CHAPTER FOURTEEN

Mechanistic Repair-Based Padé Linear-Quadratic Model for Cell Response to Radiation Damage

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Abstract

This work is on a novel radiobiologal theory of cell survival after radiation of unspecified modality or quality. The analyzed biophysical model, the Padé linear-quadratic model, for cell surviving fractions and the related observable of clinical usefulness is equally applicable to photon beams, as well as to light (electrons) and heavy (atomic nuclei) charged particles of low, intermediate, or high energies. The presented formalism is valid for both the single cell and entire cell populations. The analyzed description can

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be incorporated into any type of radiation delivery, including all fractionated treatments ranging from the conventional (2 Gy per fraction, one fraction per day), through hyperfractionation (more than one smaller fraction per day) to hypofractionation (larger doses with shorter overall exposure time, as in stereotactic radiosurgery). The major clinical application of the proposed theory is envisaged to be in providing a better input to dose planning systems for radiotherapy, as expected from the clear biological meaning of the derived parameters. The main strength of the Padé linear-quadratic model is in its foundation on the mechanistic description of radiation damage through enzymatic repair systems governed by the Michaelis–Menten catalysis. It is from this latter origin, which passed the test of time in mainstream biochemistry, that the present theory derives its biomedical adequacy. This, in turn, yields a powerful outperformance of the standard linear-quadratic model, the current workhorse of radiobiological modeling for the purpose of radiotherapy, as amply illustrated in the present study.

1. INTRODUCTION

Radiotherapy is multifaceted, since it relies upon interdisciplinary research in order to meet with success, which is the patient's cure. Different radiation qualities or modalities (photons, charged particles, etc.), deposit their energies in the traversed tissue according to different depth-dose profiles. A typical Bragg peak is a remarkable example of such profiles for heavy ions with most energy delivered to the encountered targets, mainly near the very end the beam's traversal. Electrons and photons deposit most of their energy close to the entrance to the tissue. This makes these radiations unsuitable for treating deep-seated tumors. In sharp contrast, high-energy heavy ions can be optimally conformed to the target location deep inside the patient's body. Such a key feature is associated with negligibly small multiple scattering effects of heavy ions due to large masses of atomic nuclei relative to light electrons.

Nevertheless, irrespective of the existence of diametrically opposite dose-depth profiles, all these different radiation modalities produce cell survival curves of a similar kind, characterized by typical sigmoid shapes, as a function of the absorbed dose. Ionization density and linear energy transfer are larger for heavy ions than for X-rays. This is expected to be biologically expressed by the targeted cell in two distinct ways. Indeed, the so-called relative biological effectiveness is typically 2–3 times larger for heavy ions than that of X-rays. Yet, there are some other aspects of a less appreciable variation for different radiation qualities. For example, the numbers of double strand breaks of deoxyribo-nucleic acid (DNA) molecules could

be close to each other for heavy ions and X-rays under the comparable irradiation conditions.

It is of great importance for radiotherapy to have reliable predictions on tumor control and healthy tissue complications. This is where radiobiological modeling comes into its full function to assist tailoring dose planning systems for individual treatments of patients in a manner which is as comprehensive as possible.[1, 2] Biophysical models can, in principle, design dose distributions for each treated patient by taking into account different biological factors ranging from anatomical to physiological. As to the patient, the ultimate goal is to enhance survival and diminish toxicity to the normal tissues. This aim could be attained through several strategies. One of them is an improved understanding of the radiation-tissue interactions on molecular, cellular, and tissue levels. Among other things, this would yield the ever needed amendments of the current dose planning systems. Another strategy is a better comprehension of the individual patient feedback from the administered dose, given that the same amount of the identical irradiation could have markedly different outcomes for different patients with the same type of cancer. These two strategies among others should be considered in concert to achieve the best outcome.

There are two major variabilities in radiation-tissue interactions. One is variability of dose in the irradiated volume. The other is variability of cell response. Both variabilities are multifaceted, ranging from some self-evident to more intricate, hidden aspects. Dose varies through the irradiated tissue due to the stochastic nature of collisions between the beam species and the targeted particles. This does not imply that dose variation is completely random. Certain non-stochastic factors can also influence dose variability, e.g., organ motion, some external settings, etc. Radiation imparts damage to both normal and tumorous cells. Tumor topology is highly complex due to intertwining of healthy with diseased tissue. Critical to the variability of cell responses is the key difference in the way normal and tumor cells cope with the same radiation insult. This variability implies the existence of different interaction mechanisms of radiation with these two kinds of cells. Radically different proliferation rates represent the main cause of unequal mechanisms for healthy and tumor cells. The former have a controllable cell cycle, whereas the latter proliferate uncontrollably with time changing rates.

A key to the overall success of radiotherapy is cell repair of the imparted damage. Therefore, it is of critical importance to investigate various repair mechanisms within the context of the mentioned variabilities

of interactions between the applied radiation and the targeted tissue. This problem is addressed in the present chapter by reference to some of the existing radiobiological models, such as the linear-quadratic (LQ) model[3] as well as from the viewpoint of a recently introduced Padé linear-quadratic model (PLQ).[4–6]

The most salient feature of the three constant parameters $\{\alpha, \beta, \gamma\}$ from the PLQ model is their clear biological interpretation based upon chemical kinetics of the Michaelis–Menten[7] mechanism for cell repair through enzyme-lesion catalysis. This automatically provides a cell surviving fraction $S_{\mathrm{F}}(D)$ of universal validity at all absorbed doses D. Moreover, this biophysical model possesses the built-in correct asymptotic exponential inactivation modes at low and high doses, separated by a shoulder. Further, the passage from the intermediate shoulder region to both small and large doses occurs in a smooth manner through a typical rectangular hyperbola for the dose-modifying factor—the relative effectiveness $\mathrm{RE}(D) = \{1 + (\beta/\alpha)D\}/(1 + \gamma D)$. The main significance of this is to indicate that Barendsen's concept[8] of biologically effective dose (BED) of radiation is not connected to the total absorbed dose D by a simple relation $\mathrm{BED} = \lambda D$, with λ being a proportionality dimensionless constant (dose-independent). Rather, the cell response, mediated by the enzymatic repair of radiation damage, profoundly alters the physical dose D deposited to the tissue through a modifying factor $M(D)$, in the name of the relative effectiveness $M(D) = \mathrm{RE}(D)$. This changes the said simple proportionality relation to a more structured function $\mathrm{BED}(D) = D \cdot \mathrm{M}(D)$, which becomes linear in D at both low and high doses, as indeed is typical for most mammalian cells. Comparison with several representative sets of experimental data for cell surviving fractions is presented to assess the relative performance of the PLQ model and to challenge the LQ model, which is currently the workhorse of radiobiological modeling in radiotherapy.

2. DOSE–EFFECT CURVE (RESPONSE CURVE OR CELL SURVIVING CURVE)

2.1 Poisson distribution of radiation events, mean lethal dose

Belonging to statistical phenomena, the distribution of events involving cell-radiation interactions fluctuates following the Poisson probability. This can be understood from the arguments which run as follows. On the one hand, particle tracks traversing a tissue are certain to cross at least some of the cell structures. On the other hand, randomness of radiation-cell interactions

implies that they are intrinsically uncertain, i.e., probabilistic. For example, single and double strand breaks (SSB, DSB) or any other type of lesions from interactions between the cell and radiation, can take place only with some probability. It is precisely this lack of certainty, which classifies such events as non-deterministic. Upon irradiation, the cell finds itself in a kind of "all-or-nothing" state, as being either alive or dead with respect to its clonogenic ability for proliferation. This naturally leads to the Bernoulli statistics of binary (dichotomous) events. When the number of these events is large, the Bernoulli distribution takes the form of the Poisson distribution. A particular case of this passage from the Bernoulli to the Poisson distribution is interesting to illustrate. In order to highlight this aspect, let us consider some m independent hits that are delivered to the same target. We could inquire about the probability $\pi(m)$ that this target receives no hit. Being independent, each hit has the same probability $1/m$ to arrive at the same target. Conversely, the probability of missing this target is $1 - 1/m$. Furthermore, the probability that all the m hits will miss the target is $(1 - 1/m)^m$. This is precisely the sought probability $\pi(m)$:

$$\pi(m) = \left(1 - \frac{1}{m}\right)^m. \tag{1}$$

In the limit of large values of m, it follows:

$$\lim_{m\to\infty} \pi(m) = \lim_{m\to\infty} \left(1 - \frac{1}{m}\right)^m = \frac{1}{e} \equiv P(0). \tag{2}$$

This is a special case $P(0) = e^{-1}$ of the more general Poisson law for the distribution of a large number m of specific events[†]:

$$P(m) = \frac{x^m}{m!} e^{-x}. \tag{3}$$

Here, x is the *average* number of specific events. For $m = 0$ and $x = 1$, this expression is reduced to:

$$\begin{aligned} P(0) = \frac{1}{e} \approx 0.367879, \quad \text{or,} \\ P(0) \text{ reduced by } 36.7879\% \quad (e \approx 2.71828). \end{aligned} \tag{4}$$

[†] The word specific is used to refer to a particular kind of the cell-radiation interaction, e.g., single or double ionization, excitation, etc.

The classical hit-target model for cell-radiation interaction assumes the Poisson distribution of m events, such as creation of lesions whose average number x is supposed to be directly proportional to the absorbed dose D:

$$x = \frac{D}{D_0}, \tag{5}$$

and therefore,

$$P(m) = \frac{1}{m!}\left(\frac{D}{D_0}\right)^m e^{-D/D_0}. \tag{6}$$

In this model, the number of hits is equal to the number of events, m, and moreover each hit is assumed to lead to a cell inactivation by producing a lethal lesion (cell death). Thus, the probability of survival of a cell as a target is the chance $P(0)$ of not being hit, i.e., when no hit takes place at all, $m = 0$. In the latter case, by setting $x = 1$:

$$x = 1 = \frac{D}{D_0}, \tag{7}$$

it is possible to give the definition of the proportionality constant D_0 in (5) by reference to (3). Namely, since $x = 1$ corresponds to $D = D_0$, as per (7),

$$P(0) = \left\{e^{-D/D_0}\right\}_{x=1, D=D_0} = e^{-1}, \tag{8}$$

we can say that D_0 is a particular dose D, which yields, on the average, one lethal event per target ($x = 1$). Due to this circumstance, D_0 is usually termed *the mean lethal dose*. Moreover, according to (4) and (8), quantity D_0 is the dose at which the surviving fraction is reduced by $1/e \approx 0.367879$, or equivalently, by $36.7879\% \approx 37\%$. Due to this circumstance, D_0 is often called the "37% dose" and accordingly denoted by $D_{37} (= D_0)$. Reciprocal $1/D_0 \equiv k_0$ is the measure of cell sensitivity to radiation and it is called either the inactivation constant or the radiosensitivity constant (or radiosensitivity, for short). By reference to the special name for dose D_0, it is convenient to refer to k_0 as the mean lethal radiosensitivity, because it is also associated with the $1/e$ reduction of the cell surviving fraction. Mathematically, $1/D_0$ is the final slope of the terminal (exponential) part of the cell survival curve at high doses, e^{-D/D_0}. Note that formally the same decay law or cell surviving

fraction applies to a single cell and to a cell population consisting initially of some N_0 cells. Here, the surviving fraction $S_F(D)$ would be defined by N/N_0, with the specification $N/N_0 = e^{-D/D_0}$, where N is the number of the surviving cells after irradiation by dose D. In this case, D_0 would represent the dose needed to deliver an average of one lethal event per cell in a total population of N_0 cells.

The curve for the cell surviving fraction $S_F(D)$ plotted as a function of dose D is called the dose–effect curve or response curve. The latter name is used to indicate that $S_F(D)$ describes the response of the cell to irradiation. This response is the information about the number of cells that survived by absorbing a dose D. Such curves have different characteristics at low, intermediate, and high doses. They seem to decay exponentially at both low and high doses. However, their initial and final slopes are different for these two asymptotes when $D \to 0$ and $D \to \infty$, respectively. At relatively lower doses there is a so-called shoulder. There are three other quantifying characteristics of the dose–effect curves. These are the mean lethal dose D_0, quasi-threshold dose D_q and the extrapolation number n.

