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ORIGINAL PAPER

Mechanistic description of survival of irradiated cells: repair kinetics in Padé linear-quadratic or differential Michaelis–Menten model

Dževad Belkić · Karen Belkić

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Abstract Biophysical models for repair mechanisms for cell surviving fractions $S_{\mathrm{F}}(D)$ after exposure to radiation are studied. The principal focus is on a novel theory, the Padé-linear quadratic (PLQ), or equivalently, the differential Michaelis–Menten radiobiological model, which predicts $S_{\mathrm{F}}(D)$ as a function of the absorbed dose D in the form $S_{\mathrm{F}}(D) = \exp\{-(\alpha D + \beta D^2)/(1 + \gamma D)\}$, with a clear biological and clinical meaning of the three parameters α, β and γ. It is shown that this functional form in the PLQ model emerges directly from the simultaneous fulfillment of the requirements for the correct asymptotic behaviors of the repair function at low and high doses. Moreover, this automatically secures the purely exponential cell kill modes at both small and large D, as also encountered in the corresponding experimental data for cell surviving fractions. Further, it is demonstrated that the PLQ-based repair function, given by a rectangular hyperbola, coincides with the reaction velocity for enzyme catalysis from the Michaelis–Menten mechanism. This repair velocity is the halved harmonic mean of the low- and high-dose asymptotes of the catalytic repair function. Such circumstances constitute a firm mechanistic basis of the PLQ model, which is shown to exhibit excellent agreement with measurements. Robust applications of

Dž. Belkić (✉) · K. Belkić
Department of Oncology and Pathology, Karolinska Institute,
P.O. Box 260, 171 76 Stockholm, Sweden
e-mail: Dzevad.Belkic@ki.se

K. Belkić
School of Community and Global Health, Claremont Graduate University,
Claremont, CA, USA

K. Belkić
Institute for Prevention Research, University of Southern California School of Medicine,
Los Angeles, CA, USA

the PLQ model are anticipated, especially in hypofractionted radiotherapy, such as stereotactic radiosurgery.

Keywords Chemical kinetics · Enzyme catalysis · Michaelis–Menten model · Radiobiological models · Padé approximant · Hypofractionated radiotherapy

1 Introduction

1.1 Two principal goals of radiotherapy

The ultimate goal of radiotherapy is to improve both quality of life and survival of patients. However, the notion of cure might have different meanings for different patients. For some patients good quality of life with a co-existent tumor is a viable option. However, for others longevity is the priority, even if it is accompanied with poor quality of life. Moreover, not only private, but also professional quality of life is crucial for those patients who are struck with cancer at an age when they could still be productive at work. Returning to work during and after cancer radiotherapy is often a challenge for the patient and for work conditions. The latter conditions need judicious adjustment to avoid overprotection, and yet allow resumption of a certain degree of former professional tasks. This could enhance the patient's continued fighting chance and provide comfort of being a part of the society's work force. Both quality of life and survival might not be in reach for every patient by any of the existing treatment modalities even with never ceasing advances in technology. For this reason it would be optimal if, regarding these two human sides of the radiotherapeutic goals, patient choice could also be an element of the decision making in selecting the treatment strategy, which could best suit each individual case. This would be a component of utmost importance within the realm of biologically-optimized and, indeed, personalized radiotherapy.

The choice between the mentioned two alternatives is never easy and clear cut, as it depends upon many uncertainties. And this is where therapeutic research in oncology comes in to tap as deeply as possible into the unknowns in an attempt to reduce these uncertainties and improve predictability about tumor commencement, growth, metastasis and the overall chance for cure. Hand-in-hand with such efforts go research and practice in cancer diagnostics, as early tumor detection very often increases the overall probability of successful treatment and eventually of cure. By the exceedingly complex nature of cancer, research in this field must, by necessity, be comprehensive and interdisciplinary encompassing medicine, biology, chemistry, physics and mathematics.

The present study is precisely in this crossroad of five different disciplines, as we shall deal with theoretical descriptions of cell and tissue survival after irradiation. Our main approach to this complicated problem is through a focus on cell repair mechanisms. Radiobiological models for cell surviving fractions are of paramount importance as one of the main inputs to dose planning systems for treatment of patients with cancer. The ultimate success of radiotherapy rests upon the possibility to properly understand cell repair after irradiation. For this reason, the main emphasis of the present study will be placed on mechanistic repair-based radiobiological models.

1.2 The concept of dose

A single dose D is often viewed as the energy absorbed per unit volume per unit mass of that volume. However, such a definition is insufficiently precise, since it is not this dose D which is actually deposited to the tissue. Within the said colloquial definition, it would be legitimate to pose an otherwise wrong question, e.g: "what should be the dose D delivered to the lung?" Instead, a more precise concept should be used, as found within e.g. the corresponding microdosimetric considerations. There, a single absorbed dose D is defined as the expected value of the so-called specific energy z. Specific energy z is the energy per unit mass per unit volume deposited per event per cell nucleus. This highlights the local nature of a single absorbed dose D, which is, thus, deposited at a given spatial point $\boldsymbol{r}$ in tissue. Therefore, with this microdosimetric definition of dose, the above question is untenable, as it refers to the dose D absorbed by a whole organ. Instead, the right question is: "what should be the dose D delivered to a given point $\boldsymbol{r}$ in a spatial domain within the lung?" The reason for strictly adhering to this correct microdosimetric dose concept is of fundamental importance, since resorting to mathematical modeling of cell survival upon irradiation and, most importantly, to radiotherapy in clinical practice would be severely hampered if an equivocal definition of a single absorbed dose D is used from the outset. The main justification for adhering to the microdosimetric definition of a dose D is in capturing a key physical mechanism for energy deposition during the passage of monoenergetic beam particles through tissue. By this mechanism, a single dose D refers to the energy deposited in a single event (hit), which is conceived as a collisional interaction (ionization, excitation, electron capture,...) between a target (e.g. a sensitive site of a cell) and the traversing particles (primary, secondary,...). These radiation events are intrinsically local, i.e. limited to a given atom or molecule. Hence, a single absorbed dose D for a single event is a point-like structure which, as such, cannot be viewed as being spread out to cover a whole organ. In reality, beams are not monoenergetic, but nevertheless the meaning of a single absorbed dose D is fully preserved for energy spreading in the beam, since the mentioned interactions between a projectile and a target still constitute a single radiation event.

The above endorsement of microdosimetry on the level of the definition of a single absorbed dose D does not imply sharing the often held view that radiation damage to biological molecules can be fully understood and described by relying exclusively upon the spatial distributions of energy depositions in tissue. Quite the contrary, nothing is further from the truth than such a reductionist view, since the response of biomolecules from tissue to irradiation is strikingly multifaceted, as it widely ranges from physical through biochemical to physiological aspects of complex radiation-cell interactions. In this chain, physical deposition of the particle energy is only the initial stage. To properly cover the next step, this aspect of a beginning of the physical damage during irradiation must subsequently be connected with e.g. the associated biological damage to the cell. Most severe lesions to the cell are double strand breaks (DSB) of deoxyribonucleic acid (DNA), which is considered as the principal target molecule in assessments of the radiation damaged tissue. The appearance of DSBs is one type of severe biological damage caused by energy deposition through a physical hit of a beam particle. This is direct biological radiation damage. Likewise, DSBs

could be produced by indirect biological radiation damage. In this case, e.g. two particle tracks could produce sublethal radiation damage to DNA with the ensuing single strand breaks (SSB) whose subsequent interaction might lead to DSBs. This is one example among many other pathways in the potential development of a lethal lesion from sublethal radiation damage.

1.3 Cure and cell killing

The term "cell killing" does not necessarily mean that the cell is actually killed in the literal sense of its total disintegration. For the latter to happen, much more energy is necessary than what is actually being deposited at any given spatial point in the treated tissue using most of the conventional radiotherapeutic modalities. Rather, by convention, cell killing refers to fatal disruption of the reproductive integrity of the cell [1]. Stopping cell divisions in a tumorous tissue amounts to cessation of proliferation (as a way of forming clones, i.e colonies) and accomplishing this task is customarily considered to be equivalent to curing the treated tissue. The tumor would disappear altogether only if all the cancerous cells are eradicated. If only one tumor cell survives, tumor control probability would be equal to zero. For this reason one might be inclined to think that it is perhaps preferable to talk about cure rather than about cell kill. This differentiation is more than just semantics.

1.4 Two main variabilities in cellular radiobiology

On top of different radiation modalities (photons, charged particles, etc.), cellular radiobiology deals with two main variabilities. 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 among 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 are the two different ways in which 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.

2 Classical hit-target methodologies

The principal assumption of the hit-target model is that each cell has one or more sensitive sites [2–4]. In this formalism, it is supposed that a cell could lose its reproductive capacity only if each sensitive site absorbs a certain amount of the impinging

radiation one or more times. Here, radiation quanta are interpreted as radiation hits. As will be elaborated in the next two subsections, there are four variants within this framework, such as the single-target-single-hit (ST-SH), multi-target-single-hit (MT-SH), single-target-multi-hit (ST-MH) and multi-target-multi-hit (MT-MH) models.

2.1 Single-target-single-hit model

In the ST-SH model, only one target per cell is considered. This single target must absorb the mean lethal dose D_0 in order to be inactivated. The corresponding cell survival is:

$$S_{\mathrm{F}}^{(\mathrm{ST-SH})}(D) = \mathrm{e}^{-D/D_0}\,. \tag{2.1}$$

Equivalently, the probability P for occurrence of a single lethal event following absorption of dose D is:

$$P_{\mathrm{F}}^{(\mathrm{ST-SH})}(D) = 1 - S_{\mathrm{F}}^{(\mathrm{ST-SH})}(D) = 1 - \mathrm{e}^{-D/D_0}\,. \tag{2.2}$$

Mean lethal dose D_0, which is also known as the D_{37} dose, represents the dose which reduces cell survival by $1/\mathrm{e} \approx 0.37$, or equivalently, by 37 % along the final (terminal) part of the dose-effect curve. For this reason, D_0 is often called the "final D_0".

