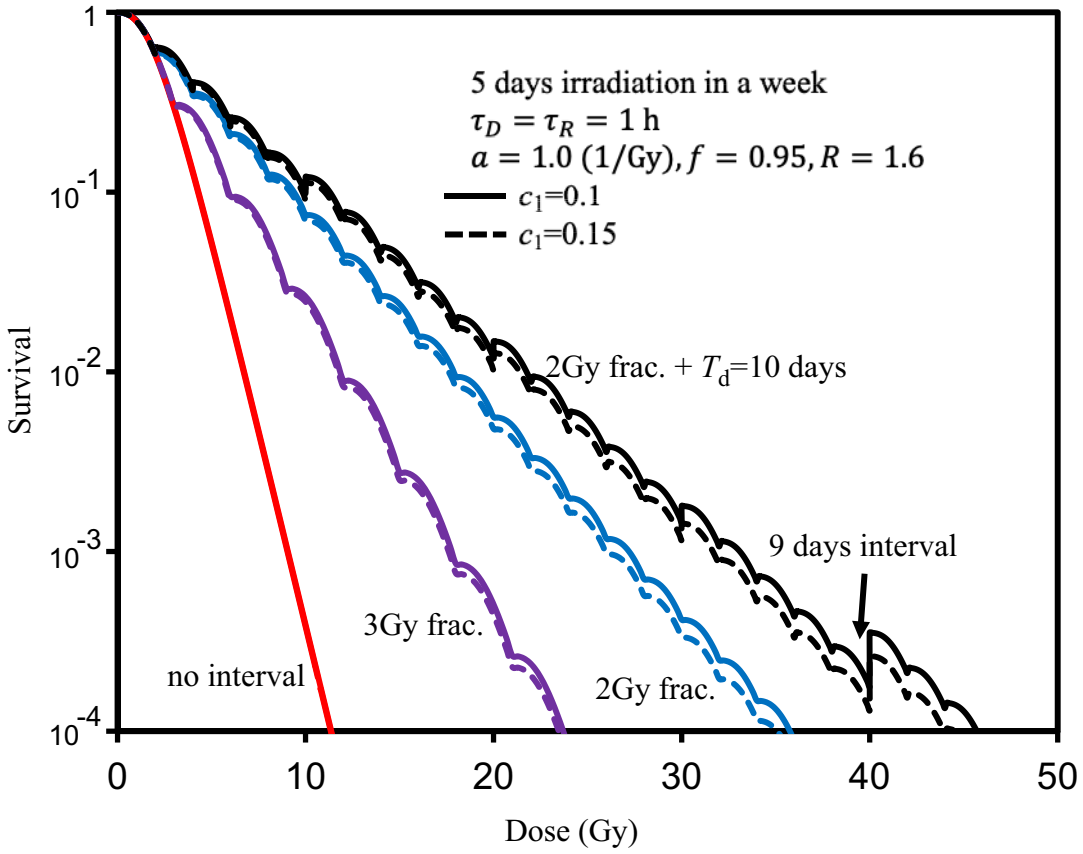

FIG. 4. Effect of the fractionated irradiation on the survival curves. The first curve (red curve) has no interval. The second (purple curve) 3 Gy fractionated dose for every day. The third (blue curve) 2 Gy fractionated dose for every day. The 4th (black curve) 2 Gy fractionated dose for weekdays with 9 days machine trouble. In the case of the 4th, the parameter T_d was set to 10 days as the doubling time. All calculations were performed using two values of c_1 (solid curve: = 0.1, dotted curve: c_1 = 0.15).

they can be confirmed from the shape of the curve. So, it is easy to predict that the solution, especially fR, is close to the true value. (ii) If fR is kept to the result of step (i) in the full data fitting of the next step, f and a are free parameters under condition of $R = \frac{(\text{fixed } fR)}{f}$. With this method, R does not diverge, so there is no problem of large changing R in the second fitting. As for a, the first fitting gives a result close to the true value, so the second fitting brings it even closer to the true value. One can take the result of the second fitting as the final value of a. If the amount of data is insufficient, this two-step method may be effective.

RESULTS OF FITTING

Fitting Performance for a Wide Range of Radiation Doses

In cases where the radiation dose exceeds approximately 5 Gy, the proposed model with repairability could consistently explain the experimental data of the survival curve. We investigated the fitting performance of the new model [Eq. (9)] in comparison to others by calculating the Akaike Information Criterion (AIC). As the formula of AIC under the framework of weighted least squares estimation (*31*), we used the following equation. Here, the weight of the squared residual is given by the standard deviation (σ_i) of each data.

$$\mathrm{AIC} = 2k_\mathrm{P} + n\ln(2\pi) + 2\sum_{i=1}^{n}\ln\sigma_i + \sum_{i=1}^{n}\frac{(y_i - F(x_i))^2}{{\sigma_i}^2} \tag{19}$$