2.2 Extrapolation number and quasi-threshold dose

A shoulder in the response curve $S_F(D)$ is situated in the low-dose region, where cell inactivation per unit dose is noticeably smaller than that at high doses. The passage from these two regions of low and high doses is anything but abrupt. Therefore, a transition dose for delineation of the precise extent of the shoulder cannot be sharply determined. Nevertheless, an approximate procedure could still be designed to obtain a reasonable estimate of a dose located near the transition point (threshold) between the terminal part of the dose–effect curve and the shoulder region. For this reason, such a dose is called a threshold dose, or more appropriately, a quasi-threshold dose because of the said uncertainty. An alternative name for the same dose is the shoulder width or the quasi-width. Both names are associated with the symbol D_q. In order to determine D_q, we introduce the high-dose exponential tail or asymptote $S_F^{\infty}(D)$ of $S_F(D)$ as:

$$S_F^{\infty}(D) \equiv e^{\lambda - D/D_0}, \tag{9}$$

or equivalently,

$$S_F^{\infty}(D) \equiv ne^{-D/D_0}, \tag{10}$$

where λ is a positive constant connected to the extrapolation number n by the relation:

$$\lambda = \ln n > 0, \quad n > 1. \tag{11}$$

When this definition is linked to a cell survival curve versus dose, the value D_q is seen as the dose located at a point at which the tangent to $S_F^{\infty}(D)$ crosses the horizontal line parallel to the abscissa D at the height of the ordinate reaching the maximal cell survival, $S_F(0) = 1$:

$$\begin{aligned} &\{\text{Maximal surviving fraction}\}_{D=0} \\ &\quad = \{\text{High dose asymptote of surviving fraction}\}_{D=D_q}. \end{aligned} \tag{12}$$

In other words, D_q is the dose to which the terminating exponential region of $S_F(D)$ is back-extrapolated to the 100% survival level. Relation (12) represents the condition for isosurvival at which the same value of the cell surviving fraction is obtained for two different doses $D = 0$ and $D = D_q$:

$$\left.\begin{aligned} 1 &= e^{\lambda - D_q/D_0} \\ \text{or} \qquad 1 &= n e^{-D_q/D_0} \end{aligned}\right\} \quad \text{(Isosurviving fractions)}. \tag{13}$$

In this case, isosurvival, as the identical surviving fraction at both $D = 0$ and $D = D_q$ is obtained if $\lambda - D_q/D_0 = 0$, so that $e^{\lambda - D_q/D_0} = 1$. Here, 1 (unity) is the maximal survival at $D = 0$, signifying the 100% survival, as it ought to be for any form of $S_F(D)$. Therefore, the isosurvival condition $\lambda - D_q/D_0 = 0$ from (13), or equivalently:

$$\left.\begin{aligned} \ln 1 = 0 &= \lambda - \frac{D_q}{D_0} \\ \ln 1 = 0 &= \ln n - \frac{D_q}{D_0} \end{aligned}\right\}, \tag{14}$$

gives the shoulder quasi-width, or the quasi-threshold dose, D_q as:

$$D_q = D_0 \ln n. \tag{15}$$

If a shoulder is viewed as an indication of the existence of accumulation of sublethal damage, then, e.g., a wide shoulder width D_q would mean that the amount of repaired sublethal damage is large. The name extrapolation number stems from "extrapolating" the terminal, high-dose asymptote ne^{-D/D_0} of the survival curve $S_F(D)$ back to the zero dose ($D = 0$). The intercept of the asymptote ne^{-D/D_0} and the ordinate gives the extrapolation number, $\{ne^{-D/D_0}\}_{D=0} = n$.

3. THE LINEAR-QUADRATIC MODEL

3.1 Biological effect, relative effectiveness, and biologically effective dose

The cell surviving fraction in the linear-quadratic model (LQ) is introduced by:

$$S_{\mathrm{F}}^{(\mathrm{LQ})}(D) = e^{-\alpha D - \beta D^2}, \tag{16}$$

or equivalently,

$$S_{\mathrm{F}}^{(\mathrm{LQ})}(D) = e^{-\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}(D)}, \tag{17}$$

where $\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}$ is the biological effect (BE):

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} \equiv -\ln S_{\mathrm{F}}^{(\mathrm{LQ})}(D) = \alpha D + \beta D^2. \tag{18}$$

This expression can be written in the following two alternative forms:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} = \alpha \mathrm{BED}^{(\mathrm{LQ})}, \tag{19}$$

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} = \xi \mathrm{RE}^{(\mathrm{LQ})}, \tag{20}$$

where ξ is the approximate expected number of lethal lesions:

$$\xi \equiv \alpha D \quad \text{(Expected number of lethal lesions)}. \tag{21}$$

The quantity $\mathrm{BED}^{(\mathrm{LQ})}$ is the LQ-based biologically effective dose:

$$\mathrm{BED}^{(\mathrm{LQ})} = D + \frac{\beta}{\alpha} D^2, \tag{22}$$

whereas the quantity $\mathrm{RE}^{(\mathrm{LQ})}$ is the relative effectiveness (RE) from the LQ model:

$$\mathrm{RE}^{(\mathrm{LQ})} \equiv 1 + \frac{\beta}{\alpha} D. \tag{23}$$

The $\mathrm{BED}^{(\mathrm{LQ})}$ and $\mathrm{RE}^{(\mathrm{LQ})}$ are interconnected through the relationship:

$$\mathrm{BED}^{(\mathrm{LQ})} = D \cdot \mathrm{RE}^{(\mathrm{LQ})}. \tag{24}$$

Thus, the effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}$ can also be understood as being given by the product of the expected number of lesions αD and the relative effectiveness $\mathrm{RE}^{(\mathrm{LQ})}$.

3.2 The Barendsen formula

The simple form (22) of $\mathrm{BED}^{(\mathrm{LQ})}$ is attractive especially in fractionated radiotherapy, because only the ratio β/α is employed, but the separate values of α and β are not required. Based upon the LQ model, the ratios α/β are estimated to be about 3 Gy and 10 Gy for healthy and tumorous tissues, respectively. The specific numerical values for α/β can be fully meaningful only if they are provided by a mechanistically-based radiobiological model which is universally valid at all doses of interest. However, the LQ model is a low-dose approximation. As a consequence, in order to cover all the needed doses, one might be required to perform several (say J) separate fits to the given experimental data resulting in different sets of values $\{\alpha_j/\beta_j\}(j \leqslant J)$ for the selected J dose intervals. This has the drawback of yielding a dose-range dependence of the $\mathrm{BED}^{(\mathrm{LQ})}$, which severely limits inter-comparisons of different patterns of radiation delivery in fractionated radiotherapy. Therefore, it would be desirable to have a model which would give the biologically effective dose applicable to all doses for the same quantifying parameters estimated by using *all* the available experimental data points. Such a feature would enable the extraction of the biologically effective dose from the reconstructed parameters that do not change when passing from one to another dose range. The occurrence that the mentioned ratios α/β are so different for tumorous and normal tissue is an indication of the existence of substantially different mechanisms by which these two types of tissues respond to irradiation. As stated in the Introduction, the main reason for this difference is in the cell proliferation which is uncontrolled (chaotic) in tumor, and well regulated by the cell cycle growth in normal tissue.

What made the LQ model clinically useful was precisely Barendsen's[8] idea about linking the radiation dose with the ensuing biological effect. In general, irrespective of any particular model, this concept states that the biologically effective dose is equal to the product of the total dose D and a dose-modifying factor, which is the relative effectiveness:

$$\text{Biologically effective dose} = \{\text{Total dose}\} \cdot \{\text{Modifying factor}\}, \quad (25)$$

$$\mathrm{BED} = D \cdot \mathrm{RE}. \quad (26)$$

It is through the modifying factor, the RE, that a particular pattern of radiation delivery can be taken into account. This is especially important for fractionated radiotherapy, where the RE can help improve the effectiveness of the specific dose-time schedule by means of which the total dose is administered. In searching for some plausible ways that could make the LQ model clinically applicable, Barendsen[8] entered only the ratio β/α into the dose-dependent relative effectiveness $\mathrm{RE}^{(\mathrm{LQ})}$, but not the individual parameters α and β. Because the quotients of the form β/α are tissue-specific parameters, quantity $\mathrm{RE}^{(\mathrm{LQ})} = 1 + (\beta/\alpha)D$ from (23) can express the differences in radiation effects for various tissues. In other words, $\mathrm{RE}^{(\mathrm{LQ})}$ can be employed to investigate the differences in biological effectiveness among various tissues as a consequence of alterations in the dose delivery patterns. Thus, since different tissue effects are associated with different values of the quotient β/α, it is possible to use Eq. (26) to evaluate alterations in the therapeutic ratio due to changes in fractionation. The therapeutic ratio can be improved by e.g., reducing dose per fraction, in which case there should be proportionally more sparing of the healthy (late reacting) than tumorous (early reacting) tissues. These considerations indicate that the LQ model can be used as a predictive model, when considering certain alternative radiation treatments aimed at maximizing tumorous cell kill effects, while simultaneously minimizing some of the adverse healthy-tissue effects (e.g., normal tissue complication rates). The Barendsen relation (26) is general, as it is not limited to fractionated radiotherapy. Rather, it can be used for an arbitrary kind of radiation treatment. Note that Barendsen[8] originally coined a term "extrapolated response dose" (ERD) in (26). This was subsequently renamed by Fowler[9] to the "biologically effective dose," or the BED, as a better terminology for Barendsen's idea.

3.3 Low- and high-dose asymptotes of biological effect and surviving fraction

The effect (18) in the LQ model has the following asymptotic behavior at infinitesimally small and infinitely large values of D:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} \underset{D\to 0}{\longrightarrow} \alpha D, \tag{27}$$

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} \underset{D\to \infty}{\longrightarrow} \beta D^2, \tag{28}$$

respectively. This gives the corresponding asymptotes for $\mathrm{BED}^{(\mathrm{LQ})}$ as:

$$\mathrm{BED}^{(\mathrm{LQ})} \underset{D\to 0}{\longrightarrow} D, \tag{29}$$

$$\mathrm{BED}^{(\mathrm{LQ})} \underset{D\to \infty}{\longrightarrow} \frac{\beta}{\alpha} D^2. \tag{30}$$

Using the asymptotes (29) and (30) for $\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}$, it follows that the survival curve given by $S_{\mathrm{F}}^{(\mathrm{LQ})}(D)$ from (16) is mainly exponential and Gaussian at small and large values of D:

$$S_{\mathrm{F}}^{(\mathrm{LQ})}(D) \underset{D\to 0}{\longrightarrow} e^{-\alpha D}, \tag{31}$$

$$S_{\mathrm{F}}^{(\mathrm{LQ})}(D) \underset{D\to \infty}{\longrightarrow} e^{-\beta D^2}, \tag{32}$$

respectively. A stronger repair, with a significant ratio β/α, is seen in the plot of cell surviving fraction as a more pronounced shoulder due to the Gaussian with its quadratic term βD^2, which yields a more curved function $S_{\mathrm{F}}^{(\mathrm{LQ})}(D)$. For small β/α, cell kill prevails and $S_{\mathrm{F}}^{(\mathrm{LQ})}(D)$ is less curvy because of the dominance of the purely exponential function. As such, the ratio β/α appears as a measure of the curvature of $S_{\mathrm{F}}^{(\mathrm{LQ})}(D)$ and this influences the cell response to radiation. Moreover, the smaller β/α implies that the dose-response relationship will be less sensitive to fractionation when fractionated radiotherapy is applied. Conversely, the larger β/α means that radiation damage was accumulated to a sufficient level to produce various lesions in DNA molecules. In such a case of an elevated β/α, the repairing molecules are triggered more proactively, so that repair of repairable lesions can become a key factor in determining the overall biological response of the cell to radiation.

The number of lesions could be assumed to be proportional to D as indicated in (21). Therefore, the LQ-based effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} = (\alpha D)(1 + \beta D/\alpha)$ from Eq. (18), interpreted as the yield of elementary lesions, is proportional to the product of the average number of primary lesions ($\sim D$) and the average energy deposited around the lesions ($\sim \{1 + \beta D/\alpha\}$). This can also be written as:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} = \beta D(\zeta + D) = \beta D\,(z_{\mathrm{D}} + D)\,, \tag{33}$$

where,

$$\zeta \equiv z_D = \frac{\alpha}{\beta}. \tag{34}$$

Parameter ζ (or $z_D \equiv \bar{z}_D$) is a microdosimetric quantity called the "dose-averaged" specific energy, which is given in terms of a sequence of increments of the specific energy z associated with single events:

$$z_D \equiv \zeta = \frac{1}{z_F}\int_0^\infty dz\, z^2 f_1(z), \quad z_F = \int_0^\infty dz\, z f_1(z), \tag{35}$$

where $\bar{z}_F \equiv z_F$ is the "frequency-averaged" specific energy.‡ The term "frequency" refers to the frequency of occurrence of single events in a given volume. Quantity $f_1(z)dz$ is the probability distribution in z, where the subscript "1" refers to single events alone. Event distributions appear in the analysis because ionizing collisions are random and, therefore, the energy deposited in the tissue by such collisions represents a stochastic quantity or variable. In the microdosimetric formalism, the average number of events $\bar{N}$ at a fixed dose D is given by $\bar{N} = \lceil D/z_F \rceil$, where $\lceil r \rceil$ is the ceiling symbol which denotes the largest integer obtained by rounding up the number r, which can be a rational or any other real number or a real value of any function.