2.2 Multi-target-single-hit model

Generalizing the simplest ST-SH model to the case with some n identical targets per cell yields the MT-SH model. This time, a given cell would be killed whenever all its sensitive sites (targets) are hit once. Thus, by assuming the identical radiosensitivity $1/D_0$ for all the n targets per cell, the probability for a lethal event in the MT-SH model becomes:

$$P_{\mathrm{F}}^{(\mathrm{MT-SH})}(D) = \left(1 - \mathrm{e}^{-D/D_0}\right)^n. \tag{2.3}$$

The associated surviving fraction reads as:

$$S_{\mathrm{F}}^{(\mathrm{MT-SH})}(D) = 1 - P_{\mathrm{F}}^{(\mathrm{MT-SH})}(D) = 1 - \left(1 - \mathrm{e}^{-D/D_0}\right)^n. \tag{2.4}$$

The asymptotic behavior of this dose-effect curve at large doses D reads as:

$$S_{\mathrm{F}}^{(\mathrm{MT-SH})}(D) \underset{D\to\infty}{\longrightarrow} n\mathrm{e}^{-D/D_0}\,, \tag{2.5}$$

where n is the extrapolation number. In a semilogarithmic graph of cell surviving fraction S_{F} as a function of dose D, the terminal part of this functional relationship is a straight line with the slope $1/D_0$. If this final portion of the dose-effect curve is extrapolated back to the ordinate $S_{\mathrm{F}}(D)$, then the intercept of the said straight line

with the ordinate at $D = 0$, i.e. the location of point $S_F(0)$, would represent precisely n via $\{S_F(D) \approx n e^{-D/D_0}\}_{D=0} = n$. This is how the name "extrapolation number" was assigned to quantity n from the high-dose asymptote of $S_F(D)$ in (2.5). Such a plausible geometric interpretation of n with a graphical illustration has been given by Atwood and Norman [5]. Subsequently, the same interpretation and terminology were reintroduced by Alper et al. [6]. In the MT-SH model, extrapolation number n is biologically interpreted as the number of targets (critical sites) in a given cell (in which case $n = 1, 2, 3, \ldots$). The initial slope of cell survival curve $S_F^{(MT-SH)}(D)$ in the limit of small doses ($D \to 0$) is zero. This is the result from the definition of the initial slope s_i, as the derivative of the surviving fraction, $(d/dD)S_F^{(MT-SH)}(D)$, taken at $D = 0$:

$$\text{MT} - \text{SH model}: \quad \begin{cases} \text{Initial slope} \equiv s_i = 0 \\ \text{Final slope} \equiv s_f = k_0 = \dfrac{1}{D_0} \end{cases} . \tag{2.6}$$

The initial slope $s_i = 0$ is biologically interpreted as an underestimation of the effect of low-dose radiation. It should be noted, however, that zero-valued initial slopes are not customarily confirmed by most experimental measurements on typical cell lines encountered in radiobiology.

3 Two component model

3.1 Overcoming zero-valued initial slope of the classical hit-target model

It would be desirable to overcome the main drawback of the MT-SH model, i.e. the zero-valued initial slope. This limitation can be lifted by using e.g. the two component or two compartment (2C) model [7]:

$$\begin{aligned} S_F^{(2C)}(D) &= e^{-D/D_1}\left[1 - \left(1 - e^{-D/D_n}\right)^n\right] \\ &= S_F^{(1)}(D) S_F^{(2)}(D) \qquad (n = 2, 3, 4, \ldots). \end{aligned} \tag{3.1}$$

The first component $S_F^{(1)}(D) = e^{-D/D_1}$ describes a single-hit-single-target inactivation mode, where $1/D_1$ is the initial radiosensitivity as well as the initial non-zero slope. In analogy to the mentioned alternative terminology "final D_0" for the mean lethal dose D_0, we shall refer to D_1 as the "initial D_0" to denote survival reduction by 1/e in the *initial* part of the dose-effect curve. The second component in (3.1) is $S_F^{(2)}(D) = 1 - (1 - e^{-D/D_n})^n$, which represents the multi-target inactivation mode with the associated radiosensitivity $1/D_n$. Here, D_n with $n \geq 2$ is termed the "MT-final D_0" of the multi-target part of inactivation, which is D_0 dose required to reduce survival by 1/e along the *final* portion of the dose-effect curve. The alternative labels for D_1 and D_n encountered in the literature are ${}_1D_0$ and ${}_nD_0$, respectively:

$$D_1 \equiv {}_1D_0 \quad , \quad D_n \equiv {}_nD_0 \, . \tag{3.2}$$

In the high-dose limit, we have $S_{\mathrm{F}}^{(2)}(D) \sim n\mathrm{e}^{-D/D_n}$, so when this is multiplied by e^{-D/D_1} from $S_{\mathrm{F}}^{(1)}(D)$, according to (3.1) it follows:

$$\begin{aligned} S_{\mathrm{F}}^{(2\mathrm{C})}(D) &\underset{D\to\infty}{\longrightarrow} n\mathrm{e}^{-D/D_1-D/D_n} \\ &\equiv n\mathrm{e}^{-D/D_0}\,, \end{aligned} \tag{3.3}$$

where D_0, as the final slope, is defined by:

$$\frac{1}{D_0} \equiv \frac{1}{D_1} + \frac{1}{D_n} \quad \text{or} \quad D_0 = \frac{D_1 D_n}{D_1 + D_n}\,, \tag{3.4}$$

$$D_0 < D_1\,. \tag{3.5}$$

The surviving fraction in the 2C model can alternatively be expressed as:

$$S_{\mathrm{F}}^{(2\mathrm{C})}(D) = \mathrm{e}^{-D/D_1}\left\{1 - \left[1 - \mathrm{e}^{-D(1/D_0 - 1/D_1)}\right]^n\right\}\,, \tag{3.6}$$

where, by reference to (3.4), dose D_n from the part $S_{\mathrm{F}}^{(2)}(D)$ of $S_{\mathrm{F}}^{(2\mathrm{C})}(D)$ in (3.1) is formally written in terms of the so-called "harmonic difference" of D_0 and D_1 :

$$\frac{1}{D_n} = \frac{1}{D_0} - \frac{1}{D_1}\,. \tag{3.7}$$

3.2 Effective dose as a halved harmonic mean of two asymptotes

Dose D_0 from (3.4) is, by definition, the so-named effective dose, which is recognized as the halved harmonic mean of D_1 and D_n. In general, the harmonic mean (average) $\mathrm{h}(a_1, a_2)$ of any two quantities or functions a_1 and a_2 is:

$$\frac{1}{\mathrm{h}(a_1, a_2)} = 2\left(\frac{1}{a_1} + \frac{1}{a_2}\right), \quad \mathrm{h}(a_1, a_2) = 2\frac{a_1 a_2}{a_1 + a_2} \quad \text{(Harmonic mean)}\,. \tag{3.8}$$

A related quantity, which is frequently used in applications, is the halved harmonic mean of a_1 and a_2 called the effective value a_{eff} :

$$\frac{1}{a_{\mathrm{eff}}} = \frac{1}{a_1} + \frac{1}{a_2} \quad , \quad a_{\mathrm{eff}} = \frac{a_1 a_2}{a_1 + a_2}\,. \tag{3.9}$$

In this way, the reciprocal of the final slope $1/D_0$ from (3.4) in the 2C model appears as the effective dose $D_0 = D_{\mathrm{eff}}$ where:

$$D_{\mathrm{eff}} = \frac{D_1 D_n}{D_1 + D_n} = D_0\,. \tag{3.10}$$

It is well-known that for rate processes or rate reactions, the truest average of two given quantities is provided by the so-called harmonic mean. Thus, $D_{\mathrm{eff}} = D_0$ from

(3.10) is the truest average of D_1 and D_n in a modified hit-target theory given by the two component model (3.3).

3.3 Radiosensitivities and dose reciprocals

Reciprocals of doses D_0 , D_1 and D_n are the corresponding positive-definite radiosensitivities k_0 , k_1 and k_n, respectively:

$$\left.\begin{array}{ccccc} k_0 = \dfrac{1}{D_0} & , & k_1 = \dfrac{1}{D_1} & , & k_n = \dfrac{1}{D_n} \\ k_0 > 0 & , & k_1 > 0 & , & k_n > 0 \end{array}\right\} . \tag{3.11}$$

In analogy to the mentioned mean lethal doses ${}_1D_0$ and ${}_nD_0$ for D_1 and D_n, the alternative notations for the associated slopes k_1 and k_n are ${}_1k_0$ and ${}_nk_0$, respectively:

$$k_1 \equiv {}_1k_0 \quad , \quad k_n \equiv {}_nk_0 \, , \tag{3.12}$$

with the same meaning ${}_1k_0 = ({}_1D_0)^{-1}$ and ${}_nk_0 = ({}_nD_0)^{-1}$. Thus, using (3.5) and (3.11), we have:

$$k_0 > k_1 \, . \tag{3.13}$$

The initial and final slope in the 2C model are given by:

$$\text{2C model} : \quad \left\{\begin{array}{l} \text{Initial slope} \equiv s_{\text{i}} = k_1 = \dfrac{1}{D_1} \\ \text{Final slope} \equiv s_{\text{f}} = k_0 = \dfrac{1}{D_0} \end{array}\right. . \tag{3.14}$$

It is also useful both in experiment and theory to consider the quotient of the initial and final slopes or the associated doses. For example, the dose quotient D_1/D_0 is called "the initial-to-final mean lethal dose ratio". Its reciprocal $(1/D_1)/(1/D_0) = k_1/k_0$ has three alternative names such as "the initial-to-final slope ratio", "the initial-to-final radiosensitivity ratio" and "the initial-to-final inactivation constant ratio". For brevity, quotient k_1/k_0 shall hereby be denoted by a positive dimensionless constant f whose value belongs to the interval (0,1):

$$\left.\begin{array}{c} f = \dfrac{k_1}{k_0} \quad \text{(Initial}-\text{to}-\text{final slope ratio)} \\ f = \dfrac{D_0}{D_1} \quad \text{(Final}-\text{to}-\text{initial mean lethal dose ratio)} \\ 0 < f < 1 \end{array}\right\} , \tag{3.15}$$

where (3.5) and (3.13) are employed to deduce the stated inequality. Using these definitions, we can rewrite the reciprocal $1/D_0$ from (3.4) as:

$$k_0 = k_1 + k_n \, . \tag{3.16}$$

Thus, while dose D_0 from (3.4) is the halved harmonic mean of D_1 and D_n, the associated radiosensitivity k_0 in (3.16) is the doubled arithmetic mean. Furthermore:

$$f + g = 1\,, \tag{3.17}$$

where g is associated with the multitarget inactivation mode:

$$\left.\begin{array}{c} g = \dfrac{k_n}{k_0}\ \text{(Ratio of final slopes : multi}-\text{target}-\text{to}-\text{single}-\text{target)} \\ g = \dfrac{D_0}{D_n}\ \text{(Ratio of final } D_{37} \text{ doses : single}-\text{target}-\text{to}-\text{multi}-\text{target)} \\ 0 < g < 1 \quad , \quad n \geq 2 \end{array}\right\}\,. \tag{3.18}$$