Where, (x_i, y_i) is a data set of dose and survival fraction, F is the result of calculation, n is the number of survival data, k_P is the number of parameters in F. Typical data of survival for large dose is shown in Fig. 5 with fitting curves for LQ (dotted line) and the new (solid line) models. Here, parameters f and c_1 are fixed at 0.9 and 0.1. Data in the range of 24 Gy indicates survival of V-79 cells exposed to X rays (*32*). AIC was −258 and −264 for LQ (2 parameters) and the present model (2 parameters), respectively. Parameters a and R were 0.709 (1/Gy) and 2,57 in Eq. (9). Data in the range 10 Gy represents the survival of human mammary epithelial cell line MCF-12A exposed to 200 kV X-rays (*16*), with AIC of −38 and −43

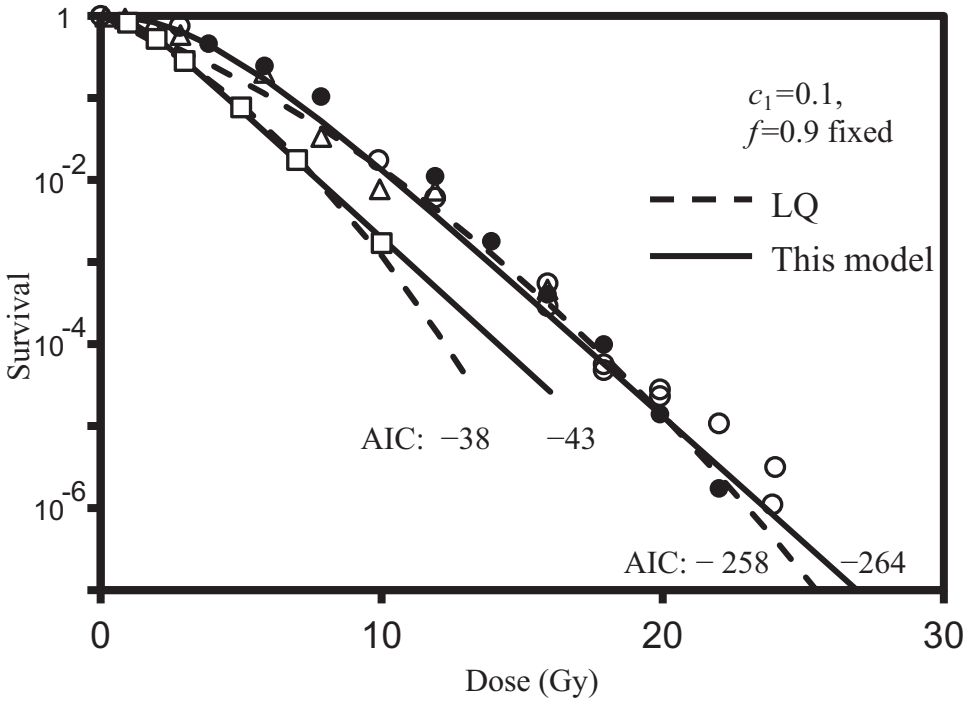

FIG. 5. Fitting performance of the proposed model for a wide range of irradiated doses. Solid curves are the results of fitting with the new model. Dashed curves are the results of the LQ model. Closed circles, open circles, closed triangles, and open triangles are the data of V-79 cells exposed by X rays (*32*). The symbols are the same as in the original. Open squares are the data of MCF-12A exposed by X rays (*16*).

for LQ and the present model, respectively. Parameters a and R were 0.720 (1/Gy) and 0.349 in Eq. (9). The error of the survival data of V-79 was obtained from the original paper. The relative errors of MCF-12A were set as 10% for small doses (<8 Gy) and 20% for large doses, from the evaluation of data fluctuation. Fitting is performed using the least square method with weight calculated as the reciprocal of the squared error. In the proposed model, there is a complementary fitting correlation between R and a, and when the amount of data at a large dose is insufficient, R tends to diverge. The standard deviation calculated with error propagation for parameter a was 4% (V-79), 3% (MCF-12A) and the error for R was 25% (V-79), 38% (MCF-12A). The magnitude of the error is thought to be related to the tendency of R to diverge as described before. The values of AIC of the proposed model show a small difference in comparison to linear quadratic, but it is not a significant difference. Here, we do not include the number of the parameters which are kept fixed value in the calculation of AIC. So, the AIC values cannot be simply compared between LQ and the present model. Assuming that the fixed parameters have degrees of freedom, the number of parameters should be considered in the AIC value, and as the result, the AIC values are very similar between different models.