4. THE PADÉ LINEAR-QUADRATIC MODEL

4.1 Differentiation between physical and biological doses

As mentioned, the two most salient aspects of the cell surviving fraction, $S_F(D)$, are the direct cell kill and cell repair. They can be simultaneously taken into account by introducing a biological dose D_B to be determined for the given physical, single radiation dose D. The sought dose D_B can be found from the Poisson statistics. In the context of radiation damage, the targeted cell is certain to survive if it receives no dose when the dose D_B is expected to be absorbed. The chance for such an event to occur is given by the Poisson probability:

$$P(0) = e^{-\mu D_B}, \tag{36}$$

‡ In microdosimetry, a single absorbed dose D is defined as the expected value of the so-called specific energy z. On the other hand, specific energy z is the energy per unit mass per unit volume deposited per event per cell nucleus.

where μ is the repair constant in units of Gy^{-1}. The constant $\mu \geqslant 0$ is connected to the repair time τ during which the cell becomes effectively insensitive to any two consecutive hits (events, particle or ray traversals through the treated tissue) whenever they follow each other within the time interval Δt, which is smaller than the recovery time ($\Delta t < \tau$). When the repair mechanism is activated, the delivered physical dose D is reduced and becomes only an apparent dose D_{appar}. On the other hand, the true dose D_{true}, which is actually received by the cell, represents the biological dose D_{B}. In other words, repair effectively diminishes the values of D and transforms it to D_{B}. The difference between D and D_{B} is that the latter accounts for a correction due to the missed/wasted hits during the time lag $\Delta t < \tau$ whenever $\tau > 0$. Such a discrepancy between D and D_{B} can be modeled by the said Poisson probability $P(0)$. This settles the issue of the *definition* of $D_{\mathrm{B}} = D_{\mathrm{B}}(D)$ for a fixed D as:

$$D_{\mathrm{B}} P(0) = D, \tag{37}$$

or explicitly,

$$D_{\mathrm{B}} e^{-\mu D_{\mathrm{B}}} = D, \tag{38}$$

where,

$$D \leqslant D_{\mathrm{B}}. \tag{39}$$

Employing the alternative notation:

$$D_{\mathrm{appar}} \equiv D, \quad D_{\mathrm{true}} \equiv D_{\mathrm{B}}, \tag{40}$$

we can rewrite (38) as:

$$D_{\mathrm{true}} e^{-\mu D_{\mathrm{true}}} = D_{\mathrm{appar}}, \tag{41}$$

$$D_{\mathrm{appar}} \leqslant D_{\mathrm{true}}. \tag{42}$$

It will also prove useful to introduce a repair degree by the following quotient of doses:

$$\nu \equiv \frac{D_{\mathrm{appar}}}{D_{\mathrm{true}}} = \frac{D}{D_{\mathrm{B}}}, \quad 0 \leqslant \nu \leqslant 1 \quad \text{(Cell repair measure or degree)}. \tag{43}$$

The mechanism driving the pattern (38), or equivalently (41), which describes the cell recovery during the repair time τ consists of the following twofold pattern:

(a) What is usually considered to be a single absorbed dose D is modified by repair to become merely an apparent dose D_{appar}, which is smaller than the true dose D_{true}, which is expected to be deposited to the sensitive part of the cell.

(b) A measure or degree of the cell repair is the quotient ν of D_{appar} and D_{true} from (43) as given by the Poisson probability (38) that the cell receives no dose when the dose $D_{\text{true}} = D_{\text{B}}$ is anticipated. This degree varies from 0 to 1 due to its coincidence with the Poisson probability (36) via $\nu = P(0) = e^{-\mu D_{\text{true}}} = e^{-\mu D_{\text{B}}}$.

The inequality in (39) is evident from e.g., (41) where D_{true} has to be exponentially damped via $D_{\text{true}} e^{-\mu D_{\text{true}}}$ to become equal to D_{appar} as $D_{\text{true}} e^{-\mu D_{\text{true}}} = D_{\text{appar}}$. Stated equivalently, the apparent dose $D_{\text{appar}} = D$ is smaller than its true counterpart $D_{\text{true}} = D_{\text{B}}$ because D ought to be enhanced by a positive factor $1/P(0) = e^{\mu D_{\text{B}}}$ in order to match the value D_{B} through:

$$D e^{\mu D_{\text{B}}} = D_{\text{B}}. \tag{44}$$

Parameter μ could be related to the microdosimetric dose-averaged specific energy $z_{\text{D}} = \zeta$ from (34). In microdosimetric formalism, the probability of receiving no dose when the dose D_{B} is expected is given by $P(0) = e^{-D_{\text{B}}/z_{\text{D}}}$. This is the same Poisson formula which is in the formalism of this Section denoted by $P(0) = e^{-\mu D_{\text{B}}}$ in (36). Therefore, the parameter μ from (36) or (38) could have a microdosimetric meaning, in which case it would represent the reciprocal of the dose average specific energy:

$$\mu = \frac{1}{z_{\text{D}}} \equiv \frac{1}{\zeta}. \tag{45}$$

With this relation, a link to the parameters α and β from the LQ model can readily be made. Parameter z_{D}, which appears in the second moment of the dose-averaged specific energy has already been identified in dosimetry as $z_{\text{D}} = \alpha/\beta$ and, therefore:

$$\mu = \frac{\beta}{\alpha}. \tag{46}$$

It is important to formulate the following inverse dose problem for radiobiological modeling:

$$\left.\begin{array}{l}\text{Given the physical dose } D \text{ applied to the treated tissue,}\\ \text{what would be the biological dose } D_{\text{B}} \text{ received by}\\ \text{the irradiated cells when the cell repair system is active?}\end{array}\right\}. \tag{47}$$

Within the Poisson statistics (36), one of the possible answers to this question is given by the exact real-valued solution D_{B} of the transcendental equation (38).

If D_{B} were known, the dose which was applied to the tissue could be retrieved by a direct computation of the so-called Ricker function, $D_{\mathrm{B}}e^{-\mu D_{\mathrm{B}}}$. Then the inverse Ricker function would give D. In reality, however, the biological dose D_{B} is unknown, but could nevertheless be determined by finding the inverse Ricker function. Although the exact inverse Ricker function is known and can be used through the Lambert function,[4, 10] in the present work we shall deal with a simpler and more instructive exposition. To this end, we shall derive an approximate solution for D_{B} from the non-linear, transcendental equation (38) through the process of linearization, by using only the known simplest elementary functions. With this goal, we start from (44) where we use the series for the exponential $e^{\mu D_{\mathrm{B}}}$ as:

$$e^{\mu D_{\mathrm{B}}} = 1 + \frac{\mu D_{\mathrm{B}}}{1!} + \frac{(\mu D_{\mathrm{B}})^2}{2!} + \cdots, \tag{48}$$

where the rhs converges for every value of μD_{B}. A further simplification of the rhs of Eq. (45) can be deduced by assuming that the recovery time is short ($\tau \ll 1$ or $\mu \ll 1$) and that the dose D permits the relation $\mu D_{\mathrm{B}} \ll 1$. In such a case, it is justified to retain e.g., only the first 2 terms of the series from (48), so that (44) becomes:

$$D_{\mathrm{B}} = De^{\mu D_{\mathrm{B}}} \approx D(1 + \mu D_{\mathrm{B}}) \quad (\mu D_{\mathrm{B}} \text{ small}). \tag{49}$$

This implicit, linearized version of the non-linear Eq. (38) can be written more explicitly by collecting the unknown D_{B} on the same side of the equation to yield:

$$D_{\mathrm{B}} \approx \frac{D}{1 - \mu D} \quad (\mu D_{\mathrm{B}} \text{ small}). \tag{50}$$

The expression $D/(1 - \mu D)$ from (50) is the diagonal Padé approximant (PA)[11] to $D_{\mathrm{B}}(D)$, as a quotient of two polynomials of the same first degree in variable D. This PA possesses an equivalent representation obtained by employing the binomial series:

$$D_{\mathrm{B}} \approx \frac{D}{1 - \mu D} = D\{(1 + \mu D) + (\mu D)^2 + \cdots\}, \tag{51}$$

which converges for $\mu D < 1$. If we keep only the first two terms within the square brackets from the rhs of Eq. (51), we will finally arrive at:

$$D_{\mathrm{B}} \approx D(1 + \mu D) \quad (\mu D \text{ small}), \tag{52}$$

or equivalently, by reference to (39):

$$D_{\mathrm{true}} = D_{\mathrm{appar}}(1 + \mu D_{\mathrm{appar}}) \quad (\mu D_{\mathrm{appar}} \text{ small}). \tag{53}$$

As discussed for the exact relation (38), we see that the corresponding approximation (52) also obeys the inequality $D \leqslant D_{\mathrm{B}}$ from (39), since a non-negative term ($\mu D^2 \geqslant 0$) must be added to $D \geqslant 0$ to obtain an approximate D_{B}. Division of (52) by D or (53) by D_{appar} yields:

$$\frac{D_{\mathrm{B}}}{D} \approx 1 + \mu D, \tag{54}$$

so that,

$$\nu = \frac{1}{1 + \mu D}. \tag{55}$$

Using (46), the rhs of Eq. (54) can be identified as the relative effectiveness $\mathrm{RE}^{(\mathrm{LQ})}$ from Eq. (23). Thus, the quantity $\mathrm{RE}^{(\mathrm{LQ})}$ can equivalently be conceived as the quotient D_{B}/D of an approximate expression for the biological dose D_{true} (or D_{B}) and the apparent dose D_{appar} (or D):

$$\mathrm{RE}^{(\mathrm{LQ})} = \frac{D_{\mathrm{B}}}{D}. \tag{56}$$

The approximate formula for the effect E_{B} related to (52) is now given by:

$$\mathrm{E}_{\mathrm{B}} \approx \alpha D_{\mathrm{B}} \approx \alpha D + \beta D^2. \tag{57}$$

Therefore, the definition (46) permits a connection of Eqs. (52) and (57) with the LQ model via:

$$D_{\mathrm{B}} \approx D_{\mathrm{B}}^{(\mathrm{LQ})}, \quad \mathrm{E}_{\mathrm{B}} \approx \mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}, \tag{58}$$

where $\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}$ is defined in (18), and:

$$D_{\mathrm{B}}^{(\mathrm{LQ})} = D\left(1 + \frac{\beta}{\alpha} D\right). \tag{59}$$

The binomial series (51) for D_B can alternatively be obtained by solving the implicit, linearized equation (49) through iterations. The first iterate is generated via the replacement of D_B from the rhs of Eq. (49) by $D(1+\mu D_B)$ so that $D_B \approx D\{1+\mu[D(1+\mu D_B)]\}$. If in the rhs of the latter equation, D_B is written as $D(1+\mu D_B)$, the second iterate follows, $D_B \approx D(1+\mu D+\mu^2 D^2+\mu^3 D_B)$. The higher iterates within this procedure of self-substitutions shall yield the binomial series, which sums up to closed expression $D_B \approx D/(1-\mu D)$ for $\mu D<1$ in agreement with Eq. (51).

The approximate solution (52) for D_B is the sum of the linear ($\sim D$) and quadratic ($\sim D^2$) terms. Without repair, all the impinging radiation quanta are absorbed by the targeted cell, so that:

$$D_B = D, \quad \mu = 0 \ (\tau = 0\colon \text{ no repair}), \tag{60}$$

and this goes for both (38) and (59). However, with repair ($\tau > 0, \mu > 0$), there would be some wasted radiation quanta, as if they were removed from the beam or annihilated in the traversed tissue and this gives the quadratic term $\sim D^2$. Our derivation shows that the quadratic term $\sim D^2$ is directly rooted in the cell repair mechanism and brought about by reconstruction of the unknown biological dose $D_B \approx D_B^{(LQ)}$ from the given physical dose D. This gives the approximate answer (52) to the stated inverse dose problem (47). By reference to (59), it follows that the quantity $\mathrm{BED}^{(LQ)}$ coincides with $D_B^{(LQ)}$:

$$\mathrm{BED}^{(LQ)} = D_B^{(LQ)}. \tag{61}$$

In the present formulation of the LQ model, parameters α and β are associated in a distinct manner with the cell kill and cell repair per Gy^{-1} and Gy^{-2}, respectively. However, in the present derivation of the approximate effect $E_B^{(LQ)}$ from (18), these two parameters are correlated through the relationship (46). Thus, if μ were known, only α would be a free parameter when reconstructing $E_B^{(LQ)}$ from e.g., its least-square adjustment to the corresponding experimental data. Parameter $\mu = \beta/\alpha$ is the measure of the deviation of the parabola $\alpha D + \beta D^2$ from the straight line αD plotted versus D as the abscissa. The higher the μ, the more parabolic the effect $E_B^{(LQ)}$ and the more significant the repair βD^2. Conversely, the lower the μ, the more straight line behavior of $E_B^{(LQ)}$ and the more pronounced the cell kill αD.