3.4 Relative radiosensitivity

Within the 2C model, it is useful to have a measure of the effect of the multi-target radiosensitivity. This can be assessed by means of the relative radiosensitivity introduced through the quotient of the multi- and single-target dimensionless radiosensitivities $1/D_n$ and $1/D_1$, respectively:

$$m \equiv \frac{D_1}{D_n} = \frac{k_n}{k_1} \quad , \quad m > 0\,. \tag{3.19}$$

By means of (3.19), one can express the quotients of sensitivities $1/D_0$ and $1/D_1$ as well as of $1/D_0$ and $1/D_n$ via:

$$\frac{D_1}{D_0} = 1 + m = \frac{k_0}{k_1} \quad , \quad \frac{D_n}{D_0} = \frac{1+m}{m} = \frac{k_0}{k_n}\,. \tag{3.20}$$

Thus, the "initial-to final D_0 ratio" D_1/D_0 is expressed as $1+m$. The three radiosensitivity ratios k_1/k_0, k_n/k_0 and k_n/k_1 written in terms of parameters f and g take the form:

$$\frac{k_1}{k_0} = f \quad , \quad \frac{k_n}{k_0} = g \quad , \quad \frac{k_n}{k_1} = \frac{g}{f}\,. \tag{3.21}$$

Likewise, the quantities f and g expressed by means of m read as:

$$f = \frac{1}{1+m} \quad , \quad g = \frac{m}{1+m} \quad , \quad g = mf\,. \tag{3.22}$$

It follows from (3.20) that very large values of m would stem from very small values of k_1 that are, in turn, associated with negligibly small or near-to-zero initial slope of the surviving fraction. Given that $m > 0$, as per (3.19), the first of the relations from (3.20), i.e. $1+m = k_0/k_1$ evidently implies $k_0/k_1 > 1$, in agreement with (3.4). On the other hand, writing the second relation from (3.20) as $1 + 1/m = k_0/k_n$, it obviously follows that $1 + 1/m = k_0/k_n > 1$, so that $0 < g < 1$, as in (3.18).

Using parameter m, dose D_n associated with the multi-target inactivation becomes:

$$D_n = \frac{1+m}{m}\frac{D_\mathrm{q}}{\ln n} = \frac{1}{g}\frac{D_\mathrm{q}}{\ln n}\,, \tag{3.23}$$

where D_q is the quasi-threshold dose which represents the width of a shoulder in a survival curve:

$$D_\mathrm{q} = D_0 \ln n\,. \tag{3.24}$$

In a semilogarithmic plot for $S_\mathrm{F}(D)$ versus D, the location of dose D_q is precisely at the point of intersection of the back-extrapolated linear, terminal part of the dose-effect curve with the horizontal straight line at the level of 100 % survival with $S_\mathrm{F}(D_\mathrm{q}) = 1$, where $D_\mathrm{q} \neq 0$.

3.5 Different, equivalent forms of cell surviving fractions

The 2C model from (3.1) can be cast in different forms involving radiosensitivities as:

$$S_\mathrm{F}^{(2\mathrm{C})}(D) = \mathrm{e}^{-D/[(1+m)D_0]}\left\{1-\left(1-\mathrm{e}^{-mD/[(1+m)D_0]}\right)^n\right\}\,, \tag{3.25}$$

or equivalently,

$$S_\mathrm{F}^{(2\mathrm{C})}(D) = \mathrm{e}^{-k_1 D}\left[1-\left(1-\mathrm{e}^{-k_n D}\right)^n\right]\,. \tag{3.26}$$

Employing (3.16) to write radiosensitivity k_n as the "arithmetic difference":

$$k_n = k_0 - k_1\,, \tag{3.27}$$

we can express the part $S_\mathrm{F}^{(2)}(D)$ from $S_\mathrm{F}^{(2\mathrm{C})}(D)$ in (3.26) in terms of k_0 and k_1 :

$$S_\mathrm{F}^{(2\mathrm{C})}(D) = \mathrm{e}^{-k_1 D}\left\{1-\left[1-\mathrm{e}^{-(k_0-k_1)D}\right]^n\right\}\,. \tag{3.28}$$

The cell surviving fraction $S_\mathrm{F}^{(2\mathrm{C})}(D)$ written in terms of f and g takes the form:

$$S_\mathrm{F}^{(2\mathrm{C})}(D) = \mathrm{e}^{-fD/D_0}\left\{1-\left[1-\mathrm{e}^{-gD/D_0}\right]^n\right\}\,. \tag{3.29}$$

All of the above equivalent expressions, such as (3.1), (3.25), (3.28) and (3.29) for the dose-effect curve $S_\mathrm{F}^{(2\mathrm{C})}(D)$ in the 2C model have three parameters, involving one of these three-element sets: $\{n; D_1, D_n\}$, $\{n; m, D_0\}$, $\{n; k_1, k_n\}$ or $\{n; f, D_0\}$, respectively. Importantly, irrespective of which set is chosen, the parameters of the 2C model have a clear and simple biological interpretation. Common to all the sets from this model is the extrapolation number n, which represents the number of sensitive

sites or targets in the given cell. The considered cell is viewed as killed if radiation hits every single target in that cell once. Further, parameters $k_1 = 1/D_1$ and $k_0 = 1/D_0$ are the initial and final radiosensitivities. Here, alongside the mean lethal dose D_0, we have dose D_1 which is associated with the single-target inactivation mode $S_{\mathrm{F}}^{(1)}(D) = \mathrm{e}^{-D/D_1} = \mathrm{e}^{-k_1 D}$. Similarly, parameter $k_n = 1/D_n$ is the radiosensitivity, which corresponds to the multi-target inactivation mode $S_{\mathrm{F}}^{(2)}(D) = (1 - \mathrm{e}^{-D/D_n})^n = (1 - \mathrm{e}^{-k_n D})^n$. As per (3.15), parameter $1+m = k_0/k_1$ is "the final-to-initial radiosensitivity ratio". On the other hand, the difference $k_0 - k_1$ coincides precisely with k_n, which is the radiosensitivity from the multi-target cell kill mode, $k_n = k_0 - k_1 = 1/D_0 - 1/D_1$. Likewise, mathematical and graphical illustration of parameters such as n, k_1 and k_0 is also straightforward. Thus, n is the extrapolation of the terminal, exponential section of the dose-effect curve back to the maximal, i.e. 100 % surviving fraction. Moreover, k_1 and k_0 are the initial and final slopes of the same dose-effect curve $S_{\mathrm{F}}^{(2\mathrm{C})}(D)$ in the two component model.

4 The concept of cell repair

4.1 The prescribed behaviors of surviving fractions at low and high doses

Physically, it is expected that a repair system will not be active at small and large doses [1]. This is plausible because insufficient cell damage at very low doses is unlikely to trigger the repair system. Likewise, at very high doses, a large number of lesions would overwhelm and, thus, inactivate any repair system, which could itself be damaged by strong radiation. In both cases, without a functioning repair mechanism, a purely exponential cell kill would prevail [8–10]:

$$-\ln S_{\mathrm{F}}(D) \underset{D\to 0}{\longrightarrow} k_1 D\,, \tag{4.1}$$

$$-\ln S_{\mathrm{F}}(D) \underset{D\to \infty}{\longrightarrow} k_0 D - \ln n\,, \tag{4.2}$$

where k_1 and k_0 retain the same meaning of the initial and final slopes of the dose-effect curve as in the ST-SH model. Here, parameter n is also called the extrapolation number which, however, unlike the MT-SH model, is unrelated to the number of targets. Nevertheless, repair models also retain the generic relation (3.24) from the MT-SH model to connect the extrapolation number n with the mean lethal dose D_0 and the quasi-threshold dose D_{q}. Moreover, ratio $f = k_1/k_0$ of the initial-to-final slope from (3.15) from the hit-target description has an additional meaning in repair models, where it is re-labeled by $f_{\mathrm{u}} = k_1/k_0$, and interpreted as the fraction of unrepaired lesions. Consequently, the complement $1 - f_{\mathrm{u}}$ is the fraction of repaired lesions as labeled by g_{r} with $g_{\mathrm{r}} = (1 - f_{\mathrm{u}})/k_0 \equiv k_2/k_0$:

$$\left.\begin{array}{rl} f_{\mathrm{u}} = \dfrac{k_1}{k_0} & \text{(Fraction of unrepaired lesions)} \\ g_{\mathrm{r}} = \dfrac{k_2}{k_0} & \text{(Fraction of repaired lesions)} \\ f_{\mathrm{u}} + g_{\mathrm{r}} = 1 & (0 < f_{\mathrm{u}} < 1 \quad , \quad 0 < g_{\mathrm{r}} < 1) \end{array}\right\}, \tag{4.3}$$

where similarly to (3.16) we have,

$$k_0 = k_1 + k_2 \,. \tag{4.4}$$

This is reminiscent of (3.21) from the hit-target formalism, where ratio k_n/k_0 from (3.18) is denoted by g such that $f + g = 1$ as per (3.17). We see that in repair models, quantity k_2 from (4.3) formally resembles the final slope k_n associated with the multi-target inactivation mode in the MT-SH model. Similar relationships also hold among the equivalent quantities that are dose reciprocals from (3.11):

$$\left.\begin{array}{cccccccc} D_0 = \dfrac{1}{k_0} & , & D_1 = \dfrac{1}{k_1} & , & D_2 = \dfrac{1}{k_2} & , & D_0 < D_1 \\ k_0 > 0 & , & k_1 > 0 & , & k_2 > 0 & , & k_0 > k_1 \end{array}\right\} , \tag{4.5}$$

where D_0 has the same meaning of the mean lethal dose as in the hit-target theory. Further, in repair models, dose D_2 is the formal counterpart of dose D_n from the multi-target framework. However, in repair models, D_1 and D_2 are interpreted as doses required to produce the fractions f_u and g_r of unrepairable and reparable lesions, respectively. These formal similarities of parameters from repair and hit-target models should not be taken too literally. Such resemblances are mentioned here merely to make a symbolic reference to a more frequently used hit-target formalism rather than drawing its potential mechanistic link to repair models. In fact, a deeper relation between the two descriptions is precluded by the occurrence that repair models make no recourse whatsoever to the notion of a target in the biological interpretation of the cell response to radiation.