Effect of Dose Rate

We assessed the effect of dose rate in the lethal and potentially lethal (LPL) model by using the formula in the original paper (*23*) by removing the contradiction contained in the low-dose-rate region of the original data. For two data series with very small dose rates in the original data, reversed order occurs, therefore the new model that gives meaning to the parameters introduces a distortion in the fitting. After removing one data series with the lowest dose rate, the proposed method [Eq. (16)], LQ2 model (*29*) and sub-lethal damage repair (SLDR) model (*33*) were applied to describe the data, by using the least mean square method with weights (30% error, as a preliminary estimation). Since the calculation results are very similar, only the results of the proposed method are shown in Fig. 6. Conditions under which proliferation is suppressed in experiments are assumed. The number of free parameters used for fitting is four [$a = 0.563 \pm 4.4\%$ (1/Gy), $f = 0.838 \pm 2.3\%$, $R = 4.12 \pm 12\%$ and $\tau_S = 4.68 \pm 8.9\%$ (h), c_1 is fixed at 0.15, and τ_R is set at the same value as τ_S]. Error (%) was calculated as previously described. When the dose rate is high, this curve is dominated by "the slope of a" indicating the total amount of damage. In Fig. 6, a comparison of AIC for three models shows that the present model (−816) is very similar to those of LPL (−791), LQ2 (−788) and SLDR (−815). In the new model, temporal depletion of repairability is substituted for sublethal state changes, and thus comparable fitting performance is obtained to other models.

c_1 is a parameter that indicates the range of influence by one hit, and 0.15 for low LET is considered to be acceptable within the range of ambiguity regarding the definition of the domain in a cell.

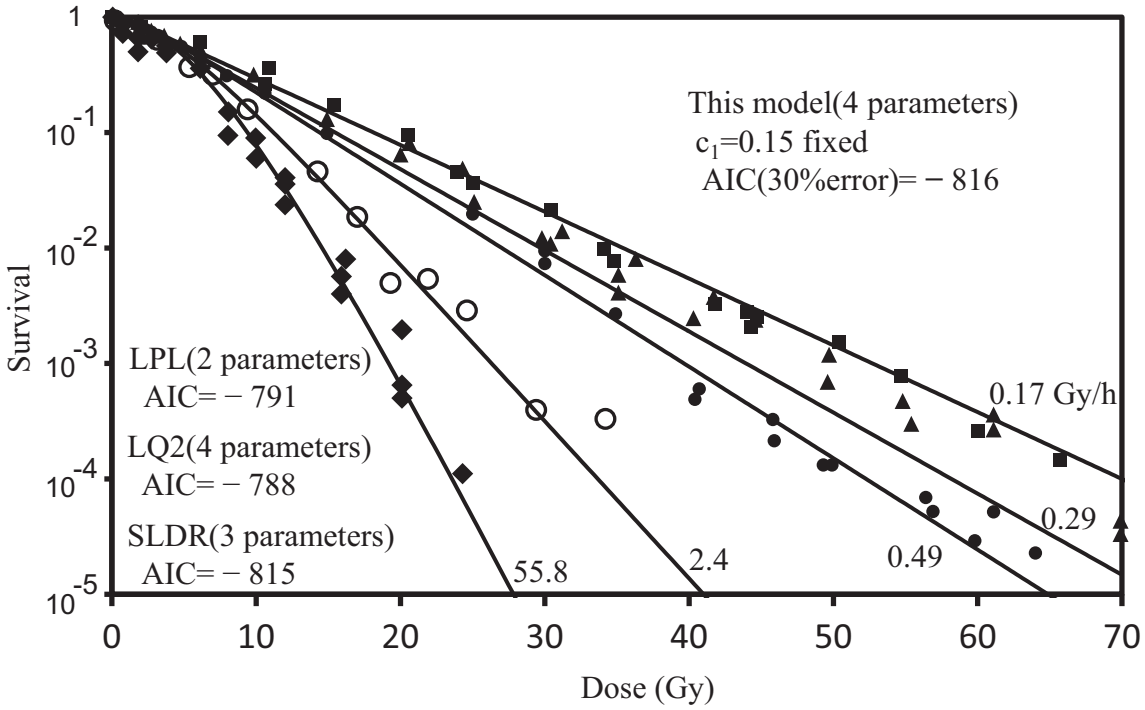

FIG. 6. Survival curves of the new model for low-dose-rate irradiation. Data are described in the analysis of the LPL model (*23*). The dose rate is varied from 0.17 Gy/h to 55.8 Gy/h. The symbol is different for each dose rate.

Systematic Fitting Using Crossover Parameters

A systematic fitting with many data (*34–37*) is performed by using this model. In the proposed model, each parameter has a clear meaning, and in principle, it is possible to use common parameters for experimental data having common conditions. A method of performing fitting of different data sets all at once using common parameters is proposed by using crossover parameters determined by radiation type and cell type. This method requires fewer parameters than traditional methods.