This derivation clearly demonstrates that the LQ model represents a low-dose approximation of a more general model,[4] which solves the

transcendental equation (38) exactly, rather than using the approximate solution (54), which is valid for small μD. More specifically, we employed the convergence radius $\mu D < 1$ in the result $D_B/D \approx 1 + \mu D$ from (54). This latter low-dose restriction is due to the use of the binomial series for $1/(1 - \mu D)$, which is meaningful only for $\mu D < 1$. Retaining the first two terms in this series via $1/(1 - \mu D) \approx 1 + \mu D$ leads straight to the LQ model. The binomial $1/(1 - \mu D)$ itself is the Padé approximant as a ratio of the simplest two polynomials of degree 0 and 1 in the numerator and denominator, respectively, according to $1/(1 - \mu D) = P_0(D)/Q_1(D)$, where $P_0(D) = 1$ and $Q_1(D) = 1 - \mu D$.

4.2 Repair-mediated non-linear damping of linear direct cell kill mechanism

At larger values of D, experimental data for $S_F(D)$ usually exhibit an exponential fall-off, $S_F(D) \sim e^{-D/D_0} = P(0)$, where D_0 is the dose at which the surviving fraction is reduced by $1/e \approx 0.367879$ or by 36.7879%, as per (4). In other words, the final slope of most measured curves for cell surviving fractions is given by $1/D_0$. This is opposed to the LQ-type high-dose dominance of the Gaussian $S_F^{(LQ)}(D) \sim e^{-\beta D^2}$ from (32), which continues to bend and thus has no final slope. In the LQ model, the initial slope, determined by the low-dose asymptote $S_F^{(LQ)}(D) \sim e^{-\alpha D}$ from (31), is given by α which is associated with single radiation events (single hits) to a sensitive part of the cell. Even in the low-dose limit, the LQ model was seen to deviate from experimental data[12] thus pointing to unreliable numerical values of the parameters α and β in the LQ-based cell surviving fraction $S_F^{(LQ)}(D)$. According to the above derivation, α is also present in β. The said drawbacks of the LQ model at both low- and high-dose asymptotic regions could partially be attributed to the assumption that the linear part $\xi = \alpha D$ is associated exclusively with lethal events as in the classical hit-target model. We shall relax this limitation and modify the term αD so as to allow for cell repair. In other words, as opposed to the hit-target model, where the direct hits ($\sim \alpha D$) describe irreparable lesions that cause cell death, we shall permit that even direct hits could be repaired. As discussed, this can be done by damping αD when the dose is progressively augmented. To this end, we shall modify the LQ model by introducing the repairable lesion ξ_B in lieu of ξ as:

$$\xi_B e^{\omega \xi_B} \equiv \xi \quad \therefore \ \xi_B \leqslant \xi, \tag{62}$$

where $\omega \geqslant 0$ is a dimensionless repair-related constant. Here,

$$\left.\begin{array}{l}\xi_{\mathrm{B}} = \text{Expected number of repairable lesions from direct hits} \\ \xi = \text{Expected number of irreparable lesions from direct hits}\end{array}\right\}, \tag{63}$$

The inequality $\xi_{\mathrm{B}} \leqslant \xi$ from (62) is evident from the defining relation $\xi_{\mathrm{B}} e^{\omega \xi_{\mathrm{B}}} = \xi$, since ξ_{B} needs to be multiplied by a non-negative number $e^{\omega \xi_{\mathrm{B}}} \geqslant 0$ to be equalized to ξ. Moreover, biologically, the plus sign of ξ_{B} in the argument of the exponential in $\xi_{\mathrm{B}} e^{\omega \xi_{\mathrm{B}}}$ from the lhs of Eq. (62) coheres with the fact that repair diminishes the number of expected lethal lesions from direct hits (single interaction of radiation with the cell). At this point of the analysis, it suffices to find an approximate solution of the transcendental equation (62). This can be done if in Eq. (62), rewritten as $\xi_{\mathrm{B}} = \xi e^{-\omega \xi_B}$, we replace the exponential $e^{-\omega \xi_{\mathrm{B}}}$ by its first-order diagonal Padé approximant[11] in variable $\omega \xi_{\mathrm{B}}/2$ as:

$$e^{-\omega \xi_{\mathrm{B}}} \approx \frac{1 - \omega \xi_{\mathrm{B}}/2}{1 + \omega \xi_{\mathrm{B}}/2} \quad \text{(Padé approximant for exponential)}. \tag{64}$$

This transforms the transcendental equation (62) into a quadratic equation for the unknown ξ_{B}:

$$\frac{1}{2} \omega \xi_{\mathrm{B}}^2 + Q \xi_{\mathrm{B}} - \xi = 0, \tag{65}$$

where,

$$Q = 1 + \frac{1}{2} \omega \xi = 1 + \gamma D, \tag{66}$$

$$\gamma = \frac{1}{2} \omega \alpha. \tag{67}$$

The roots of the quadratic equation (66) are:

$$\xi_{\mathrm{B}}^{\pm} = \frac{Q}{\omega} \left(-1 \pm \sqrt{1 + \frac{2 \omega \xi}{Q^2}} \right), \tag{68}$$

where $\xi_{\mathrm{B}}^{+} > 0$ (physical) and $\xi_{\mathrm{B}}^{-} < 0$ (unphysical). We retain only the positive-definite root ξ_{B}^{+}, which is re-labeled as $\xi_{\mathrm{B}}^{(\mathrm{P})}$:

$$\xi_{\mathrm{B}}^{+} \equiv \xi_{\mathrm{B}}^{(\mathrm{P})}. \tag{69}$$

Next, the term $(1+2\omega\xi/Q^2)^{1/2}$ is expanded in a series with powers of $2\omega\xi/Q^2$:

$$\left(1+\frac{2\omega\xi}{Q^2}\right)^{1/2}=\left\{1+\frac{\omega\xi}{Q^2}\right\}+\frac{3}{8}\frac{(\omega\xi)^2}{Q^4}+\cdots. \tag{70}$$

By keeping solely the first two terms, i.e., the terms from the curly brackets, and using (66), it follows:

$$\left(1+\frac{2\omega\xi}{Q^2}\right)^{1/2}\approx 1+\frac{\omega\xi}{Q^2}. \tag{71}$$

In this way, Eqs. (68) and (69) yield the final result $\xi_{\mathrm{B}}\approx\xi_{\mathrm{B}}^{(\mathrm{P})}\approx\xi/Q$ or:

$$\xi_{\mathrm{B}}\approx\xi_{\mathrm{B}}^{(\mathrm{P})}\approx\frac{\xi}{1+\gamma D}=\frac{\alpha D}{1+\gamma D}. \tag{72}$$

The replacement of the term ξ by its Padé-equivalent $\xi_{\mathrm{B}}^{(\mathrm{P})}$ yields the Padé Linear-Quadratic model, as denoted by PLQ, for the biological effect of radiation:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}\equiv\xi_{\mathrm{B}}^{(\mathrm{P})}(1+\mu D), \tag{73}$$

or equivalently,

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}=\frac{\alpha D}{1+\gamma D}(1+\mu D). \tag{74}$$

The corresponding cell surviving fraction in the PLQ model reads as:

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)\equiv e^{-\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}}. \tag{75}$$

If parameter μ is chosen according to (46), we can cast Eqs. (74) and (75) into the forms:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}=\frac{\alpha D+\beta D^2}{1+\gamma D}, \tag{76}$$

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)=e^{-\frac{\alpha D+\beta D^2}{1+\gamma D}}. \tag{77}$$

The numerator of the quotient from the rhs of Eq. (76) represents the effect in the LQ model, so that we can also write:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} = \frac{\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}}{1+\gamma D}. \tag{78}$$

As per derivation of the PLQ model, there are two "repair ratios" $\Gamma_{\beta\alpha}$ and $\Gamma_{\gamma\alpha}$ that can be introduced by:

$$\Gamma_{\beta\alpha} = \frac{\beta}{\alpha}, \quad \Gamma_{\gamma\alpha} = \frac{\gamma}{\alpha}, \tag{79}$$

in terms of which, the biological effect (76) can be rewritten as:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} = \frac{D+\Gamma_{\beta\alpha}D^2}{\delta+\Gamma_{\gamma\alpha}D}, \quad \delta = \frac{1}{\alpha}. \tag{80}$$

Quotient $\Gamma_{\beta\alpha}$ is a repair degree β/α, which gives the relative importance of the linear (D) and quadratic (D^2), as also encountered in the LQ model, according to (59) and (61). The additional repair ratio $\Gamma_{\gamma\alpha}$ in the PLQ model is a repair measure γ/α of the strength of some higher-order mechanisms appearing through all the powers of dose D that are implicitly present in (80) and could be made explicit by expanding the binomial $1/(\delta+\Gamma_{\gamma\alpha}D)$ into its Macularin series. The quotient of $\Gamma_{\beta\alpha}$ and $\Gamma_{\gamma\alpha}$ is useful, since it gives the degree of the departure of the PLQ from the LQ model:

$$\Gamma_{\beta\gamma} = \frac{\Gamma_{\beta\alpha}}{\Gamma_{\gamma\alpha}} = \frac{\beta}{\gamma}. \tag{81}$$

This quantity is also the final slope of the dose–effect curve $S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)$, as will be discussed later on. The expression (73) for the effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$ in the PLQ model was obtained in the two main steps: (i) derivation of the approximate biological dose $D_{\mathrm{B}} = D(1+\mu D)$ from (52), which by way of the definition $\mu = \beta/\alpha$ from (46) coincides with the biologically effective dose $\mathrm{BED}^{(\mathrm{LQ})}$ in the LQ model, $D_{\mathrm{B}} = \mathrm{BED}^{(\mathrm{LQ})}$, as per (61), and (ii) replacement of the lethal (irreparable) lesions $\xi = \alpha D$ in the effect $\mathrm{E}_{\mathrm{B}} \equiv \alpha D_{\mathrm{B}} = \xi(1+\mu D)$ from (61) by the sublethal (repairable) lesion $\xi_{\mathrm{B}}^{(\mathrm{P})}$ via $\xi \Longrightarrow \xi_{\mathrm{B}}^{(\mathrm{P})} = \xi/(1+\gamma D) = (\alpha D)/(1+\gamma D)$. The net result of the steps (i) and (ii), through the product of $\xi_{\mathrm{B}}^{(\mathrm{P})}$ and the relative effectiveness $1+\mu D$ as $\xi_{\mathrm{B}}^{(\mathrm{P})}(1+\mu D)$ represents the effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} = (\alpha D+\beta D^2)/(1+\gamma D)$

from (73) in the PLQ model. This recapitulation through the said two steps (i) and (ii) illustrates the origin of the name "Padé + Linear-Quadratic" and the associated acronym PLQ for this new radio-biological model which has originally been introduced in our recent works.[4–6]

4.3 Initial slope, final slope, and extrapolation number

For the choice $\mu = \beta/\alpha$ from (46), the low- and high-dose asymptotes of $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$ read as:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} \underset{D\to 0}{\longrightarrow} \alpha D, \tag{82}$$

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} \underset{D\to \infty}{\longrightarrow} \frac{\beta}{\gamma} D, \tag{83}$$

respectively. For brevity, the high-dose asymptote (83) is written to exhibit only the leading term ($\sim D$), whereas the constant ($\sim D^0$) is ignored. As it stands, Eq. (76) is the para-diagonal Padé approximant with the numerator and denominator polynomial of the second- and first-degree, respectively in variable D.