By reference to (3.19), we can introduce the quotient of the radiosensitivities k_2 and k_1 as:

$$\mu = \frac{k_2}{k_1} \quad , \quad \mu > 0 \,, \tag{4.6}$$

or alternatively by means of (4.3):

$$\mu = \frac{g_\mathrm{r}}{f_\mathrm{u}} \,. \tag{4.7}$$

With these definitions, similarly to (3.22), the lesion fractions f_u and g_r can be written in terms of μ via:

$$f_\mathrm{u} = \frac{1}{1+\mu} \quad , \quad g_\mathrm{r} = \frac{\mu}{1+\mu} \quad , \quad g_\mathrm{r} = \mu f_\mathrm{u} \,, \tag{4.8}$$

as in (3.22) from the 2C model where m is used instead of $\mu = k_2/k_1$ with $m = k_n/k_1$. Employing (3.24), (4.3) and (4.6), we can write the radiosensitivity k_2 by means of the quasi-threshold dose D_q, the natural logarithm $\ln n$ of the extrapolation number n

and the fraction of repaired lesions g_r :

$$k_2 = g_r \frac{\ln n}{D_q}\,, \tag{4.9}$$

or equivalently, using the relation $D_2 = 1/k_2$ from (4.5):

$$D_2 = \frac{1}{g_r}\frac{D_q}{\ln n}\,, \tag{4.10}$$

which has the form (3.23) from the 2C model.

4.2 Repair function

The effect of cell repair will be in mitigating the damage from radiation by reducing the influence of the direct cell kill mechanism ($\sim D$). This can be modeled at any dose D by requiring that $-\ln S_F(D)$ has two components as:

$$-\ln S_F(D) = k_0 D - F(D)\,, \tag{4.11}$$

$$S_F(D) = \mathrm{e}^{-k_0 D + F(D)}\quad,\quad F(D) > 0\,,\ \forall D\,. \tag{4.12}$$

Here, $F(D)$ is a positive-definite unspecified repair function which, however, must have the correct asymptotes prescribed by (4.1) and (4.2) at low and high doses:

$$F(D) \approx \begin{cases} F_0 \equiv kD\,, & D \longrightarrow 0 \\ F_\infty \equiv \ln n\,, & D \longrightarrow \infty\,, \end{cases} \tag{4.13}$$

with,

$$k \equiv k_0 - k_1 > 0\,, \tag{4.14}$$

where the inequality follows from (4.5). The ansatz $F(D) \approx F_0 \equiv kD$ at $D \to 0$, with the definition $k \equiv k_0 - k_1$ from (4.14), automatically secures the correct limit $F(D) \approx k_1 D$ at small doses from (4.1) via:

$$-\ln S_F(D) = k_0 D - F(D) \underset{D\to 0}{\longrightarrow} k_0 D - F_0 = k_0 D - kD = k_0 D - (k_0 - k_1)D = k_1 D$$

$$\therefore\quad -\ln S_F(D) \underset{D\to 0}{\longrightarrow} k_1 D \qquad \text{(QED)}.$$

Similarly, $F(D) \approx F_\infty \equiv \ln n$ at $D \to \infty$ from (4.13) guarantees the existence of the proper asymptote (4.2) through:

$$-\ln S_{\mathrm{F}}(D) = k_0 D - F(D) \underset{D\to\infty}{\longrightarrow} k_0 D - F_\infty = k_0 D - \ln n$$

$$\therefore \quad -\ln S_{\mathrm{F}}(D) \underset{D\to\infty}{\longrightarrow} k_0 D - \ln n \qquad \text{(QED)}.$$

By reference to (4.4), quantity k is identified as the radiosensitivity k_2 :

$$k = k_2\,. \tag{4.15}$$

Thus, it follows that all the repair models that are constrained to satisfy the prescribed, correct boundary conditions at both dose limits $D \to 0$ and $D \to \infty$, according to (4.11) and (4.13), formally have the same three parameters $\{k_1, k_0, n\}$ as in the two component model $\{k_1, k_0, n\}$. However, the meanings of n and $k_0 - k_1$ are different in the 2C model where $k_0 - k_1 = k_n$ and repair models for which $k_0 - k_1 = k_2$.

An adequate repair model should have a plausible working hypothesis in assuming the existence of a cell repair system, which is active at low-to-intermediate doses, but whose capacity and effectiveness declines with increased doses, until it eventually ceases to function for high irradiation. In this hypothesis, all the potentially lethal lesions would become truly lethal at very large doses. This signifies that the repair system is saturated in the sense of being completely consumed, i.e. used up for repair and/or itself inactivated by radiation. The goal of this hypothesis is that the same function $F(D)$ yields a surviving fraction $S_{\mathrm{F}}(D)$, which would then be universally valid at all doses, from the regions of weak through intermediate to strong irradiations. This gives an opportunity for the introduction of a novel universal model, which is the subject of the next section.

5 Padé linear-quadratic or differential Michaelis–Menten model

5.1 Effective repair function as a halved harmonic mean of two asymptotes

The occurrence that $F(D)$ is left unspecified, except for the imposed asymptotic behaviors in (4.13) is convenient, since it permits the introduction of various repair models for different choices of function $F(D)$. With this goal, we are presently seeking a biologically-interpretable surviving fraction $S_{\mathrm{F}}(D)$, which would simultaneously encompass the correct low- and high-dose limits (4.1) and (4.2), respectively. This would make the dose-effect curve universal due to a simultaneous and proper extrapolation to small and large doses. Moreover, the same response function $S_{\mathrm{F}}(D)$ must also correctly interpolate from both ends ($D \to 0$ and $D \to \infty$) to the intermediate dose region, where a shoulder of the survival curve resides. In other words, the sought function ought to have simultaneously interpolating and extrapolating features, with a smooth passage from low through intermediate to high doses. Among such functions there is the well-known category of rational functions in the mathematical theory of approximations. The most prominent example of these functions is the Padé approximant (PA) [11].

It will be shown in this section that the PA need not be introduced ad hoc as a new radiobiological model. Rather, this function shall emerge naturally from the simple concept of the halved harmonic mean of the two extreme limits of very small and very large doses for the repair function $F(D)$ in the biological effect (BE), $\mathrm{E_B} \equiv -\ln S_\mathrm{F}(D) = k_0 D - F(D)$, from (4.11). The same surviving fraction in the ensuing approximation called the Padé linear-quadratic (PLQ) [12–15] model will also be shown later to be rooted in the repair mechanism of Michaelis–Menten type [16].

Because surviving phenomena are intrinsically based upon rate processes, it is appropriate to specify the unknown function $F(D)$ as the halved harmonic mean of the low- and high-dose asymptotes F_0 and F_∞ of $F(D)$ from (4.13). This defines the effective repair function $F_\mathrm{eff}(D)$ according to (3.9):

$$F(D) \approx F_\mathrm{eff}(D)\,, \tag{5.1}$$

where

$$\frac{1}{F_\mathrm{eff}(D)} = \frac{1}{F_0} + \frac{1}{F_\infty} \quad , \quad F_\mathrm{eff}(D) = \frac{F_0 F_\infty}{F_0 + F_\infty} \quad ; \quad F_0 = k_2 D \quad , \quad F_\infty = \ln n\,. \tag{5.2}$$

By reference to (3.4), this is symbolically reminiscent of the introduction of the effective dose D_eff, as the mean lethal dose D_0, by the halved harmonic mean of D_1 and D_n for the single- and multi-target inactivations in the 2C model. An alternative expression for $F_\mathrm{eff}(D)$ is deduced from (4.13) and (5.1) via:

$$F_\mathrm{eff}(D) = \frac{k_2 D}{1 + \gamma D}\,, \tag{5.3}$$

with

$$\gamma = \frac{k_2}{\ln n}\,. \tag{5.4}$$

Using (4.9), parameter γ can be expressed as the ratio of the number of repaired lesions g_r and the quasi-threshold dose D_q :

$$\gamma = \frac{g_\mathrm{r}}{D_\mathrm{q}}\,. \tag{5.5}$$

With the relations (5.4) and (5.5) at hand, the repair function (5.3) can alternatively be written as:

$$F_\mathrm{eff}(D) = \left(\frac{\gamma D}{1 + \gamma D}\right) \ln n = \left(\frac{g_\mathrm{r} D / D_\mathrm{q}}{1 + g_\mathrm{r} D / D_\mathrm{q}}\right) \ln n\,. \tag{5.6}$$

This transparently shows that $F_\mathrm{eff}(D)$ reduces to the logarithm of the extrapolation number at large doses, i.e. $F_\mathrm{eff}(D) \longrightarrow \ln n$ as $D \gg 1/\gamma$. In the opposite limit of

small doses, it directly follows from (5.6), with the help of (5.4), that $F_{\mathrm{eff}}(D) \longrightarrow k_2 D$ as $D \ll 1/\gamma$. Taken together, these two limits of small and high doses are seen to fully preserve the asymptotes in (4.13) on account of (4.15).

For the choice (5.1) via $F(D) \approx F_{\mathrm{eff}}(D)$, with $F_{\mathrm{eff}}(D)$ given by (5.4), we can cast Eq. (4.11) for the negative logarithmic surviving fraction, or equivalently, the BE, denoted by $\mathrm{E_B}$, to the following form:

$$\begin{aligned} -\ln S_{\mathrm{F}}(D) = \mathrm{E_B} &\approx k_0 D - F_{\mathrm{eff}} = \frac{D}{D_0} - \left(\frac{\gamma D}{1+\gamma D}\right) \ln n \\ &= \frac{\alpha D + \beta D^2}{1+\gamma D}\,, \end{aligned} \tag{5.7}$$

where,

$$\alpha = k_1 \quad , \quad \beta = k_0 \gamma\,. \tag{5.8}$$

Since $\ln n > 0$, $k_0 > 0$ and $k_1 > 0$, as per (3.11), it follows that all three parameters α, β and γ are also positive-definite:

$$\alpha > 0 \quad , \quad \beta > 0 \quad , \quad \gamma > 0\,. \tag{5.9}$$

The result (5.7) is associated with the PLQ model, which has recently been introduced in Refs. [12–15] in a completely different way:

$$-\ln S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) = \mathrm{E_B^{(PLQ)}}\,. \tag{5.10}$$

Here, $\mathrm{E_B^{(PLQ)}}$ is the BE in the PLQ model:

$$\mathrm{E_B^{(PLQ)}} = \frac{\alpha D + \beta D^2}{1+\gamma D}\,, \tag{5.11}$$

in terms of which the surviving fraction reads as:

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) = \mathrm{e}^{-\mathrm{E_B^{PLQ}}} = \mathrm{e}^{-\frac{\alpha D + \beta D^2}{1+\gamma D}}\,. \tag{5.12}$$

The name of this model and its acronym PLQ stem from a formal appearance of the BE from the linear-quadratic (LQ) model [17]:

$$\mathrm{E_B^{(LQ)}} = \alpha D + \beta D^2\,, \tag{5.13}$$

in the numerator of the rational function $(\alpha D + \beta D^2)/(1+\gamma D)$ from (5.10), which itself is a particular form of the general PA [11]. The PLQ model can alternatively be called the "Differential Michaelis–Menten" (DMM) model for the reason which will become clear later when we examine the link of the investigated repair pathway with the Michaelis–Menten mechanism of enzyme catalysis [16].