In an example of the fitting, parameter optimization by the least square method was performed once using all data in Figure 7. Data included 3 types of cell lines, and one cell line provided oxic and hypoxic conditions (*38*)(*39*)(*40*). In the case of conventional two- or three-parameter fitting (LQ or LQL or others) for 11 sets of data, 22 or 33 parameters are necessary. On the other hand, this fitting with common parameters can reduce the degrees of freedom. Fitting was carried out in consideration of experimental errors for all data. The figure shows an error only in the case of HSG irradiated by X-rays. In the preliminary calculation, the fitting parameter f results in very similar values for all cases considered. Therefore, the parameter f is set finally as identical to the value of 0.9. Data of hypoxic state can be expressed by using a parameter of Oxygen Enhancement Ratio (OER). It was defined to affect only as a coefficient of parameter a. Parameters a and R are common for both states. The number of free parameters in fitting with the present model was 11 in Table 1 except for 4 fixed parameters. As previously mentioned, the fitting instability which depends on the relationship between parameters a and R must be overcome by devising an appropriate calculation method. Here R_ons is pre-decided by the method. The method of predetermining R is similar to step (i) above, but here f is kept to predetermined value. All parameters calculated by fitting are given %errors. It was found that the error of a particular parameter (R) exceeded 100%. The reason for this is thought to be the imbalance in sensitivity to experimental error and the instability of fitting due to the correlation between parameters. This systematic fitting using all data was performed with f, c_1 and R_ons held at predetermined values.

DISCUSSION

Comparison with LPL Model

The LPL model does not consider the temporary depletion of repairability. Instead, it considers the time taken for repair and expresses the time dependence of damage recovered after irradiation. As a result, the new model and LPL differ in their treatment of changes in survival when the dose rate is sufficiently high. In the new model, the slope is determined simply by the amount of damage. As a feature common to the two models, for a low dose rate, the slope in both models is determined by the amount of damage that cannot be repaired. In the comparison of fitting performance shown by AIC between