The expression for $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$ from (76) leads to the corresponding biologically effective dose $\mathrm{BED}^{(\mathrm{PLQ})}$ in the PLQ model:

$$\mathrm{BED}^{(\mathrm{PLQ})} \equiv \frac{\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}}{\alpha} = \frac{D + \beta D^2/\alpha}{1 + \gamma D}. \tag{84}$$

This can also be written in analogy with (24) as:

$$\mathrm{BED}^{(\mathrm{PLQ})} = D \cdot \mathrm{RE}^{(\mathrm{PLQ})}, \tag{85}$$

where $\mathrm{RE}^{(\mathrm{PLQ})}$ is the relative effectiveness in the PLQ model:

$$\mathrm{RE}^{(\mathrm{PLQ})} = \frac{1 + (\beta/\alpha)D}{1 + \gamma D} = \frac{\mathrm{RE}^{(\mathrm{LQ})}}{1 + \gamma D}. \tag{86}$$

Insertion of the asymptotes (82) and (83) for $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$ into Eq. (84) yields:

$$\mathrm{BED}^{(\mathrm{PLQ})} \underset{D\to 0}{\longrightarrow} D, \tag{87}$$

$$\mathrm{BED}^{(\mathrm{PLQ})} \underset{D\to \infty}{\longrightarrow} \frac{\beta}{\alpha\gamma} D. \tag{88}$$

As expected, the PLQ and LQ models exhibit the same low-dose behaviors in (29) and (87), but differ substantially at high doses according to (30) and (88).

The behaviors (82) and (83) of $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$ yield the following two asymptotes of $S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)$ at small and large values of D:

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) \underset{D\to 0}{\longrightarrow} e^{-\alpha D}, \tag{89}$$

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) \underset{D\to \infty}{\longrightarrow} e^{-\beta D/\gamma}, \tag{90}$$

respectively. This gives the initial and final slopes s_{i} and s_{f}, respectively, in the dose–effect curve from the PLQ model as:

$$\mathrm{PLQ}: \quad \text{Initial slope}: \ s_{\mathrm{i}} = \alpha, \quad \text{Final slope}: \ s_{\mathrm{f}} = \frac{\beta}{\gamma}. \tag{91}$$

In the high-dose asymptotes (90), only the leading term βD^2 is retained in the numerator of the biological effect $E_{\mathrm{B}}^{(\mathrm{PLQ})} = (\alpha D + \beta D^2)/(1 + \gamma D)$. However, it is also useful to extrapolate the high-dose limit of the cell surviving curve back to the ordinate axis ($D = 0$). This would give the so-called extrapolation number n. Thus, alongside the same high-dose approximation for the denominator $1 + \gamma D \approx \gamma D$, which has already been made in (90), we shall now retain the full numerator $\alpha D + \beta D^2$ in $(\alpha D + \beta D^2)/(1 + \gamma D)$ to arrive at:

$$\begin{aligned} -\ln S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) &\underset{D\to\infty}{\longrightarrow} \left\{\frac{\alpha D + \beta D^2}{1 + \gamma D} - \frac{\beta}{\gamma}\right\} + \frac{\beta}{\gamma} D \\ &= \left\{\frac{(\alpha\gamma - \beta)D}{\gamma(1 + \gamma D)}\right\} + \frac{\beta}{\gamma} D \\ &\underset{D\to\infty}{\longrightarrow} \left\{\frac{(\alpha\gamma - \beta)D}{\gamma^2 D}\right\} + \frac{\beta}{\gamma} D \\ &= \left\{\frac{\alpha\gamma - \beta}{\gamma^2}\right\} + \frac{\beta}{\gamma} D \end{aligned}$$

so that,

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) \underset{D\to\infty}{\longrightarrow} e^{\frac{\beta-\alpha\gamma}{\gamma^2} - \frac{\beta}{\gamma} D}. \tag{92}$$

This can conveniently be rewritten as:

$$\left.\begin{aligned} S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) &\underset{D\to\infty}{\longrightarrow} n e^{-\frac{\beta}{\gamma}D} \\ \ln S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) &\underset{D\to\infty}{\longrightarrow} \ln n - \frac{\beta}{\gamma}D \end{aligned}\right\}, \tag{93}$$

where the extrapolation number n is given by:

$$\begin{aligned} ln\, n &= \frac{\beta - \alpha\gamma}{\gamma^2} \\ &= \frac{\Delta s_{\mathrm{fi}}}{\gamma}, \quad \Delta s_{\mathrm{fi}} = s_{\mathrm{f}} - s_{\mathrm{i}}. \end{aligned} \tag{94}$$

Thus, the extrapolation number is proportional to the difference Δs_{fi} between the final and initial slopes, $ln\, n \sim s_{\mathrm{f}} - s_{\mathrm{i}} = \Delta s_{\mathrm{fi}}$. The extrapolation number n must be positive and this imposes the following condition:

$$ln\, n > 0 \quad \text{if} \quad \beta > \alpha\gamma. \tag{95}$$

At high doses, it might be useful to constrain the free parameter γ to the relationship:

$$\gamma = \beta D_0, \tag{96}$$

in which case (90) can alternatively be written as:

$$S_{\mathrm{B}}^{(\mathrm{PLQ})}(D) \underset{D\to\infty}{\longrightarrow} e^{-D/D_0} \quad \text{at} \quad \gamma = \beta D_0. \tag{97}$$

With the selection (96), the extrapolation number n from (94) becomes:

$$ln\, n = \frac{1 - \alpha D_0}{\beta D_0^2} \quad \text{at} \quad \gamma = \beta D_0, \tag{98}$$

where the restriction condition (95) is now specified as:

$$ln\, n > 0 \quad \text{if } \alpha < \frac{1}{D_0} \quad \text{at} \quad \gamma = \beta D_0. \tag{99}$$

This positivity requirement (99) for the extrapolation number $n > 0$ reflects the proper relationship between the initial (α) and final $(1/D_0)$ slopes when the third parameter γ in the PLQ model is not adjustable, but rather fixed via $\gamma = \beta D_0$:

$$\text{Initial slope } (\alpha) < \text{Final slope } (1/D_0) \quad \text{at} \quad \gamma = \beta D_0. \tag{100}$$

We re-emphasize that when γ is constrained to the relation $\gamma = \beta D_0$, the high-dose limit of the PLQ model becomes $S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) \sim e^{-D/D_0}$, as required by the experimental data. Of course, any constraint imposed on one parameter inevitably introduces a bias into the estimates of the remaining parameters. However, irrespective of whether γ is pre-assigned to be of the form $\gamma = \beta D_0$ or kept free, the other two parameters α and β are always mutually dependent, since by definition $\beta = \mu\alpha$. Moreover, in view of (67) instead of γ, we could use $\omega\alpha/2$, where ω takes the role of an adjustable parameter. This shows that in the general case without resorting to (96), the third parameter $\omega\alpha/2$ in the PLQ model is connected to the direct cell kill component α. Overall, the unconstrained version of the PLQ model is negligibly more involved than the LQ model from the computational viewpoint due to the presence of merely one additional parameter γ or equivalently, $\omega\alpha/2$. The constrained variant of the PLQ model, with γ fixed by the prescription $\gamma = \beta D_0$, has only two parameters α and β, since D_0 can be considered as the input data to be read off from the final slope of the experimentally measured cell surviving fraction at larger values of D. In either case, the advantage of the PLQ over the LQ model is at least twofold:

- (A) a richer mathematical function with the underlying mechanisms and,
- (B) a smooth switch from the incorrect quadratic (Gaussian) to the correct (exponential) asymptote at high doses, as required by the measurements.

4.4 The Padé linear-quadratic model and the Michaelis–Menten kinetics

Inserting (18) for $\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}$ into the numerator of $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$ from the Padé quotient (78), we can alternatively write the biological effect in the PLQ model as:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} = v_0(\zeta + D) = v_0(z_{\mathrm{D}} + D), \tag{101}$$

where,

$$v_0 = \frac{\beta D}{1 + \gamma D}. \tag{102}$$

In (101), use is made of the quantity ζ, or equivalently, z_{D} from (34), where z_{D} is the dose-averaged specific energy from microdosimetry. The quantity v_0 is velocity or rate, which is equivalent to the initial reaction velocity from the enzyme kinetics of Michaelis–Menten (MM)[7] for the following irreversible chemical reaction (enzyme catalysis) with formation and destruction of the enzyme-lesion complex:

$$[\mathrm{E}] + [\mathrm{L}] \underset{k_1}{\longrightarrow} [\mathrm{EL}] \underset{k_2}{\longrightarrow} [\mathrm{E}] + [\mathrm{R}]. \tag{103}$$

Here [E], [L], [EL], and [R] are the concentrations of the free enzyme molecules, lesions (primarily DNA), enzyme-lesion complex and repaired lesions, respectively. Quantities k_1 and k_2 are the rate coefficients for formation and destruction/dissociation of the intermediate complex molecule [EL]. In this chemical reaction, the free enzyme molecule [E] binds the radiation damaged DNA molecule (a lesion [L]) into an intermediate and temporarily living unstable complex molecule [EL]. This compound facilitates the enzymatic synthesis of DNA. After completion of this intermediate stage of the reaction, the complex [EL] decays, thus producing the repaired lesions [R] and enzymes [E] that are again free for further bindings with other lesions. As mentioned earlier in (21), the number of lesions is usually assumed to be proportional to dose D:

$$[\mathrm{L}] \sim D = \kappa D \equiv D, \tag{104}$$

where κ could be taken as $\kappa = k_0 \equiv 1/\mathrm{D}_0$ or as a constant of unit absolute value ($\kappa \equiv 1$). When writing $[\mathrm{L}] = D$ in (104) and afterwards, it is understood that $[\mathrm{L}] = D \equiv 1 \cdot D$, where "1" takes care of the proper units in the passage from a dose to a molar concentration. This convention is done to avoid introducing a superfluous parameter only for the purpose of conversion of the units. In this way, Eq. (102) can equivalently be written as:

$$v_0 = \frac{\beta[\mathrm{L}]}{1 + \gamma[\mathrm{L}]}. \tag{105}$$

Using Eq. (104) and the definition:

$$K_{\mathrm{M}} \equiv \frac{1}{\gamma}, \tag{106}$$

we can cast expression (105) into its form used in the MM kinetics:

$$v_0 = \frac{v_{\max}[\mathrm{L}]}{K_{\mathrm{M}} + [\mathrm{L}]}, \tag{107}$$

where $\upsilon_{\max}$ is the maximal velocity given by:

$$\upsilon_{\max} \equiv \frac{\beta}{\gamma}. \tag{108}$$

Velocities υ_0, and consequently, $\upsilon_{\max}$ are given in units Gy^{-1}. On the other hand, in the original Michaelis–Menten velocity for irreversible reaction (103), we have:

$$K_{\mathrm{M}} = \frac{k_2}{k_1}, \tag{109}$$

$$\upsilon_{\max} = k_2[\mathrm{E}]_0, \tag{110}$$

where $[\mathrm{E}]_0$ is the initial concentration of enzymes (the number of enzymes at the onset of the reaction), which is assumed to be constant throughout and, therefore, equal to the total enzyme concentration $[\mathrm{E}] \equiv [\mathrm{E}]_{\mathrm{tot}}$ at any subsequent time. Quantity K_{M} is the Michaelis–Menten[7] constant with the dimension of concentration. More specifically, this constant for irreversible variant (103) of the general MM enzyme catalysis, represents the concentration of lesions ($[\mathrm{L}] \approx K_{\mathrm{M}}$) at which velocity υ_0 attains one half of $\upsilon_{\max}$, as follows $\{\upsilon_0\}_{[\mathrm{L}]\approx K_{\mathrm{M}}} \approx \upsilon_{\max}[\mathrm{L}]/([\mathrm{L}] + [\mathrm{L}]) = \upsilon_{\max}/2$:

$$\upsilon_0 \approx \frac{\upsilon_{\max}}{2} \quad \text{at} \quad [\mathrm{L}] \approx K_{\mathrm{M}}. \tag{111}$$

In the same approximation, the biological effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$ becomes:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} \approx \frac{\upsilon_{\max} + \alpha}{2} K_{\mathrm{M}} \quad \text{at} \quad [\mathrm{L}] \approx K_{\mathrm{M}}. \tag{112}$$

At small concentration of lesions, the reaction velocity υ_0 is reduced to:

$$\upsilon_0 = \frac{\upsilon_{\max}[\mathrm{L}]}{K_{\mathrm{M}}\,(1 + [\mathrm{L}]/K_{\mathrm{M}})} \underset{[\mathrm{L}]/K_{\mathrm{M}} \ll 1}{\approx} \upsilon_{\min}, \tag{113}$$

where,

$$\upsilon_{\min} = \frac{\upsilon_{\max}[\mathrm{L}]}{K_{\mathrm{M}}}. \tag{114}$$