It is well-known that a given function $f(x)$, possessing the known series expansion in powers of the independent variable x, can be optimally represented by a rational function through the unique ratio of two polynomials P_L/Q_K of degrees L and K :

$$f(x) \approx \frac{P_L(x)}{Q_K(x)} \equiv [L/K]_f(x)\,. \tag{5.14}$$

This is a general PA of the order or rank $[L/K]$ as symbolized by $[L/M]_f(x)$. Regarding this special and admittedly curious historical notation, only the letter f for the name of the general dependent variable appears in the subscript of the Padé symbol $[L/K]$. On the other hand, the independent variable x is written as the argument of $[L/K]$, i.e. on the same line as the symbol $[L/K]$ via $[L/K]_f(x)$. The diagonal and nondiagonal versions of the PA are associated with the equal and unequal polynomial degrees $L = K$ and $L \neq K$, respectively. In particular, the cases $L = K - 1$ and $L = K + 1$ are called the paradiagonal PAs. Thus, the BE in (5.7) from the PLQ model is the paradiagonal PA ($L = K + 1$, $K = 1$) of the rank [2/1] to the corresponding exact (exa), but otherwise unknown BE, $\mathrm{E}_\mathrm{B}^{(\mathrm{exa})}(D) = \mathrm{E}_\mathrm{B}^{(\mathrm{exa})}$:

$$\begin{aligned} \mathrm{E}_\mathrm{B}^{(\mathrm{exa})}(D) &\approx \mathrm{E}_\mathrm{B}^{(\mathrm{PLQ})}(D) \\ &= \frac{\alpha D + \beta D^2}{1 + \gamma D} \\ &= [2/1]_{\mathrm{E}_\mathrm{B}^{(\mathrm{exa})}}(D)\,. \end{aligned} \tag{5.15}$$

Instead of the unavailable $\mathrm{E}_\mathrm{B}^{(\mathrm{exa})}(D)$, we can use the BEs measured in experiments (exp), $\mathrm{E}_\mathrm{B}^{(\mathrm{exp})}(D)$, which might be modeled by $\mathrm{E}_\mathrm{B}^{(\mathrm{PLQ})}(D)$:

$$\mathrm{E}_\mathrm{B}^{(\mathrm{exp})}(D) \approx \mathrm{E}_\mathrm{B}^{(\mathrm{PLQ})}(D)\,. \tag{5.16}$$

In such a case, $\mathrm{E}_\mathrm{B}^{(\mathrm{exp})}(D)$ would be parametrized according to the BE in the PLQ model, so that $\mathrm{E}_\mathrm{B}^{(\mathrm{exp})}(D) \approx (\alpha D + \beta D^2)/(1 + \gamma D)$. Overall, the dose-effect survival (5.7) is derived here from the general conditions (4.11)–(4.15) that every adequate repair model must satisfy. The obtained specific formula (5.7) is plausible and straightforward because it directly exploits the threefold prior information:

(a) The general prescription (4.11) or (4.12) for the introduction of a repair function $F(D)$,
(b) The expressions (4.13)–(4.15) for the simultaneously imposed asymptotic behaviors F_0 and F_∞ of the unknown repair function $F(D)$ in the limits of small ($D \to 0$) and large ($D \to \infty$) doses, respectively, and,
(c) The fact that for the rate-based phenomena, such as cell survival, the truest average value of the given asymptotes F_0 and F_∞ is the halved harmonic mean or the effective repair function $F_\mathrm{eff}(D)$ from (5.2).

Finally, the three steps (a)–(c), together with the approximation of the unknown function $F(D)$ by the effective repair functions $F_\mathrm{eff}(D)$ via $F(D) \approx F_\mathrm{eff}(D)$, led

straight to the novel expressions (5.7) in the field of radiobiological modeling of cell surviving fractions after irradiation. Since the general 3-parameter form (4.11) for all repair models is used from the outset, this new model (5.7) also has three parameters. According to (5.7) these parameters are specified as α, β and γ.

5.2 The biological meaning of the parameters and their correlations

The presented derivation is instructive, since it shows that the parameters α, β and γ possess a clear biological meaning. This follows from the connection of the triple $\{\alpha, \beta, \gamma\}$ with the extrapolation number n, as well as the initial (k_1) and final (k_0) slopes of a cell survival curve through the relations:

$$\alpha = k_1 \quad , \quad \beta = \frac{k_0(k_0 - k_1)}{\ln n} \quad , \quad \gamma = \frac{k_0 - k_1}{\ln n} \, , \tag{5.17}$$

where the link $\beta = k_0\gamma$ from (5.8) is preserved such that,

$$\frac{\gamma}{\beta} = \frac{1}{k_0} = D_0 \, . \tag{5.18}$$

Thus, in the PLQ model, there exists an inter-parameter dependence, with both β and γ being correlated to α. It is useful to make this fact transparent on the level of the principal observables, the BE and the surviving fraction, as well:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} = \frac{k_1 D + k_0 \dfrac{k_0 - k_1}{\ln n} D^2}{1 + \dfrac{k_0 - k_1}{\ln n} D} \, , \tag{5.19}$$

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) = \exp\left(- \frac{k_1 D + k_0 \dfrac{k_0 - k_1}{\ln n} D^2}{1 + \dfrac{k_0 - k_1}{\ln n} D} \right) . \tag{5.20}$$

If the initial and final slopes were equal ($k_0 = k_1$), parameters $\beta = k_0(k_0 - k_1)/(\ln n) = k_0\gamma$ and $\gamma = (k_0 - k_1)/(\ln n)$ in the numerator and denominator of the rational function from (5.20) or (5.19) would become zero. In this case, Eq. (5.20) would coincide with the ST-SH surviving fraction (2.1), which exhibits a purely exponential cell-kill mode with no shoulder:

$$\left\{ S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) \right\}_{k_0 = k_1} = S_{\mathrm{F}}^{(\mathrm{ST-SH})}(D) = \mathrm{e}^{-k_0 D} \, , \tag{5.21}$$

as in (2.1) where we used the relation $k_0 = 1/D_0$. This is a straight line in a semi-logarithmic plot of $S_{\mathrm{F}}(D)$ versus dose D associated with a dose-effect curve with no shoulder. Conversely, a shoulder would appear in the same plot whenever $k_0 \neq k_1$.

5.3 Full-effect plot

Also illustrative is the so-called Fe-plot (Fe = Full effect) [18] for a graphical display of the function $-(1/D)\ln S_{\mathrm{F}}(D)$ against dose D for any surviving fraction $S_{\mathrm{F}}(D)$:

$$k_D \equiv -\frac{1}{D}\ln S_{\mathrm{F}}(D) \equiv \mathrm{Fe}(D) \qquad \text{(Full effect)}\,. \tag{5.22}$$

There is yet another alternative name for the Fe-plot and that is the reactivity [19], which is denoted by $R(D)$:

$$\mathrm{Fe}(D) = R(D) = -\frac{1}{D}\ln S_{\mathrm{F}}(D) \equiv \mathrm{Fe}(D)\,. \tag{5.23}$$

In the case of the PLQ model, from the defining relation:

$$k_D^{(\mathrm{PLQ})} \equiv -\frac{1}{D}\ln S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) = \mathrm{Fe}^{(\mathrm{PLQ})}(D)\,, \tag{5.24}$$

we have,

$$\begin{aligned} k_D^{(\mathrm{PLQ})} &= \frac{k_1 + k_0\gamma D}{1+\gamma D} \\ &= \frac{k_1 + k_0\dfrac{k_0-k_1}{\ln n}D}{1+\dfrac{k_0-k_1}{\ln n}D}\,, \end{aligned} \tag{5.25}$$

or equivalently, by reference to (3.11):

$$\begin{aligned} k_D^{(\mathrm{PLQ})} &= \frac{1/D_1 + \gamma D/D_0}{1+\gamma D} \\ &= \frac{1/D_1 + \dfrac{1/D_0 - 1/D_1}{D_0\ln n}D}{1+\dfrac{1/D_0-1/D_1}{\ln n}D}\,. \end{aligned} \tag{5.26}$$

By employing (4.3) in (5.25), the ratio $k_D^{(\mathrm{PLQ})}/k_0$ can be expressed in terms of the fractions of unrepaired (f_{u}) and repaired (g_{r}) lesions alongside the quasi-threshold dose D_{q} as:

$$\frac{k_D^{(\mathrm{PLQ})}}{k_0} = \frac{f_{\mathrm{u}} + g_{\mathrm{r}}D/D_{\mathrm{q}}}{1+g_{\mathrm{r}}D/D_{\mathrm{q}}} = \frac{f_{\mathrm{u}}+\gamma D}{1+\gamma D}\,, \tag{5.27}$$

$$\frac{k_D^{(\mathrm{PLQ})}}{k_0} \underset{D\to\infty}{\longrightarrow} 1\,. \tag{5.28}$$

On account of the relation $f_u = 1 - g_r$ from (4.3), it is seen that the rhs of Eq. (5.27) contains only two unknown parameters g_r and D_q. Using the relation $\gamma = g_r/D_q$ from (5.5), these unknown parameters could equivalently be f_u and γ, in which case Eq. (5.27) becomes $k_D^{(PLQ)}/k_0 = (f_u + \gamma D)/(1 + \gamma D)$. In the Fe-plot, function $k_D^{(PLQ)}/k_0$ versus D appears as a rectangular hyperbola, which levels off (saturates) at large doses by being reduced to a constant (unity), as per (5.28). A similar pattern is seen in the second-order kinetics for enzyme catalysis in the Michaelis–Menten formalism [16].