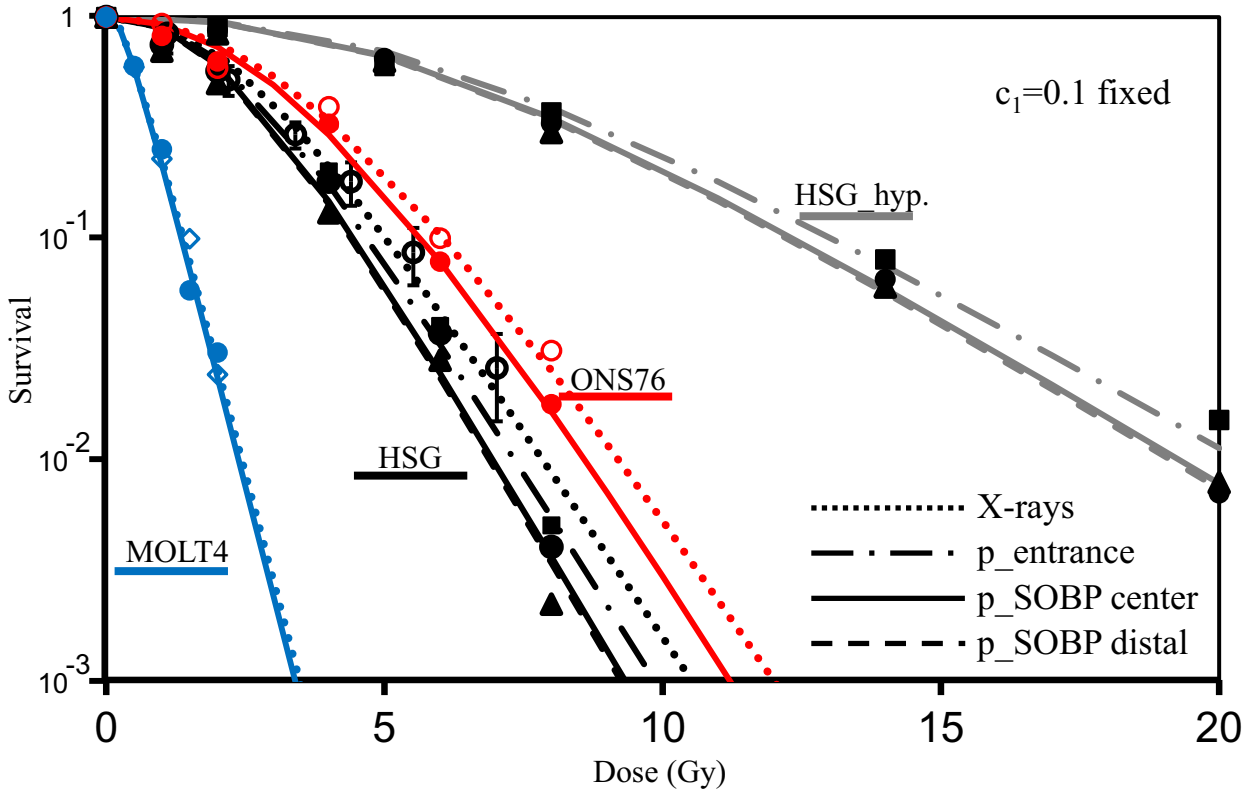

FIG. 7. Systematic fitting with crossover parameters for three cell types including hypoxic condition. Cell lines are indicated by color. Black: HSG, Red: ONS76, Blue: MOLT4 and, Gray: Hypoxic HSG. Closed symbols are data of protons at three different depths (entrance: closed square, SOBP center: closed circle, SOBP distal end: closed triangle) (*38, 39*). Open symbols are data for X rays (*40*). The dotted curve is the result of fitting for cells exposed by X rays. Dash-dot curves, solid curves, and dashed curves are the results of fitting for protons entrance, SOBP center, and SOBP distal.

this model and LPL model, no significant difference was observed.

Comparison with SR and SRS Model

The saturated repair (SR) model proposed by Ando *et al.* (*26*) is characterized by using two parameters and is easy to fit the survival data. The definition of repairability is very similar to that of the proposed model. Since the SR model does not have an independent parameter that determines the slope at low doses, it is impossible to treat the repairability and the unrepairable damage independently. The simple repair saturation (SRS) model uses a very similar scheme of formulation in the differential equation as the present model (*41*). As the result, the survival curve for one fractionated dose has a similar formulation to each other, (i.e., A, B_0, and A/C are analogous to a, f, and R, respectively). The difference between this study and the SRS model is the consideration of the range of the spread of damage (parameter c_1) on one or two domains by one hit of radiation.

Limitations of the New Model

As mentioned above, compared to the LQ model, which shows stable fitting performance, the fitting of this model has instability due to the correlation between R and a. The two-step method proposed here is one solution in case of

TABLE 1
Parameters of Fitting in Fig. 7

cell	MOLT4		HSG					HSG_hyp			ONS76	
radiation	p_center	X	p_entrance	p_center	p_distal	X		p_entrance	p_center	p_distal	p_center	X
R	R_molt 0.146 (106%)					R_hsg 2.193 (112%)					R_ons, 4.0 fixed	
a	a_molt_c, 2.210 (9.2%)	a_molt_X, 2.262 (10%)	a_e, 0.970 (26%)	a_c, 1.023 (25%)	a_d, 1.033 (25%)	a_hsg_X, 0.911 (30%)	OER, 2.774 (2.5%)	a_e/OER	a_c/OER	a_d/OER	a_ons_c, 0.966 (2.3%)	a_ons_X, 0.901 (2.5%)
f	f_X and f_p = 0.9 fixed, c_1 = 0.1 fixed											
precondition	R_ons is manually determined consistent values. Parameter f is identical for X-ray and proton.											

Notes. Here, "hyp" means the condition of hypoxic. "p" or "X" means irradiation by protons or X rays. "e -entrance", "c - center" and "d - distal" mean the positions in the spread-out Bragg peak (SOBP) of proton depth dose distribution. Numbers in parentheses are percent uncertainty.

getting instability in the fitting. In some calculation, fitting is performed by keeping fixed values as 1 and 2 parameters to avoid instability, and the number of parameters is not considered in AIC. So, the AIC values can't be simply compared between curves as a result in the case of appearance of instability. Considering the fixed parameters, it is thought that the difference in AIC will be very small. This means that the fitting likelihood is equivalent for the models used here.

To effectively use systematic fitting, data should not include contradictory values as components. The inclusion of contradictory data not only affects parameters but also greatly hinders fitting. In other words, this technique may be used to detect data anomalies.

Insensitivity to repair activation at a low dose (*7, 11*) is not considered in this model. To consider it we require modification of the repair component and also need more data in the low-dose region. The saturation of damage that occurs at an ultra-high dose rate is not included in this model (*42*). The new concept of DSB drifting and pairing (*22*) is also not considered in this study.

SUMMARY

The fitting performance for a wide range of irradiation doses was presented. The values of AIC of the new model do not show a statistically significant difference in comparison to LQ or others. The new model enables an explanation of the survival curve that changes with the dose rate as well as the LPL model. The difference in concept from LPL produces formula differences, especially under high-dose-rate conditions. As with other models, systematic fitting under different experimental conditions is important for a holistic view of radiation quality and biological properties. This model with 11 free and 4 fixed parameters was shown to reduce the number of parameters required in this systematic fitting in comparison to LQ model with 22 parameters. The disadvantage of this model is the instability of parameter optimization. The complementary correlation of the two parameters may cause the fitting to diverge. A two-step method has been proposed to address this. In addition, if R can be fixed in advance, stability of calculation can be obtained. By using a time-dependent equation, the effects of fractionated radiation can be calculated under various conditions. The effects of restoration of repairability, intermittent irradiation, cell proliferation, etc. can be calculated. In the case of explaining the shape of the survival model, we've assumed some values of parameters without fitting process, but it's important to make all parameters, such as doubling time, realistic values for practical use with big data of radiation biology.