The use of Eqs. 106 and (108)–(110) permits connecting e.g., the final slope (β/γ) in the PLQ model with the enzyme kinetic parameters as:

$$\text{Final slope}: \quad \Gamma_{\beta\gamma} = \frac{\beta}{\gamma} = \upsilon_{\max} = k_2[\mathrm{E}]_0. \tag{115}$$

A similar connection can also be deduced for the extrapolation number using Eq. (94) as follows: $\ln n = (\beta - \alpha\gamma)/\gamma^2 = (\beta/\gamma - \alpha)/\gamma = (\upsilon_{\max} - \alpha)K_{\mathrm{M}}$, so that:

$$\text{Logarithm of the extrapolation number:} \quad \ln n = (\upsilon_{\max} - \alpha)K_{\mathrm{M}}. \tag{116}$$

Hence, the larger (the smaller) the product of the enzyme concentration $[\mathrm{E}]_0$ and the dissociation rate constant k_2, the steeper (the shallower) the final slope of the dose–effect curve. This is correct, since more significant values of $k_2[\mathrm{E}]_0$ would enhance the chance for a greater enzymatic activity with the ensuing larger concentration [R] of repaired lesions. Such an outcome should mitigate the influence of the direct cell kill mechanism (αD) and, therefore, would increase cell survival, as manifested by a departure from the pure exponential bending $\mathrm{e}^{-\alpha D}$ in the dose–effect curve. Consequently, a shouldered cell surviving curve appears, as a signature of the enzymatic repair of radiation-induced lesions. This is also reflected in the repair ratio $\Gamma_{\beta\alpha} = \beta/\alpha$ from (79), which can be rewritten in the form:

$$\Gamma_{\beta\alpha} = \frac{\beta}{\alpha} = \Gamma_{\gamma\alpha}\{k_2[\mathrm{E}]_0\}, \tag{117}$$

where the second repair ratio $\Gamma_{\gamma\alpha}$ is equal to γ/α, according to (79). The larger values of β/α imply a more noticeable influence of repair. Expression (117) confirms this expectation through a direct proportionality between the quotient β/α and the enzyme concentration $[\mathrm{E}]_0$ available for repair. Moreover, the same ratio β/α is also directly proportional to the catalysis rate k_2 and, thus, to the efficiency of the enzymatic repair system in converting the radiation damage [L] to the repaired lesions [R] in the final reaction path $[\mathrm{EL}] \underset{k_2}{\longrightarrow} [\mathrm{E}] + [\mathrm{R}]$, so that:

$$\Gamma_{\beta\alpha} \sim k_2[\mathrm{E}]_0. \tag{118}$$

In the equivalence relation (118), the proportionality constant is $\Gamma_{\gamma\alpha}$, where $\Gamma_{\gamma\alpha} = \gamma/\alpha$ from (117). This constant is associated with linear and nonlinear contributions from all the powers that are inherent in the binomial $(\delta + \Gamma_{\gamma\alpha}D)^{-1}$, as mentioned earlier.

Rewriting (104) as $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} = (\alpha D + \beta D^2)/(1 + \gamma D) = (\beta/\gamma)(\alpha/\beta + D) \times (1/\gamma + D)$ and using (106) and (108) for $1/\gamma = K_{\mathrm{M}}$ and $\beta/\gamma = \upsilon_{\max}$,

respectively, we can equivalently express the biological effect (76) and the cell surviving fraction (77) in the Michaelis–Menten representation as:

$$\begin{aligned} \mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} &= \upsilon_0 \left(z_{\mathrm{D}} + [\mathrm{L}]\right) \\ &= \left(\frac{\upsilon_{\max}[\mathrm{L}]}{K_{\mathrm{M}} + [\mathrm{L}]}\right)\left(z_{\mathrm{D}} + [\mathrm{L}]\right), \end{aligned} \tag{119}$$

and,

$$\begin{aligned} S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) &= e^{-\upsilon_0 (z_{\mathrm{D}} + [\mathrm{L}])} \\ &= e^{-\left(\frac{\upsilon_{\max}[\mathrm{L}]}{K_{\mathrm{M}} + [\mathrm{L}]}\right)(z_{\mathrm{D}} + [\mathrm{L}])}. \end{aligned} \tag{120}$$

The connection among the three parameters $\{\alpha, \beta, \gamma\}$ with the equivalent triple $\{z_{\mathrm{D}}, \upsilon_{\max}, K_{\mathrm{M}}\}$ from the PLQ model is summarized as:

$$\left.\begin{array}{ll} z_{\mathrm{D}} = \frac{\alpha}{\beta}; & \text{Direct/Indirect mechanisms , (Cell kill)/(Cell repair)} \\ \upsilon_{\max} = \frac{\beta}{\gamma}; & \text{Experimentally measurable maximal enzyme velocity} \\ K_{\mathrm{M}} = \frac{1}{\gamma}; & \text{Experimentally measurable Michaelis–Menten constant} \end{array}\right\}. \tag{121}$$

Overall, the MM rate constant K_{M} and the maximal enzyme velocity $\upsilon_{\max}$ can be measured in standard enzyme experiments. Moreover, the initial (α) and final $(\upsilon_{\max})$ slopes can be extracted from the experimental data for the given cell surviving curve and so could the extrapolation number n. Also, as soon as the triple $\{\alpha, \upsilon_{\max}, K_{\mathrm{M}}\}$ becomes available, the extrapolation number can be obtained from Eq. (116). Thus, the basic elements of the dose–effect curve in the PLQ model are recapitulated via:

$$\left.\begin{array}{ll} \mathrm{s}_i = \alpha; & \text{Initial slope} \\ \mathrm{s}_f = \upsilon_{\max}; & \text{Final slope} \\ \ln n = (\upsilon_{\max} - \alpha) K_{\mathrm{M}}; & \text{logarithm of the extrapolation number} \end{array}\right\}. \tag{122}$$

When parameter γ is pre-assigned as $\gamma = \beta D_0$, by reference to (96), then according to (100) the final slope β/γ becomes $1/D_0$, so that:

$$D_0 = \frac{1}{\upsilon_{\max}} = \frac{1}{k_2[\mathrm{E}]_0} \quad \text{at} \quad \gamma = \beta D_0. \tag{123}$$

This result $(D_0 \sim 1/k_2)$ shows that the mean lethal dose D_0 is proportional to the reciprocal of rate constant k_2 for enzyme-mediated creation of a

repaired lesion [R], which is the product substance in reaction (103) for enzyme catalysis.

At high doses, the enzyme-lesion reaction velocity v_0 tends to the constant value $v_{\max}$, which is the fastest rate possible for the given enzyme concentration $[\mathrm{E}]_0$. This means that the rectangular hyperbola $v_0 = \alpha D/(1 + \gamma D)$ from (102) as a function of D has reached a plateau at larger doses. Stated equivalently, the curve $v_0 = v_{\max}[\mathrm{L}]/(K_{\mathrm{M}} + [\mathrm{L}])$ from (107), as a function of $[\mathrm{L}]$ is leveled off for higher lesion concentrations, $[\mathrm{L}]$. Such a high-dose or a high concentration of lesions described by the reaction velocity v_0 in terms of the independent variable D or $[\mathrm{L}]$ is due to the limited amount of enzymes ($\sim$ 100 enzyme molecules per lesion) that are available for repair of radiation-damaged cells. At high doses, the average number of lesions is sufficiently large to overwhelm and thus inactivate the enzyme repair system, after which point every radiation damage is essentially lethal. This saturation of enzymes by lesions is the signature for a switch from the cell repair to the cell kill mechanism corresponding to the passage from the second- to the first-order Michaelis–Menten kinetics.

Expressions (119) and (120) are written in a way which separates the two parts of the PLQ model, by exhibiting the contributions from: the enzyme velocity $v_0 = v_{\max}[\mathrm{L}]/(K_{\mathrm{M}} + [\mathrm{L}])$ and the precipitation of the dose-averaged specific energy around the lesion $z_{\mathrm{D}} + [\mathrm{L}]$. This is merely a formal separation, since the dose-averaged specific energy z_{D} is not a quantity which is independent of the enzymatic repair. Quite the contrary, combining the definition $z_{\mathrm{D}} = \beta/\alpha$ with $\beta = v_{\max}/K_{\mathrm{M}}$, we have:

$$z_{\mathrm{D}} = \alpha \left\{ \frac{v_{\max}}{K_{\mathrm{M}}} \right\}. \tag{124}$$

Thus, the enzyme repair system effectively modifies the cell radiosensitivity α by the multiplying factor $v_{\max}/K_{\mathrm{M}}$ due to the Michaelis–Menten chemical kinetics. Because of this inter-connection between z_{D} and $\{v_{\max}, K_{\mathrm{M}}\}$, the product $v_0(z_{\mathrm{D}}) + [\mathrm{L}]$, or equivalently, $v_0(z_{\mathrm{D}} + D)$ appearing in the effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$ from the PLQ model should not be taken too literally to mean a true separation of the two independent mechanisms, the one being enzymatic repair (v_0) and the other being of microdosimetric origin ($z_{\mathrm{D}} + D$). It is merely for the reason of drawing an analogy rather than making a one-to-one correspondence that we used the notation z_{D} from microdosimetry for the defining quotient α/β of the two parameters in the PLQ model for the cell kill (α) and cell repair (β) mechanisms of the cell response to radiation. The microdosimetric parameter z_{D} was also employed earlier in Eq. (33)

for the effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}$ in the LQ model. There, following Kellerer and Rossi,[13] we expressed the defining relation $\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} = \alpha D + \beta D^2 = \beta D(\alpha/\beta + D)$ as $\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} = \beta D(z_{\mathrm{D}} + D)$, where $z_{\mathrm{D}} = \alpha/\beta$. Using the assumed direct proportionality between the lesion number (concentration) [L] and dose D, via $[\mathrm{L}] = \kappa D \equiv D$, as per (106) and (108), we can further write:

$$\begin{aligned} \mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} &= \beta D\,(z_{\mathrm{D}} + D) \\ &= \{\beta[\mathrm{L}]\}\,(z_{\mathrm{D}} + [\mathrm{L}]) \\ &\equiv \upsilon_0^{(\mathrm{LQ})}\,(z_{\mathrm{D}} + [\mathrm{L}])\,, \end{aligned}$$

where,

$$\begin{aligned} \upsilon_0^{(\mathrm{LQ})} &= \beta[\mathrm{L}] \\ &= \frac{\upsilon_{\max}[\mathrm{L}]}{K_{\mathrm{M}}}. \end{aligned} \tag{125}$$

In this way, the effect (33) and the surviving fraction (16) from the LQ model can be cast in the following form of the Michaelis–Menten terminology:

$$\begin{aligned} \mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} &= \upsilon_0^{(\mathrm{LQ})}\,(z_{\mathrm{D}} + [\mathrm{L}]) \\ &= \left(\frac{\upsilon_{\max}[\mathrm{L}]}{K_{\mathrm{M}}}\right)(z_{\mathrm{D}} + [\mathrm{L}])\,, \end{aligned} \tag{126}$$

and,

$$\begin{aligned} S_{\mathrm{F}}^{(\mathrm{LQ})}(D) &= e^{-\upsilon_0^{(\mathrm{LQ})}(z_{\mathrm{D}}+[\mathrm{L}])} \\ &= e^{-\left(\frac{\upsilon_{\max}[\mathrm{L}]}{K_{\mathrm{M}}}\right)(z_{\mathrm{D}}+[\mathrm{L}])}. \end{aligned} \tag{127}$$

Notice that both surviving fractions (120) and (127) in the PLQ and LQ models, respectively, are expressed through *three* parameters $\{z_{\mathrm{D}}, \upsilon_{\max}, K_{\mathrm{M}}\}$. However, there is a special circumstance within $\upsilon_0^{(\mathrm{LQ})}$ in the LQ model permitting a reduction from this apparent three to only two degrees of freedom. This is possible because the two parameters $\upsilon_{\max}$ and K_{M} do not appear individually in $S_{\mathrm{F}}^{(\mathrm{LQ})}(D)$ at different places, but rather they enter Eq. (127) through $\upsilon_0^{(\mathrm{LQ})}$ exclusively as the ratio $\upsilon_{\max}/K_{\mathrm{M}}$. This leads to a reduction from $\{z_{\mathrm{D}}, \upsilon_{\max}, K_{\mathrm{M}}\}$ to $\{z_{\mathrm{D}}, \beta\}$, where $\beta = \upsilon_{\max}/K_{\mathrm{M}}$ and $z_{\mathrm{D}} = \alpha/\beta$.