The Fe-plot directly shows the quotient of the BE and dose. This is because the BE, E_B, in any model is defined by $E_B = -\ln S_F(D)$. On the other hand, the biologically effective dose (BED) and the relative effectiveness (RE) are defined by $BED = E_B/\alpha$ and $RE = BED/D$, where α is the radiosensitivity for the single-hit inactivation mode of cell kill. In this context, the term αD represents the number of expected lesions caused by the single-hit mechanism of cell kill. Therefore, the function shown in the Fe-plot is equal to the BE divided by dose or proportional to either RE or the ratio of the BED and dose:

$$\begin{aligned} -\frac{1}{D}\ln S_F(D) &= \frac{E_B}{D} \\ &= \alpha\, RE \\ &= \alpha \frac{BED}{D}. \end{aligned} \tag{5.29}$$

5.4 Universal radiosensitivity containing both the initial and final slopes

Quantity k_D from (5.22) is the dose-dependent relative radiosensitivity in terms of which the general cell surviving fraction (5.20) reads as:

$$S_F(D) = e^{-k_D D}. \tag{5.30}$$

In the PLQ model this becomes:

$$S_F^{(PLQ)}(D) = e^{-k_D^{(PLQ)} D}. \tag{5.31}$$

Further, $k_D^{(PLQ)}$ is viewed as a generalized "slope" of the dose-effect curve (5.26). The term "generalized" refers to a local, i.e. dose-dependent "slope". The use of the adjective "universal" stems from the fact the dose-dependent "slope" $k_D^{(PLQ)}$ inherently contains both the initial (k_1) and final (k_0) genuine slopes. These latter two slopes are material constants (as they ought to be) that every proper repair model of the types (4.1) and (4.2) must possess. They can be immediately identified from (5.25) in the limits $D \to 0$ and $D \to \infty$, respectively:

$$k_D^{(PLQ)} \approx \begin{cases} k_1 = \dfrac{1}{D_1}, & D \longrightarrow 0 \\ k_0 = \dfrac{1}{D_0}, & D \longrightarrow \infty. \end{cases} \tag{5.32}$$

Thus, we can see the universal applicability of the local radiosensitivity $k_D^{(\mathrm{PLQ})}$ stems from its correct limits at small and large doses.

5.5 The explicit link between the Padé linear-quadratic model and Michaelis–Menten enzyme catalysis for repair of radiation lesions

Using (5.27), the surviving fraction (5.30) can also be written in the form:

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) = \mathrm{e}^{-k_0 D \frac{f_{\mathrm{u}} + g_{\mathrm{r}} D/D_{\mathrm{q}}}{1 + g_{\mathrm{r}} D/D_{\mathrm{q}}}} . \tag{5.33}$$

Thus, the rectangular parabola $(f_{\mathrm{u}} + g_{\mathrm{r}} D/D_{\mathrm{q}})/(1 + g_{\mathrm{r}} D/D_{\mathrm{q}})$ from (5.33) is seen to represent a measure of the influence of repair to cell survival in the PLQ model relative to the purely exponential inactivation responsible for production of lethal (i.e. irreparable) lesions:

$$S_{\mathrm{F}}^{(\mathrm{Lethal})}(D) = \mathrm{e}^{-k_0 D} = \mathrm{e}^{-D/D_0} . \tag{5.34}$$

This was also encountered earlier in the surviving fraction $S_{\mathrm{F}}^{(\mathrm{ST-SH})}(D)$ from (5.21) in the ST-SH model.

An alternative display of the repair effect in the cell surviving fraction $S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)$ can be made apparent by using the relation $f_{\mathrm{u}} = 1 - g_{\mathrm{r}}$ which gives:

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) = \mathrm{e}^{-\frac{D}{D_0}\left(1 - \frac{g_{\mathrm{r}}}{1 + g_{\mathrm{r}} D/D_{\mathrm{q}}}\right)} . \tag{5.35}$$

The second term in the parenthesis isolates the repair mechanisms, the consequence of which is to reduce the single event inactivation e^{-D/D_0} by a factor $g_{\mathrm{r}}/(1 + g_{\mathrm{r}} D/D_{\mathrm{q}})$ multiplied by D/D_0. This reduction yields the repair probability $\mathrm{e}^{(D/D_0)[g_{\mathrm{r}}/(1+g_{\mathrm{r}} D/D_{\mathrm{q}})]}$ which mitigates the impact of radiation via:

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) = S_{\mathrm{F}}^{(\mathrm{Lethal})}(D) S_{\mathrm{F}}^{(\mathrm{Repair})}(D) , \tag{5.36}$$

where,

$$S_{\mathrm{F}}^{(\mathrm{Repair})}(D) = \mathrm{e}^{\frac{g_{\mathrm{r}} D/D_0}{1 + g_{\mathrm{r}} D/D_{\mathrm{q}}}} = \mathrm{e}^{k_2 D/(1 + D k_2/\ln n)} , \tag{5.37}$$

where (4.9) is used via $g_{\mathrm{r}}/D_0 = g_{\mathrm{r}}(D_{\mathrm{q}}/D_0)/D_{\mathrm{q}} = \{g_{\mathrm{r}} \ln n\}/D_{\mathrm{q}} = k_2$ and $g_{\mathrm{r}}/D_{\mathrm{q}} = k_2/\ln n = \gamma$. Thus, the cell survival $S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)$ in the PLQ model is a product of the probability $S_{\mathrm{F}}^{(\mathrm{Lethal})}(D) = \mathrm{e}^{-D/D_0}$ for radiation-induced lethal lesions and the repair probability $S_{\mathrm{F}}^{(\mathrm{Repair})}(D)$. According to (5.37), the positive logarithm of the repair probability $S_{\mathrm{F}}^{(\mathrm{Repair})}(D)$ reads as:

$$\ln S_{\mathrm{F}}^{(\mathrm{Repair})}(D) = \frac{g_{\mathrm{r}} D/D_0}{1 + g_{\mathrm{r}} D/D_{\mathrm{q}}} = \frac{k_2 D}{1 + D k_2/\ln n} . \tag{5.38}$$

This function is proportional to D at small D and it saturates towards a constant $\ln n$ at large doses:

$$\ln S_{\mathrm{F}}^{(\mathrm{Repair})}(D) \approx \begin{cases} \dfrac{g_{\mathrm{r}}}{D_0} D = k_2 D\,, & D \longrightarrow 0 \\ \ln n\,, & D \longrightarrow \infty\,. \end{cases} \tag{5.39}$$

The only parametric dependence of the surviving fraction $S_{\mathrm{F}}^{(\mathrm{Lethal})}(D)$ from (5.34) for the direct cell kill pathway with no possibility for repair is the mean lethal dose D_0. By contrast, repair is modeled by the remaining 2 parameters, the rate k_2 for production of repaired lesions and the logarithm $\ln n$ of the extrapolation number n. While D_0 and k_2 are quantities of self-evident biophysical meaning, $\ln n$ is a parameter introduced from a convenient geometrical interpretation, but its biological interpretation also needs to be established within all the repair-based models. In the classical multi-target hit model, the extrapolation n is viewed as the number of targets within the cell. In the literature, n has often been reported to belong to a set of huge numbers (1000 or more). However, it is unrealistic that killing a single cell would necessitate inactivation of thousands of its sensitive sites. Therefore, the interpretation of n as the number of targets is inadequate and should be abandoned in every radiobiological model which relies on repair mechanisms. Instead, a biophysical and biochemical meaning of the extrapolation number n is needed. This will emerge naturally from casting the PLQ model into the framework of chemical kinetics, as it will be shown here.

As usual, the concentration of radiation lesions [L] of the cell is assumed to be proportional to the absorbed dose D as, for instance:

$$[\mathrm{L}] = k_0 D = \frac{D}{D_0}\,. \tag{5.40}$$

Employing this relationship, we can cast (5.36)–(5.38) into the following forms:

$$\ln S_{\mathrm{F}}^{(\mathrm{Lethal})}(D) = -[\mathrm{L}]\,, \tag{5.41}$$

$$\ln S_{\mathrm{F}}^{(\mathrm{Repair})}(D) = v_{\mathrm{r},0}\,, \tag{5.42}$$

$$\ln S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) = -[\mathrm{L}] + v_{\mathrm{r},0}\,, \tag{5.43}$$

where $v_{\mathrm{r},0}$ and $K_{\mathrm{r,M}}$ are constants,

$$v_{\mathrm{r},0} = \frac{v_{\mathrm{r,max}}[\mathrm{L}]}{K_{\mathrm{r,M}} + [\mathrm{L}]}\,, \tag{5.44}$$

$$v_{\mathrm{r,max}} = \ln n \quad , \quad K_{\mathrm{r,M}} = \frac{\ln n}{g_{\mathrm{r}}}\,. \tag{5.45}$$

In particular, $K_{\mathrm{r,M}}$ is a special value of the concentration of lesions [L] for which the repair contribution $v_{\mathrm{r},0}$ is reduced to $v_{\mathrm{r,max}}/2$. Namely, when the varying [L] becomes equal to $K_{\mathrm{r,M}}$, it follows from (5.44) that $\{v_{\mathrm{r,max}}\}_{[\mathrm{L}]=K_{\mathrm{r,M}}} = v_{\mathrm{r,max}}/2$. Maximum $v_{\mathrm{r,max}}$ is the asymptote of $v_{\mathrm{r},0}$ in the limit $[\mathrm{L}] \to \infty$. Thus, the logarithm

$\ln S_{\mathrm{F}}^{(\mathrm{Repair})}(D) = v_{\mathrm{r},0}$ of the probability $S_{\mathrm{F}}^{(\mathrm{Repair})}(D)$ is seen to quantify the concentration of repaired lesions. This allows the following mechanistic interpretation of the PLQ model:

(A) It is assumed that dose D absorbed by the cell without activation of the repair system yields the expected concentration [L] of lethal lesions.
(B) When this assumption is made within the Poisson distribution of lesions, the predicted probability that radiation quanta would yield only cell death is given by $S_{\mathrm{F}}^{(\mathrm{Lethal})} = \mathrm{e}^{-[\mathrm{L}]}$.
(C) Activation of the repair system through a repair mechanism to be identified reduces [L] by the concentration $v_{\mathrm{r,max}}[\mathrm{L}]/(K_{\mathrm{r,M}} + [\mathrm{L}])$ of the repaired lesions and modifies $S_{\mathrm{F}}^{(\mathrm{Lethal})} = \mathrm{e}^{-[\mathrm{L}]}$ from (B) by the multiplicative factor $M([\mathrm{L}]) \equiv S_{\mathrm{F}}^{(\mathrm{Repair})}$. This increases the number of survivors to $\mathrm{e}^{-[\mathrm{L}]}M([\mathrm{L}])$, which is $S_{\mathrm{F}}^{(\mathrm{PLQ})}$:

$$S_{\mathrm{F}}^{(\mathrm{PLQ})} = \mathrm{e}^{-[\mathrm{L}]}M([\mathrm{L}]) \quad , \quad M([\mathrm{L}]) = \mathrm{e}^{v_{\mathrm{r,max}}\frac{[\mathrm{L}]}{K_{\mathrm{r,M}}+[\mathrm{L}]}} . \tag{5.46}$$

Steps (A) and (B) are common to all the radiobiological models. However, step (C) represents a distinct feature which is most responsible for the emergence of the PLQ model. In order to complete the establishment of the PLQ model, it remains to specify the repair mechanism which yields the contribution $S_{\mathrm{F}}^{(\mathrm{Repair})}(D) = \mathrm{e}^{v_{\mathrm{r},0}}$ to the surviving fraction $S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)$.