APPENDIX

The model group in Fig. 1 is divided into six categories. These are: 1.Target theory (TT) (*43*), Modified TT (*44*), Two components (*27*), Generalized TT (*37, 45*); 2. LQ and linear model [Kavanagh-Newman (*27*), NcKenna-Ahmad (*27*), LQ (*2, 3, 28, 46*), Linear 2-quadratic (*34*), Modified LQ (*30, 47*), LQ-linear (*8*), Universal survival curve (*48*) Γ-LQ (*17*)]; 3. Microdosimetric kinetic model (dual radiation action (*49*), MK (*50, 51*), Integrated MK (*33*), Modified MK (*18, 52–54*), Stochastic MK (*13*); 4. DSB simulation (two-lesion kinetic (*29, 55*), Local effect (*19, 24*), Giant loop binary lesion (*56*), Cluster lesion (*57, 58*); 5. Lethal and repair model [lethal and potentially lethal (LPL) (*23, 59*), Repair mis-repair (*60*), Repairable-conditionally repairable (*35, 61, 62*)]; and 6. Repair saturation [repair saturation (*63*), saturated repair (*25, 26*), simple repair saturation (*40*)].

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REFERENCES

1. Crowther JA. Some considerations relative to the action of X-rays on tissue cells. Proc R Soc London Ser B, Contain Pap a Biol Character. 1924; 96(674):207–11.
2. Chadwick KH, Leenhouts HP. A molecular theory of cell survival. Phys Med Biol. 1973; 18(1):78–87.
3. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol. 1989; 62(740):679–94.
4. McMahon SJ. The linear quadratic model: Usage, interpretation and challenges. Phys Med Biol. 2019; 64(1).
5. Kuperman VY, Spradlin GS. Effect of variable dose rate on biologically effective dose. Int J Radiat Biol. 2013; 89(11):889–97.
6. Ma NY, Tinganelli W, Maier A, Durante M, Kraft-Weyrather W. Influence of chronic hypoxia and radiation quality on cell survival. J Radiat Res. 2013; 54(SUPPL.1):i23–30.
7. Matsuya Y, Sasaki K, Yoshii Y, Okuyama G, Date H. Integrated Modelling of Cell Responses after Irradiation for DNA-Targeted Effects and Non-Targeted Effects. Sci Rep. 2018; 8(1):AN4849.
8. Guerrero M, Carlone M. Mechanistic formulation of a lineal-quadratic-linear (LQL) model: Split-dose experiments and exponentially decaying sources. Med Phys. 2010; 37(8):4173–81.
9. Bodgi L, Canet A, Pujo-Menjouet L, Lesne A, Victor JM, Foray N. Mathematical models of radiation action on living cells: From the target theory to the modern approaches. A historical and critical review. J Theor Biol. 2016; 394:93–101.
10. Okamoto H, Kanai T, Kase Y, Matsumoto Y, Furusawa Y, Fujita Y, et al. Relation between lineal energy distribution and relative biological effectiveness for photon beams according to the microdosimetric kinetic model. J Radiat Res. 2011; 52(1):75–81.
11. Scheidegger S, Fuchs HU, Zaugg K, Bodis S, Füchslin RM. Using state variables to model the response of tumour cells to radiation and heat: A novel multi-hit-repair approach. Comput Math Methods Med. 2013; 2013.
12. Garcia LM, Leblanc J, Wilkins D, Raaphorst GP. Fitting the linear-quadratic model to detailed data sets for different dose ranges. Phys Med Biol. 2006; 51(11):2813–23.
13. Sato T, Masunaga SI, Kumada H, Hamada N. Microdosimetric Modeling of Biological Effectiveness for Boron Neutron Capture Therapy Considering Intra- and Intercellular Heterogeneity in 10B Distribution. Sci Rep. 2018; 8(1):AN988.
14. Matsumoto Y, Matsuura T, Wada M, Egashira Y, Nishio T, Furusawa Y. Enhanced radiobiological effects at the distal end of a clinical proton beam: In vitro study. J Radiat Res. 2014; 55(4):816–22.
15. Marshall TI, Chaudhary P, Michaelidesová A, Vachelová J, Davídková M, Vondráček V, et al. Investigating the Implications of a Variable RBE on Proton Dose Fractionation Across a Clinical Pencil Beam Scanned Spread-Out Bragg Peak. Int J Radiat Oncol Biol Phys. 2016; 95(1):70–7.