As such, the apparent three parameter set $\{z_D, \upsilon_{max}, K_M\}$ is, in fact, a collection of the usual two parameters α and β from the LQ model. In the general version of the PLQ model[§], none of the three parameters could be eliminated so as to have only two remaining degrees of freedom. The reason is that, instead of the velocity $\upsilon_0^{(LQ)} = \upsilon_{max}/K_M$ from the effect $E_B^{(LQ)} = \upsilon_0^{(LQ)}(z_D + [L])$ in the LQ model, the initial enzyme velocity $\upsilon_0 = \upsilon_{max}[L]/(K_M + [L])$ appears in the corresponding effect in the LQ model via:

$$\begin{aligned} E_B^{(PLQ)} &= \upsilon_0 (z_D + [L]) = \left\{ \frac{\upsilon_{max}[L]}{K_M + [L]} \right\} (z_D + [L]) \\ &= \left\{ \frac{\upsilon_{max}[L]}{K_M} (z_D + [L]) \right\} \left(1 + \frac{[L]}{K_M} \right)^{-1} \\ &= E_B^{(LQ)} \left(1 + \frac{[L]}{K_M} \right)^{-1}, \end{aligned}$$

so that,

$$E_B^{(PLQ)} = \frac{E_B^{(LQ)}}{1 + [L]/K_M}, \tag{128}$$

as in (78). Thus, the general PLQ model possesses three parameters because any attempt to express $E_B^{(PLQ)}$ through the two parameters $\{\alpha, \beta\}$ in $E_B^{(LQ)}$ invariably leads to the emergence of the third parameter via the isolated term $1/K_M = \gamma$. The above juxtaposition of enzyme velocities $\upsilon_0^{(LQ)}$ and υ_0 from the LQ and PLQ models, respectively, is instructive, since it facilitates one of the mechanistic levels of comparison between these two formalisms. This is best seen by observing that:

$$\upsilon_0^{(LQ)} = \upsilon_{min}, \tag{129}$$

where υ_{min} is the asymptote of the reaction velocity υ_0 at small concentration of lesions, as per (113). Hence, the PLQ model with its Michaelis–Menten chemical kinetics of enzyme catalysis for lesion repair can help

[§] The general PLQ model is the one which excludes the special case in which the final slope υ_{max} is constrained to satisfy the relation $\upsilon_{max} = 1/D_0$ from (123), provided that the mean lethal dose D_0 is viewed as known by e.g., reading off the ending, exponential part of the curve for the cell surviving fraction.

understand one of the limitations of the LQ model, such as the restriction to (129). A small concentration of lesions is associated with low-dose exposure of cells to radiation. Therefore, restriction of $v_0^{(\mathrm{LQ})}$ to only small repair velocity $v_{\min}$ of enzyme molecules means that the validity of the LQ model is limited to low doses. This conclusion from the Michaelis–Menten formalism is in accordance with the well-known fact that the LQ model is a low-dose approximation to cell surviving fraction.

5. RESULTS: COMPARISON OF RADIOBIOLOGICAL MODELS WITH MEASUREMENTS

The relative performance of the PLQ and LQ models is illustrated by their comparisons with experimental data. This is done on the level of cell surviving fractions $S_{\mathrm{F}}(D)$ and also by plotting the so-named full effect graph.[4] Such twofold comparisons are deemed necessary for the reasons that run as follows.

At low-to-intermediates doses, quite different radiobiological models can still be in reasonably close agreement with experimental data when plotted as cell surviving fractions $S_{\mathrm{F}}(D)$ versus D. This is also evident from each panel (i) on Figures 14.1–14.3 when comparing the PLQ and LQ models with measurements. Of course, it is also clear from the same panel (i) on these figures that this type of relatively good agreement between these two formalisms ceases to exist at larger doses because of the prevailing Gaussian and exponential shapes of cell surviving fractions in the LQ and PLQ model, respectively. The displayed experimental data for the corresponding cell surviving fractions favor the predictions by the PLQ model at all doses. This confirms the theoretical expectation that the PLQ model is universally valid at any dose D. By contrast, at high doses the LQ model is seen to break down, as it largely underestimates the surviving fractions from the measurements.

Overall, at small and intermediate doses, survival curves do not appear to be the most suitable for differentiating among various models while evaluating their clinical usefulness in radiotherapy. Moreover, dose–effect functions $S_{\mathrm{F}}(D)$ are rarely of direct use in dose planning systems that, instead, most frequently employ the biological effect $\mathrm{E_B}(D)$ and the biologically effective dose $\mathrm{BED}(D)$. There is yet another useful relationship, which offers the possibility for a more stringent assessment of clinical adequacy of different biophysical models. This is the so-called full-effect plot, or Fe-plot,[4] which is associated with the ratio of the biological effect and the absorbed dose,

$\mathrm{Fe}(D) = (1/D)\mathrm{E_B}(D)$, or equivalently, $\mathrm{Fe}(D) = -(1/D)\ln S_\mathrm{F}(D)$. This quantity is also known by the alternative name "reactivity"[13] and denoted by $R(D)$, which is also used in panel (ii) on Figures 14.1–14.3:

$$\begin{aligned} \mathrm{Fe}(D) &\equiv R(D) \\ &= \frac{1}{D}\mathrm{E_B}(D) \\ &= -\frac{1}{D}\ln S_\mathrm{F}(D). \end{aligned} \tag{130}$$

Such a biological effect per unit dose represents the full effectiveness of radiation on cell survival for each given level of dose exposure. It is this Fe-plot, depicting $\mathrm{Fe}(D)$ versus D, or equivalently, $R(D)$ as a function of dose, which can distinguish one model from another in the most dramatic way, as is clear from panel (ii) on Figures 14.1–14.3. In the Fe-plot, the LQ model yields a linear radiation response, as displayed by a straight line of a slope β and the intercept α on the ordinate:

$$\mathrm{Fe}^{(\mathrm{LQ})}(D) = R^{(\mathrm{LQ})}(D) = \alpha + \beta D. \tag{131}$$

This means that the effectiveness of radiation at every dose level would have no bound, as it would be indefinitely increased with augmentation of D. Such a pattern is at variance with most experimental data $\mathrm{Fe}^{(\mathrm{exp})}(D)$ that are seen on plot (ii) of Figures 14.1–14.3 to saturate to some constant values at high doses. This behavior is also predicted by the PLQ model whose Fe-plot levels off to the constant final slope β/γ, as D becomes very large:

$$\mathrm{Fe}^{(\mathrm{PLQ})}(D) = R^{(\mathrm{PLQ})}(D) = \frac{\alpha + \beta D}{1 + \gamma D} \underset{D\to\infty}{\longrightarrow} \frac{\beta}{\gamma}. \tag{132}$$

Here, the rectangular hyperbola $(\alpha + \beta D)/(1 + \gamma D)$ from the PLQ model implies the existence of repair of radiation damage to the cell through a mechanism of the Michaelis–Menten type for enzyme-lesion catalysis. As such, panel (ii) on Figures 14.1–14.3 for the Fe-plot shows excellent agreement of the PLQ model with the corresponding experimental data.

Overall, we can conclude that the universal applicability of the PLQ model to all doses is demonstrated in both panels (i) and (ii) of Figures 14.1–14.3 for cell surviving fractions and the Fe-plot. Simultaneously, these comparisons prove the marked superiority of the PLQ over the LQ model. This outperformance of the latter by the former radiobiological model testifies to the adequacy of the mechanistic underpinning of the

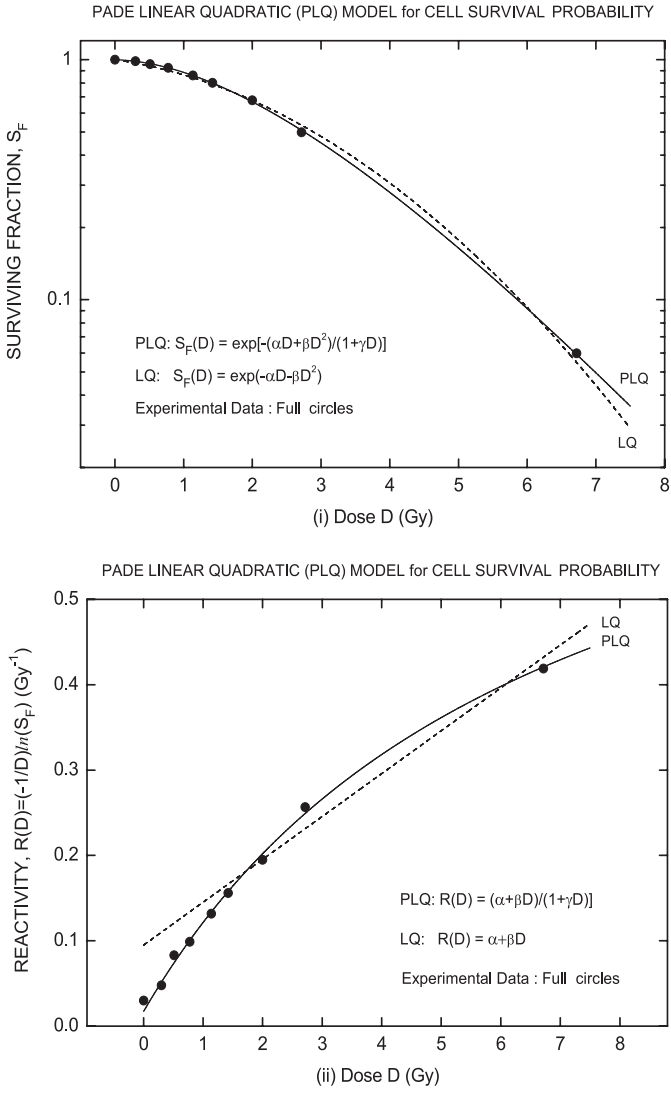

Figure 14.1 Cell surviving fractions $S_F(D)$ as a function of radiation dose D in Gy (top panel (i)). Bottom panel (ii), as the Fe-plot, shows the so-called reactivity $R(D)$ given by the product of the reciprocal dose D^{-1} and the negative natural logarithm of $S_F(D)$, as the ordinate versus D as the abscissa. Any departure of experimental data from a straight line indicates inadequacy of the LQ model for the Fe-plot. Experimental data (full circles):[30] the mean clonogenic surviving fractions $S_F(D)$ (panel(i)) and $R(D) \equiv -(1/D)\ln(S_F)$ (panel (ii)) for the human small cell lung cancer line (U1690) irradiated by 190 kVp X-rays. Theories: solid curve for the PLQ (Padé linear-quadratic) model and dashed curve for the LQ (linear-quadratic) model (the straight line $\alpha + \beta D$ on panel (ii)).

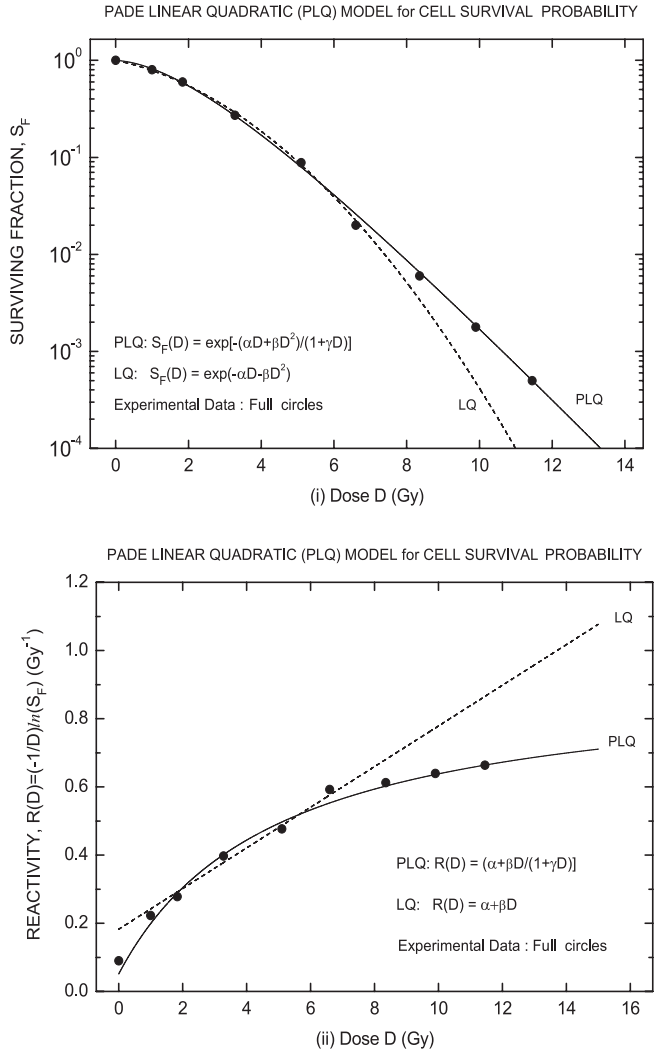

Figure 14.2 Cell surviving fractions $S_F(D)$ as a function of radiation dose D in Gy (top panel (i)). Bottom panel (ii), as the Fe-plot, shows the so-called reactivity $R(D)$ given by the product of the reciprocal dose D^{-1} and the negative natural logarithm of $S_F(D)$, as the ordinate versus D as the abscissa. Any departure of experimental data from a straight line indicates inadequacy of the LQ model for the Fe-plot. Experimental data (full circles):[17] the mean clonogenic surviving fractions $S_F(D)$ (panel(i)) and $R(D) \equiv -(1/D)\ln(S_F)$ (panel (ii)) for the Chinese hamster cells grown in culture and irradiated by 50 kVp X-rays. Theories: solid curve for the PLQ (Padé linear-quadratic) model and dashed curve for the LQ (linear-quadratic) model (the straight line $\alpha + \beta D$ on panel (ii)).