With this goal, we shall postulate that the repair mechanism in the PLQ model consists of interactions of lesions [L] with certain molecules [E] that are capable of repairing radiation damage of the cell. These substances will hereafter be called repair molecules and they shall initially be specified only by way of their bonding with [L]. The interactions between [L] and [E] will be supposed to occur through a chemical reaction which has two irreversible pathways or steps or subreactions. In the first subreaction, the lesions [L] and repair molecules [E] are assumed to interact irreversibly with a rate constant k_1 during a time t_1 by forming an intermediate complex [EL]:

$$[\mathrm{E}] + [\mathrm{L}] \underset{k_1}{\longrightarrow} [\mathrm{EL}] . \tag{5.47}$$

Complex [EL] is considered as an unstable molecule with a relatively short lifetime which leads to decay of [EL]. As such, in the second subreaction, the metastable compound molecules [EL] will irreversibly dissociate during a time t_2 with a rate constant k_2. This step is envisaged to yield the products [P], as the repaired lesions, and the free intact repair molecules [E]:

$$[\mathrm{EL}] \underset{k_2}{\longrightarrow} [\mathrm{E}] + [\mathrm{P}] . \tag{5.48}$$

In other words, unlike [L] and [P], it is assumed that repair molecules [E] do not change their state throughout the interaction. In particular, the concentration $[\mathrm{E}] \equiv [\mathrm{E}](t) \equiv [\mathrm{E}]_t$ of repair molecules at any given instant t is viewed as unaltered and

thus equal to the initial concentration $[\mathrm{E}]_0 \equiv [\mathrm{E}](0)$, which was available at the very beginning ($t = t_0$) of the interactions.

Time t_1 is inversely proportional to the concentration of lesions [L], as opposed to t_2 which is independent of [L] so that:

$$t_1 = \frac{1}{k_1[\mathrm{L}]} \quad , \quad t_2 = \frac{1}{k_2} \, . \tag{5.49}$$

The total time t_{tot} needed for completion of this two-step reaction, which is symbolized by the chain of two irreversible channels:

$$[\mathrm{E}] + [\mathrm{L}] \underset{k_1}{\longrightarrow} [\mathrm{EL}] \underset{k_2}{\longrightarrow} [\mathrm{E}] + [\mathrm{P}] \, , \tag{5.50}$$

is given by:

$$t_{\mathrm{tot}} = t_1 + t_2 = \frac{1}{k_1[\mathrm{L}]} + \frac{1}{k_2} = \frac{k_1 + k_2[\mathrm{L}]}{k_1 k_2[\mathrm{L}]} \, . \tag{5.51}$$

Usually, rate constants are not measured directly in chemical kinetics experiments. The velocity v_0 of reaction (5.50) is proportional to the reciprocal $1/t_{\mathrm{tot}}$, i.e. $v_0 \sim 1/t_{\mathrm{tot}}$. This latter relation becomes an equality by introducing a proportionality constant, which can be taken to be the initial concentration $[\mathrm{E}]_0$ of repair molecules, so that:

$$v_0 = \frac{[\mathrm{E}]_0}{t_{\mathrm{tot}}} \, . \tag{5.52}$$

Therefore, on account of (5.51) and (5.52), it follows that the velocity for reaction (5.50) is:

$$v_0 = \frac{v_{\max}[\mathrm{L}]}{K_{\mathrm{M}} + [\mathrm{L}]} \, , \tag{5.53}$$

where,

$$v_{\max} = k_2[\mathrm{E}]_0 \quad , \quad K_{\mathrm{M}} = \frac{k_2}{k_1} \, . \tag{5.54}$$

The result (5.53) agrees with (5.44) upon the identifications:

$$v_{\mathrm{r},0} = v_0 \quad , \quad v_{\mathrm{r},\max} = v_{\max} \quad , \quad K_{\mathrm{r,M}} = K_{\mathrm{M}} \, . \tag{5.55}$$

The outlined procedure leading to Eq. (5.54) for the velocity v_0 of repair molecules in reaction (5.50) is recognized as the Michaelis–Menten [16] enzyme catalysis in the derivation of van Slyke and Cullen [20]. Enzyme catalysis is a chemical reaction by

which free enzymes [E] and substrate [S] interact by giving the unaltered [E] and the product [P]:

$$[\mathrm{E}] + [\mathrm{S}] \longrightarrow [\mathrm{E}] + [\mathrm{P}]\,. \tag{5.56}$$

The Michaelis–Menten mechanism for this process is a two-step reaction through formation and destruction of the intermediate enzyme-substrate complex [ES]:

$$[\mathrm{E}] + [\mathrm{S}] \underset{k_1}{\longrightarrow} [\mathrm{ES}] \underset{k_2}{\longrightarrow} [\mathrm{E}] + [\mathrm{P}]\,. \tag{5.57}$$

Here, enzymes [E] and substrate [S] become temporarily united by forming the compound [ES]. While being in [ES], enzymes [E] are able to diminish the activation energy of [S] by rearranging the electronic configuration of the substrate to create the product molecules [P]. Enzymes then expel the product [P] and set themselves free as intact and continue binding to further molecules of substrate by way of reaction (5.57). Numerous measurements in enzymology during an entire century have confirmed that the Michaelis–Menten mechanism (5.57) operates in enzyme catalysis (5.56).

The constant K_{M} from (5.54) is the well-known Michaelis–Menten constant for the irreversible variant of enzyme catalysis, which is reaction (5.57). This realization permits identification of the repair molecules [E] from the PLQ model as enzymes, the great majority of which are proteins. Therefore, the contribution $S_{\mathrm{F}}^{(\mathrm{Repair})}(D) = \mathrm{e}^{v_{\mathrm{r},0}}$ to the surviving fraction $S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)$ from (5.54) in the PLQ model is now pinpointed as being due to the Michaelis–Menten mechanism of catalysis by which enzyme molecules can repair radiation lesions of the cell.

In biochemistry and enzymology with reference to standard experiments on enzyme catalysis, both $v_{\max}$ and K_{M} can be measured. If this is done also with the radiation damaged tissue, the expression (5.46) would be free of adjustable parameters. In such a case, modeling cell surviving fractions would amount to verifying whether measured data obeys the form $S_{\mathrm{F}}^{(\mathrm{PLQ})}$ from (5.46) as a function of the independent variable [L]. This is expected to be favorably confirmed, since the PLQ is demonstrated here to be based on the Michaelis–Menten enzyme catalysis which has successfully passed the test of time in biochemistry.

Using the established equivalence (5.55) of the Padé-based repair and the repair mechanism via enzyme catalysis, we can rewrite (5.46) directly in the Michaelis–Menten terminology as:

$$\begin{aligned} S_{\mathrm{F}}^{(\mathrm{PLQ})} &= \mathrm{e}^{-[\mathrm{L}]+v_0} \\ &= \mathrm{e}^{-[\mathrm{L}]+v_{\max}\frac{[\mathrm{L}]}{K_{\mathrm{M}}+[\mathrm{L}]}}\,, \end{aligned} \tag{5.58}$$

with the corresponding BE, $\mathrm{E}_{\mathrm{F}}^{(\mathrm{PLQ})} \equiv -\ln S_{\mathrm{F}}^{(\mathrm{PLQ})}$, given by:

$$\begin{aligned} \mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} &= [\mathrm{L}] - v_0 \\ &= [\mathrm{L}] - v_{\max}\frac{[\mathrm{L}]}{K_{\mathrm{M}}+[\mathrm{L}]}\,. \end{aligned} \tag{5.59}$$

The first term [L] in Eq. (5.59) is the concentration of lesions due to direct radiation impact in the absence of any repair activity of enzyme molecules. However, once a certain threshold of damage has been reached, this direct radiation event is counteracted in $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$ by the second term v_0, which is the initial enzyme velocity from the Michaelis–Menten equation $v_0 = v_{\max}[\mathrm{L}]/(K_{\mathrm{M}} + [\mathrm{L}])$ for catalytic repair of lesions. In this way, the BE of direct radiation damage, given through concentration [L] of lesions, becomes reduced by the action of cell repair with rate v_0 of enzyme catalysis (5.57). On the other hand, and by definition, velocity v_0 is the rate of differential change (decrease) of concentration [L] of lesions with the passage of time, i.e. the negative first derivative via $v_0 = -(\mathrm{d}/\mathrm{d}t)[\mathrm{L}](t)$. For this reason, the second term $v_0 = v_{\max}[\mathrm{L}]/(K_{\mathrm{M}} + [\mathrm{L}])$ from (5.59) is called the rate version or the differential variant of the Michaelis–Menten Eq. (5.53) for enzyme catalysis (5.57). Therefore, the ensuing PLQ model from (5.58) or (5.59) could equivalently be called the differential Michaelis–Menten model, or DMM, for cell survival after irradiation:

$$S_{\mathrm{F}}^{(\mathrm{DMM})} = S_{\mathrm{F}}^{(\mathrm{PLQ})} \quad , \quad \mathrm{E}_{\mathrm{B}}^{(\mathrm{DMM})} = \mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} \, . \tag{5.60}$$

This is an alternative to the integrated Michaelis–Menten (IMM) model [21], which determines the BE by means of the Lambert W_0 function as the result of integration of the Michaelis–Menten differential Eq. (5.53) rewritten as:

$$\frac{\mathrm{d}[\mathrm{L}]}{\mathrm{d}t} = -v_{\max}\frac{[\mathrm{L}]}{K_{\mathrm{M}} + [\mathrm{L}]} \quad , \quad [\mathrm{L}] = [\mathrm{L}](t) \, . \tag{5.61}$$

As it stands, the PLQ model from Eq. (5.58) may seem to depend on only 2 parameters, the maximal enzyme velocity $v_{\max}$ and the Michaelis–Menten constant K_{M}. However, this is not the case, since the actual independent variable for cell surviving fraction is the absorbed dose D rather than the number of lesions [L]. Thus, returning to the original independent variable D via $D = D_0[\mathrm{L}]$ would bring back the mean lethal dose D_0, as the third parameter of the PLQ model:

$$S_{\mathrm{F}}^{(\mathrm{PLQ})} = \mathrm{e}^{-D/D_0 + v_0(D)} \equiv \mathrm{e}^{-D/D_0 + v_{\max}\frac{D/D_0}{K_{\mathrm{M}} + D/D_0}} \, , \tag{5.62}$$

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} = \frac{D}{D_0} - v_0(D) = \frac{D}{D_0} - v_{\max}\frac{D/D_0}{K_{\mathrm{M}} + D/D_0} \, . \tag{5.63}$$

Therefore, one of the triplets of the parameters from the PLQ model is the set $\{D_0, v_{\max}, K_{\mathrm{M}}\}$. Once the mean lethal dose D_0 is extracted graphically as the reciprocal of the final slope via the tangent to the terminal, exponential part of the survival curve in the semi-logarithmic plot of $S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)$ versus D, the representation $\{D_0, v_{\max}, K_{\mathrm{M}}\}$ of the PLQ model becomes particularly useful because the remaining two parameters $v_{\max}$ and K_{M} can also be determined graphically by the well-known Lineweaver-Burk or Eadie-Hoftsee linearization of the Michaelis–Menten rectangular parabola $v_{\max}(D/D_0)/(K_{\mathrm{M}} + D/D_0)$ for the initial velocity v_0 [21].