16. Lehnert A, Lessmann E, Pawelke J, Dörr W. RBE of 25 kV X-rays for the survival and induction of micronuclei in the human mammary epithelial cell line MCF-12A. Radiat Environ Biophys. 2006; 45(4):253–60.
17. Scheidegger S, Lutters G, Bodis S. A LQ-based kinetic model formulation for exploring dynamics of treatment response of tumours in patients. Z Med Phys. 2011; 21(3):164–73.
18. Kase Y, Kanai T, Matsumoto Y, Furusawa Y, Okamoto H, Asaba T, et al. Microdosimetric Measurements and Estimation of Human Cell Survival for Heavy-Ion Beams. Radiat Res. 2006; 166(4):629–38.
19. Friedrich T, Durante M, Scholz M. The Local Effect Model – Principles and Applications. 2013; 5–7. Available from: https://three.jsc.nasa.gov/articles/LEM_20130426.pdf
20. Goodhead DT. Initial events in the cellular effects of ionizing radiations: clustered damage in DNA. Int J Radiat Biol. 1994; 65(1):7–17.
21. Scholz M, Kraft G. Track structure and the calculation of biological effects of heavy charged particles. Adv Sp Res. 1996; 18(1–2):5–14.
22. Vadhavkar N, Pham C, Georgescu W, Deschamps T, Heuskin AC, Tang J, et al. Combinatorial DNA damage pairing model based on x-ray-induced foci predicts the dose and LET dependence of cell death in human breast cells. Radiat Res. 2014; 182(3):273–81.
23. Curtis SB. Lethal and potentially lethal lesions induced by radiation. Radiat Res. 1986; (106):252–70.
24. Tommasino F, Friedrich T, Scholz U, Taucher-Scholz G, Durante M, Scholz M. A dna double-strand break kinetic rejoining model based on the local effect model. Radiat Res. 2013; 180(5):524–38.
25. Goodhead DT. Saturable repair models of radiation action in mammalian cells. Radiat Res Suppl. 1985; 104:S58–67.
26. Ando K, Goodhead DT. Dependence and independence of survival parameters on linear energy transfer in cells and tissues. J Radiat Res. 2016; 57(6):596–606.
27. Andisheh B, Edgren M, Belkić D, Mavroidis P, Brahme A, Lind BK. A comparative analysis of radiobiological models for cell surviving fractions at high doses. Technol Cancer Res Treat. 2013; 12(2):183–92.
28. Brenner DJ, Hlatky LR, Hahnfeldt PJ, Huang Y, Sachs RK. The linear-quadratic model and most other common radiobiological models result in similar predictions of time-dose relationships. Radiat Res. 1998; 150(1):83–91.
29. Guerrero M, Stewart RD, Wang JZ, Li XA. Equivalence of the linear-quadratic and two-lesion kinetic models. Phys Med Biol. 2002; 47(17):3197–209.
30. Guerrero M, Li XA. Extending the linear-quadratic model for large fraction doses pertinent to stereotactic radiotherapy. Phys Med Biol. 2004; 49(20):4825–35.
31. Banks HT, Joyner ML. AIC under the framework of least squares estimation. Appl Math Lett. 2017; 74:33–45.
32. Tobias CA, A. BE, Ngo FQH, Yang TCH. The Repair-Misrepair Model of Cell Survival. Lawrence Berkeley Laboratory RECENT WORK. 1980.
33. Matsuya Y, McMahon SJ, Tsutsumi K, Sasaki K, Okuyama G, Yoshii Y, et al. Investigation of dose-rate effects and cell-cycle distribution under protracted exposure to ionizing radiation for various dose-rates. Sci Rep. 2018; 8(1):AN8287.
34. Kundrät P. Detailed analysis of the cell-inactivation mechanism by accelerated protons and light ions. Phys Med Biol. 2006; 51(5).
35. Antonovic L, Brahme A, Furusawa Y, Toma-Dasu I. Radiobiological description of the LET dependence of the cell survival of oxic and anoxic cells irradiated by carbon ions. J Radiat Res. 2013; 54(1):18-26.
36. Rørvik E, Thornqvist S, Stokkevag CH, Dahle TJ, Fjæra LF, Ytre-Hauge KS. A phenomenological biological dose model for proton therapy based on linear energy transfer spectra. Med Phys. 2017; 44(6):2586-2594.
37. Zhao L, Mi D, Hu B, Sun Y. A generalized target theory and its applications. Sci Rep. 2015; 5:AN14568.
38. Gerelchuluun A, Hong Z, Sun L, Suzuki K, Terunuma T, Yasuoka K, et al. Induction of in situ DNA double-strand breaks and apoptosis by 200 MeV protons and 10 MV X-rays in human tumour cell lines. Int J Radiat Biol. 2011; 87(1):57–70.
39. Kanemoto A, Hirayama R, Moritake T, Furusawa Y, Sun L, Sakae T, et al. RBE and OER within the spread-out Bragg peak for proton beam therapy: In vitro study at the Proton Medical Research Center at the University of Tsukuba. J Radiat Res. 2014; 55(5):1028–32.