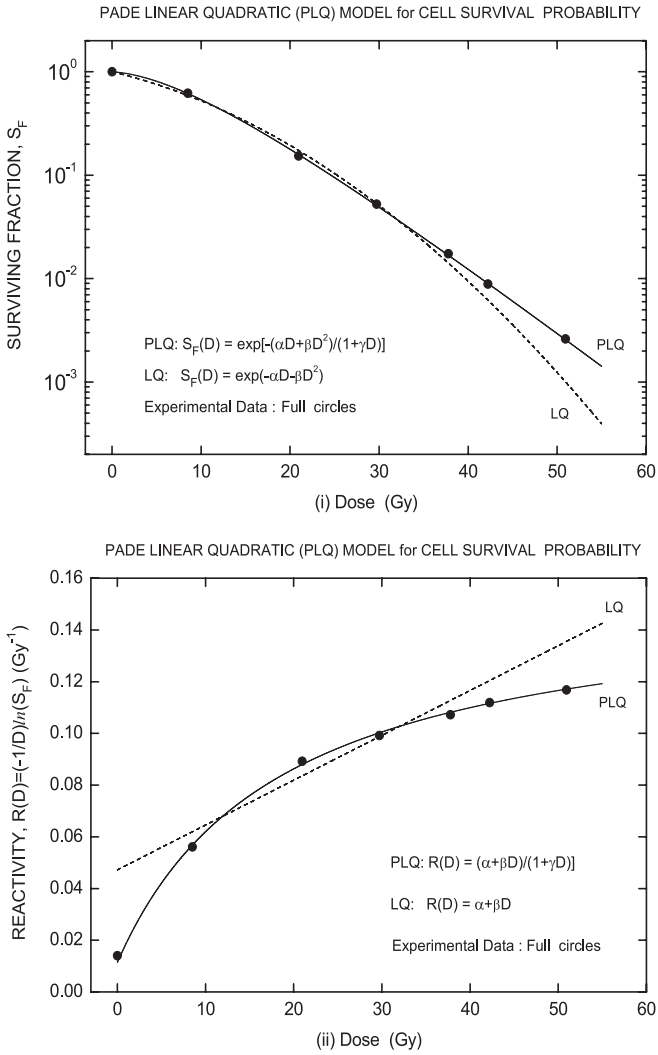

Figure 14.3 Cell surviving fractions $S_F(D)$ as a function of radiation dose D in Gy (top panel (i)). Bottom panel (ii), as the Fe-plot, shows the so-called reactivity $R(D)$ given by the product of the reciprocal dose D^{-1} and the negative natural logarithm of $S_F(D)$, as the ordinate versus D as the abscissa. Any departure of experimental data from a straight line indicates inadequacy of the LQ model for the Fe-plot. Experimental data (full circles):[31] the mean clonogenic surviving fractions $S_F(D)$ (panel(i)) and $R(D) \equiv -(1/D)\ln(S_F)$ (panel (ii)) for the asynchronous V79 Chinese hamster cells irradiated hypoxically by 250 kVp X-rays with a concurrent 30 min exposure to the sulfhydryl-binding agent, N-ethylmaleimide, of low concentration 0.75 μM. Theories: solid curve for the PLQ (Padé linear-quadratic) model and dashed curve for the LQ model (the straight line $\alpha + \beta D$ on panel (ii)).

Padé linear-quadratic formalism, which is rooted in a firm theoretical and practical basis of chemical kinetics for repair of radiation damage by means of enzyme-lesion catalytic reaction.

It should be noted that the concept of the Fe-plot is critically important for both the conventional fractionation and hypofractionation. It impacts one of the most delicate decisions by radiotherapists regarding the question: given that radiation indiscriminately damages both tumorous and healthy cells, how should the total dose vary as a function of the overall irradiation time, as well as the number of fractions, in order to maintain a constant biological end effect and also minimize complications to the normal tissues at risk?

6. DISCUSSION AND CONCLUSION

6.1 Biologically expressed response of the cell to irradiation

It has been argued that the ultimate success of radiotherapy rests upon the possibility to properly understand cell repair after irradiation.[14, 15] The main focus of this chapter is on enzymatic repair mechanisms encountered in radiobiological descriptions of dose–effect relationships. With this goal, we further elaborate the Padé linear-quadratic model, or the PLQ model[4–6] for cell surviving fraction, $S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)$, as a function of a single absorbed dose D. In this novel biophysical model, the biological effect of radiation, $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}(D) = -\ln S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)$, is given by the Padé approximant, $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}(D) = (\alpha D + \beta D^2)/(1 + \gamma D)$. By a smooth transition, this rational function becomes automatically linear at both low and high doses, $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}(D) \underset{D\to 0}{\longrightarrow} \alpha D$ and $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}(D) \underset{D\to \infty}{\longrightarrow} (\beta/\gamma)D$. Precisely such types of exponentials have been observed by numerous measurements in the said two dose limits. The PLQ model has three parameters $\{\alpha, \beta, \gamma\}$. Here, as usual, radiosensitivity α is a single event inactivation constant in units of Gy^{-1}. However, parameter β, which is in units of Gy^{-2}, is derived from the introduction of a delay time in the cell response to radiation insult. This delay is associated with the existence of a repair or recovery time τ. Any two consecutive radiation events or hits would be wasted, i.e., not registered at all by the cell, if they were separated by a time interval Δt such that $\Delta t < \tau$. The cell becomes effectively insensitive to such consecutive hits. Parameter γ is the reciprocal of the Michaelis–Menten constant, K_{M}, from the theory of chemical kinetics for enzyme catalysis. This latter quantity is the concentration of lesions at which the enzyme velocity of repair, v_0, attains one half of its maximum,[7] i.e. $v_{\max}$.

6.2 Dose–effect relationships at low, intermediate (shoulder), and high doses

One of the most important advantages of the PLQ model relative to the linear-quadratic model is of particular relevance to radiotherapy by high doses per fraction used especially in stereotactic radiosurgery. For this treatment modality, called hypofractionation, the LQ model is inadequate, since its biological effect, $\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}(D) = \alpha D + \beta D^2$, has a high-dose asymptote $\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}(D) \underset{D\to\infty}{\longrightarrow} \beta D^2$, which is at variance with the corresponding experimental data exhibiting the exponential shape, $\mathrm{E}_{\mathrm{B}}^{(\mathrm{exp})}(D) \sim D$, as $D \to \infty$. This severely hampers the proper use of one of the key quantities in dose planning systems, the so-named biologically effective dose, which is a scaled biological effect, $\mathrm{BED}(D) = (1/\alpha)\mathrm{E}_{\mathrm{B}}(D)$. Since the LQ model is not universally valid at all doses, the entire set of the given experimental data for $\mathrm{BED}^{(\mathrm{exp})}(D)$ cannot be used for extracting the biological parameters. Therefore, the usual practice is to carry out a segmentation of the given set of experimental data $\mathrm{BED}^{(\mathrm{exp})}(D)$ into different dose ranges to estimate the ratio β/α from the postulated relation $\mathrm{BED}^{(\mathrm{exp})}(D) \approx \mathrm{BED}^{(\mathrm{LQ})}(D)$, where $\mathrm{BED}^{(\mathrm{LQ})}(D) = (1/\alpha)\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}(D) = 1 + (\beta/\alpha)D$. A serious disadvantage of such a procedure is that the quotient β/α and, therefore, $\mathrm{BED}^{(\mathrm{exp})}(D)$ become dose-range dependent. This introduces complications in employing the BED concept to compare the conventional fractionation (2 Gy per fraction)[16–20] with hypofractionation.[21, 22] Such comparisons are critical for extrapolating the abundant experience with conventional fractionation to hypofractionated treatments. This is vital given that larger doses per fraction have a tendency of causing more severe late side effects relative to the conventional small size fractions. Additionally, the LQ model has difficulties in coping with cell survival curves with broad shoulders.[23, 24] Moreover, on top of continuously bending down as dose D is enlarged, pointing to the non-existence of the final slope and the extrapolation number n, the LQ model can break down at very low doses, as well.[12]

6.3 Beyond the linear-quadratic model of cell inactivation

In order to partially overcome the mentioned drawbacks of the LQ model, Paganetti and Goitein[25] introduced in 2001, within the amorphous track partition (ATP) model, a modification containing a Heaviside step function with a transition dose D_{T}. Their surviving fraction coincides with the linear-quadratic response $\mathrm{e}^{-\alpha D - \beta D^2}$ from the LQ model at $D \leqslant D_{\mathrm{T}}$

and, conversely, becomes a linear function of dose D at $D > D_T$ via $e^{-\alpha D_T - \beta D_T^2 - \gamma(D-D_T)}$. Here, γ is either a third independent fitting parameter or the final slope fixed by the continuity constraint of the derivative of the surviving fraction at $D = D_T$, which leads to $\gamma = \alpha + 2\beta D_T$. More recently in 2008, the modified LQ model from Ref. 25 has been renamed as the universal survival curve (USC) model by Park et al.,[26] and the linear-quadratic-linear (LDL) model by Astrahan.[27] However, the common feature of Refs. 25–27 is an *ad hoc* switch from the incorrect D^2 high-dose component in the LQ model to the corresponding term with a linear dose dependence ($\sim D$) in the cell surviving fraction. The transition dose $D = D_T$ at this switch has no justifiable biological significance, as it represents just another free parameter. Typical measurements of surviving fractions for most mammalian cell lines can be trustworthy only down to the 10^{-3} survival level. For this reason, extraction of parameter D_T from such experimental data could hardly be reliable. Astrahan[27] tried to attribute a clinical meaning to D_T by claiming that it delineates the region of the passage from the shoulder region to the linear component of the LQ model. Evidently, this is merely rewording the mathematical meaning of the mentioned Heaviside step function from Refs. 25–27 and, as such, cannot constitute a clinical nor biological interpretation of the transition dose D_T. Moreover, it has been found in applications[27, 28] that D_T can be anywhere in a quite wide dose range 15Gy–30 Gy. Such locations of D_T are incompatible with Astrahan's[27] interpretation of the transition dose, since shoulders do not typically extend to even the lowest limit (15 Gy) of the mentioned interval.

6.4 Mixed-order chemical kinetics for enzymatic cell repair systems

The mentioned problems with the LQ model have also been addressed within the PLQ model.[4–6] In this mechanistic description, as opposed to an empirical transition dose D_T, different passages from intermediate to high doses are governed by natural switches from various orders (zero, first, second) of chemical kinetics that underlies interactions of radiation with the cell. A key role in these different switches from one to another dose dependence of cell surviving fraction is the overall activity of enzyme molecules in the process of repair of radiation damage of the cell. This mixed-order enzyme catalysis, which is at the center of the cell repair system, guarantees the emergence of the correct asymptotes of the biological effect at both small and large doses. It also secures the existence of a shoulder of the proper width at intermediate doses in typical cell surviving fractions. Such a clear mechanism is backed by the accompanying mathematical formalism

in the PLQ model through the Padé approximant, which is known to provide optimal interpolations and extrapolations between different regions of a given function.[11] This is achieved smoothly without ever resorting to unnecessary artifices, such as sewing two different regions by a transition dose D_T placed at an empirically found point through the Heaviside step function as in Refs. 25–27. Our initial testings,[4–6] as reviewed here, and our more recent thorough comparisons of nine different models with six cell lines[28] resulted in the common conclusion that the PLQ model systematically provides the most satisfactory description of cell survival after irradiation. This is most prominently evidenced at high doses in the reconstructed dose–effect curves as well as in the associated Fe-plots.[29]

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