40. Aoki-Nakano M, Furusawa Y, Uzawa A, Matsumoto Y, Hirayama R, Tsuruoka C, et al. Relative biological effectiveness of therapeutic proton beams for HSG cells at Japanese proton therapy facilities. J Radiat Res. 2014; 55(4):812–5.
41. Sanchez-Reyes A. A simple model of radiation action in cells based on a repair saturation mechanism. Radiat Res. 1992; 130(2): 139–47.
42. Buonanno M, Grilj V, Brenner DJ. Biological effects in normal cells exposed to FLASH dose rate protons. Radiother Oncol. 2019; 139:51–5.
43. Nomiya T. Discussions on target theory: Past and present. J Radiat Res. 2013; 54(6):1161–3.
44. Ballarini F. From DNA radiation damage to cell death: Theoretical approaches. J Nucleic Acids. 2010; 2010:AID350608.
45. Zhao L, Wu D, Mi D, Sun Y. Radiosensitivity and relative biological effectiveness based on a generalized target model. J Radiat Res. 2017; 58(1):8–16.
46. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. Br J Radiol. 1985; 58(690):515–28.
47. Rutz HP, Coucke PA, Mirimanoff RO. A linear-quadratic model of cell survival considering both sublethal and potentially lethal radiation damage. Radiother Oncol. 1991; 21(4):273–6.
48. Park C, Papiez L, Zhang S, Story M, Timmerman RD. Universal Survival Curve and Single Fraction Equivalent Dose: Useful Tools in Understanding Potency of Ablative Radiotherapy. Int J Radiat Oncol Biol Phys. 2008; 70(3):847–52.
49. Kellerer AM, Rossi HH. A generalized formulation of dual radiation action. Radiat Res. 1978; 75(3):471–88.
50. Hawkins RB. A microdosimetric-kinetic model of cell death from exposure to ionizing radiation of any LET, with experimental and clinical applications. Int J Radiat Biol. 1996; 69(6):739–55.
51. Hawkins RB. A microdosimetric-kinetic theory of the dependence of the RBE for cell death on LET. Med Phys. 1998; 25(7 I): 1157–70.
52. Kase Y, Kanai T, Matsufuji N, Furusawa Y, Elsässer T, Scholz M. Biophysical calculation of cell survival probabilities using amorphous track structure models for heavy-ion irradiation. Phys Med Biol. 2008; 53(1):37–59.
53. Kase Y, Yamashita W, Matsufuji N, Takada K, Sakae T, Furusawa Y, et al. Microdosimetric calculation of relative biological effectiveness for design of therapeutic proton beams. J Radiat Res. 2013; 54(3):485–93.
54. Matsufuji N. Selection of carbon beam therapy: Biophysical models of carbon beam therapy. J Radiat Res. 2018; 59:i58–62.
55. Stewart RD. Two-lesion kinetic model of double-strand break rejoining and cell killing. Radiat Res. 2001; 156(4):365–78.
56. Herr L, Friedrich T, Durante M, Scholz M. A model of photon cell killing based on the spatio-temporal clustering of DNA damage in higher order chromatin structures. PLoS One. 2014; 9(1):e83923.
57. Ballarini F, Merzagora M, Monforti F, Durante M, Gialanella G, Grossi GF, et al. Chromosome aberrations induced by light ions: Monte Carlo simulations based on a mechanistic model. Int J Radiat Biol. 1999; 75(1):35–46.
58. Ballarini F, Bortolussi S, Clerici AM, Ferrari C, Protti N, Altieri S. From radiation-induced chromosome damage to cell death:

Modelling basic mechanisms and applications to boron neutron capture therapy. Radiat Prot Dosimetry. 2011; 143(2–4): 523–7.

59. Gordon Steel G, Deacon JM, Duchesne GM, Horwich A, Kelland LR, Peacock JH. The dose-rate effect in human tumour cells. Radiother Oncol. 1987; 9(4):299–310.

60. Tobias CA. The repair-misrepair model in radiobiology: comparison to other models. Radiat Res Suppl. 1985; 8:S77–95.

61. Makris N, Edgren M, Mavroidis P, Lind BK. Investigation of the dose-and time-dependence of the induction of different types of cell death in a small.-cell lung cancer cell line: Implementation of the repairable-conditionally repairable model. Int J Oncol. 2013; 42(6):2019–27.

62. Iwata H, Matsufuji N, Toshito T, Akagi T, Otsuka S, Shibamoto Y. Compatibility of the repairable-conditionally repairable, multi-target and linear-quadratic models in converting hypofractionated radiation doses to single doses. J Radiat Res. 2013; 54(2): 367–73.

63. Ekstrand KE. The Hug-Kellerer equation as the universal cell survival curve. Phys Med Biol. 2010; 55(10).