By using (5.54) to make the quotient $v_{\max}/K_{\mathrm{M}}$, we can reconstruct the fraction g_{r} of repaired lesions as:

$$g_{\mathrm{r}} = \frac{v_{\max}}{K_{\mathrm{M}}} \,. \tag{5.64}$$

Comparing (5.45) with (5.54) yields the relationships:

$$\ln n = k_2[\mathrm{E}]_0 \quad , \quad g_{\mathrm{r}} = k_1[\mathrm{E}]_0 \,. \tag{5.65}$$

This provides a direct interpretation of the extrapolation number n and the fraction g_{r} of repaired lesions in terms of the rate constants from reaction (5.50) and the concentration $[\mathrm{E}]_0$ of repair molecules.

5.6 The main biological observables

The BE, $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$, in (5.11) from the PLQ model can be related to the corresponding LQ-based BE, $\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}$, from (5.13) by the relation:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} = \frac{\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}}{1+\gamma D} \,. \tag{5.66}$$

Further, it follows from (5.11) that the low- and high-dose asymptotes of $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$ are given by:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} \underset{D\to 0}{\longrightarrow} \alpha D \,, \tag{5.67}$$

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})} \underset{D\to \infty}{\longrightarrow} \frac{\beta}{\gamma} D \,, \tag{5.68}$$

respectively. For brevity, the high-dose asymptote (5.68) is written to exhibit only the leading term ($\sim D$), whereas the constant ($\sim D^0 = 1$) is ignored.

The expression for $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$ from (5.11) leads to the corresponding biologically effective dose $\mathrm{BED}^{(\mathrm{PLQ})}$ in the PLQ model:

$$\mathrm{BED}^{(\mathrm{PLQ})} \equiv \frac{\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}}{\alpha} = \frac{D+\beta D^2/\alpha}{1+\gamma D} \,. \tag{5.69}$$

This can also be written as:

$$\mathrm{BED}^{(\mathrm{PLQ})} = D \cdot \mathrm{RE}^{(\mathrm{PLQ})} \,, \tag{5.70}$$

where $\mathrm{RE}^{(\mathrm{PLQ})}$ is the PLQ-based RE:

$$\mathrm{RE}^{(\mathrm{PLQ})} = \frac{1+(\beta/\alpha)D}{1+\gamma D} = \frac{\mathrm{RE}^{(\mathrm{LQ})}}{1+\gamma D} \,. \tag{5.71}$$

The corresponding quantities in the LQ model are given by:

$$\mathrm{BED}^{(\mathrm{LQ})} = D + \frac{\beta}{\alpha} D^2 \,, \tag{5.72}$$

$$\mathrm{RE}^{(\mathrm{LQ})} = 1 + \frac{\beta}{\alpha} D \,, \tag{5.73}$$

$$\mathrm{BED}^{(\mathrm{LQ})} = D \cdot \mathrm{RE}^{(\mathrm{LQ})} \,. \tag{5.74}$$

Insertion of the asymptotes (5.67) and (5.68) for $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$ into Eq. (5.69) yields:

$$\mathrm{BED}^{(\mathrm{PLQ})} \underset{D\to 0}{\longrightarrow} D \,, \tag{5.75}$$

$$\mathrm{BED}^{(\mathrm{PLQ})} \underset{D\to \infty}{\longrightarrow} \frac{\beta}{\alpha\gamma} D \,. \tag{5.76}$$

The associated behaviors in the LQ model read as:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} \underset{D\to 0}{\longrightarrow} \alpha D \,, \tag{5.77}$$

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})} \underset{D\to \infty}{\longrightarrow} \beta D^2 \,, \tag{5.78}$$

$$\mathrm{BED}^{(\mathrm{LQ})} \underset{D\to 0}{\longrightarrow} D \,, \tag{5.79}$$

$$\mathrm{BED}^{(\mathrm{LQ})} \underset{D\to \infty}{\longrightarrow} \frac{\beta}{\alpha} D^2 \,. \tag{5.80}$$

5.7 Correct and smooth asymptotic behaviors at low and high doses

As expected, the PLQ and LQ models formally exhibit the same low-dose behaviors in (5.79) and (5.75), albeit with possibly different *numerical* values of parameter α. However, these two models differ substantially at high doses according to (5.80) and (5.76). As a consequence of the behaviors (5.67) and (5.68) for $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}$, the following two asymptotes of $S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)$ exist at small and large values of D :

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) \underset{D\to 0}{\longrightarrow} \mathrm{e}^{-\alpha D} \,, \tag{5.81}$$

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) \underset{D\to \infty}{\longrightarrow} \mathrm{e}^{-\beta D/\gamma} \,. \tag{5.82}$$

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

$$\mathrm{PLQ}: \quad \begin{cases} \text{Initial slope} \equiv s_{\mathrm{i}} = \alpha \\ \text{Final slope} \equiv s_{\mathrm{f}} = \dfrac{\beta}{\gamma} \end{cases} . \tag{5.83}$$

In the high-dose asymptotes (5.82), only the leading term βD^2 is retained in the numerator of the BE, $E_{\mathrm{B}}^{(\mathrm{PLQ})} = (\alpha D + \beta D^2)/(1 + \gamma D)$. 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 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 (5.82), we shall now retain the full numerator $\alpha D+\beta D^2$ in $(\alpha D+\beta D^2)/(1+\gamma D)$ to arrive at $-\ln S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) \underset{D\to\infty}{\longrightarrow} (\alpha\gamma - \beta)\gamma^2 + (\beta/\gamma)D$, so that:

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) \underset{D\to\infty}{\longrightarrow} \mathrm{e}^{\frac{\beta-\alpha\gamma}{\gamma^2} - \frac{\beta}{\gamma}D} . \tag{5.84}$$

This can conveniently be cast into the form:

$$\left.\begin{array}{l} S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) \underset{D\to\infty}{\longrightarrow} n\mathrm{e}^{-\frac{\beta}{\gamma}D} \\ \ln S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) \underset{D\to\infty}{\longrightarrow} \ln n - \frac{\beta}{\gamma}D \end{array}\right\} , \tag{5.85}$$

where the extrapolation number n is identified as:

$$\begin{aligned} \ln n &= \frac{\beta - \alpha\gamma}{\gamma^2} \\ &= \frac{\Delta s_{\mathrm{fi}}}{\gamma} \quad , \qquad \Delta s_{\mathrm{fi}} = s_{\mathrm{f}} - s_{\mathrm{i}} . \end{aligned} \tag{5.86}$$

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

$$\ln n > 0 \qquad \text{if} \quad \beta > \alpha\gamma . \tag{5.87}$$

In this derivation, α, β and γ are considered as independent, uncorrelated parameters. However, in the present formulation of the PLQ model, the inter-parameter correlations from (5.17) constrains the relations among these parameters. Such correlations can be exploited to check whether e.g. the condition $\alpha\gamma/\beta < 1$ from (5.87) is fulfilled. Thus, using (3.4) and (5.17) it follows:

$$\frac{\alpha\gamma}{\beta} = \alpha\left(\frac{\gamma}{\beta}\right) = k_1 D_0 = \frac{k_1}{k_0} < 1 \qquad \text{(QED)}. \tag{5.88}$$

Similarly, with the help of the relationships from (3.4) and (5.17), we have that the initial and final slopes from (5.83) coincide with those from (3.14) via $s_{\mathrm{i}} = \alpha = k_1$ and $s_{\mathrm{f}} = \beta/\gamma = 1/D_0 = k_0$. Likewise, the logarithm of the extrapolation number from (5.86) is reduced to an identity:

$$\ln n = \frac{\beta - \alpha\gamma}{\gamma^2} = \frac{k_0(k_0 - k_1)/(\ln n) - k_1(k_0 - k_1)/(\ln n)}{[(k_0 - k_1)/(\ln n)]^2}$$
$$= \frac{k_0 - k_1}{(k_0 - k_1)/(\ln n)} = \ln n \quad \text{(QED)}.$$

Moreover, comparing Eqs. (3.16) and (5.86), it follows that Δs_{fi} and the multi-target inactivation constant k_2 are the same:

$$\Delta s_{\mathrm{fi}} = k_2 \,. \tag{5.89}$$

Remarkably, by reference to (5.88), the number of unrepaired lesions f_{u} from (4.3) appears now as a constant, which embodies all three parameters α , β and γ of the PLQ model via:

$$f_{\mathrm{u}} = \frac{\alpha\gamma}{\beta} \,. \tag{5.90}$$

Using this relation and recalling that in dosimetry [15,19], the ratio α/β is the dose-averaged specific energy z_{D}, we can write:

$$\gamma = \frac{f_{\mathrm{u}}}{z_{\mathrm{D}}} \,, \tag{5.91}$$

where,

$$z_{\mathrm{D}} = \frac{\alpha}{\beta} \,. \tag{5.92}$$

Thus, the 3rd parameter γ from the PLQ model is the quotient of the fraction f_{u} of unrepairable, lethal lesions and the dose-averaged specific energy z_{D}.

6 Results and discussion

The PLQ model is presently tested by comparing its predictions with the experimental data for Chinese Hamster cell lines irradiated by 250 kVp X-rays[1]. Both cell surviving fractions as dose-effect curves (Fig. 1) and the corresponding relative radiosensitivities of the cell as the Fe-plots (Fig. 2) are used in these comparisons between measurements and theory. The LQ model is also employed. The parameters of the LQ and PLQ models are reconstructed from non-linear least-square minimizations of weighted variances set up with the theoretical and experimental results for cell surviving fractions. All the experimental data points for $S_{\mathrm{F}}^{(\mathrm{exp})}(D)$ are used in these minimizations. The results for the Fe-plot are obtained from the deduced radiosensitivities $-(1/D)\ln S_{\mathrm{F}}^{(\mathrm{exp})}(D)$, $-(1/D)\ln S_{\mathrm{F}}^{(\mathrm{LQ})}(D)$ and $-(1/D)\ln S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)$. The findings are displayed using the linear axis for dose D as the abscissa, whereas the

[1] For our earlier applications of the PLQ model to different cell lines, see Refs. [12–15] and [22].

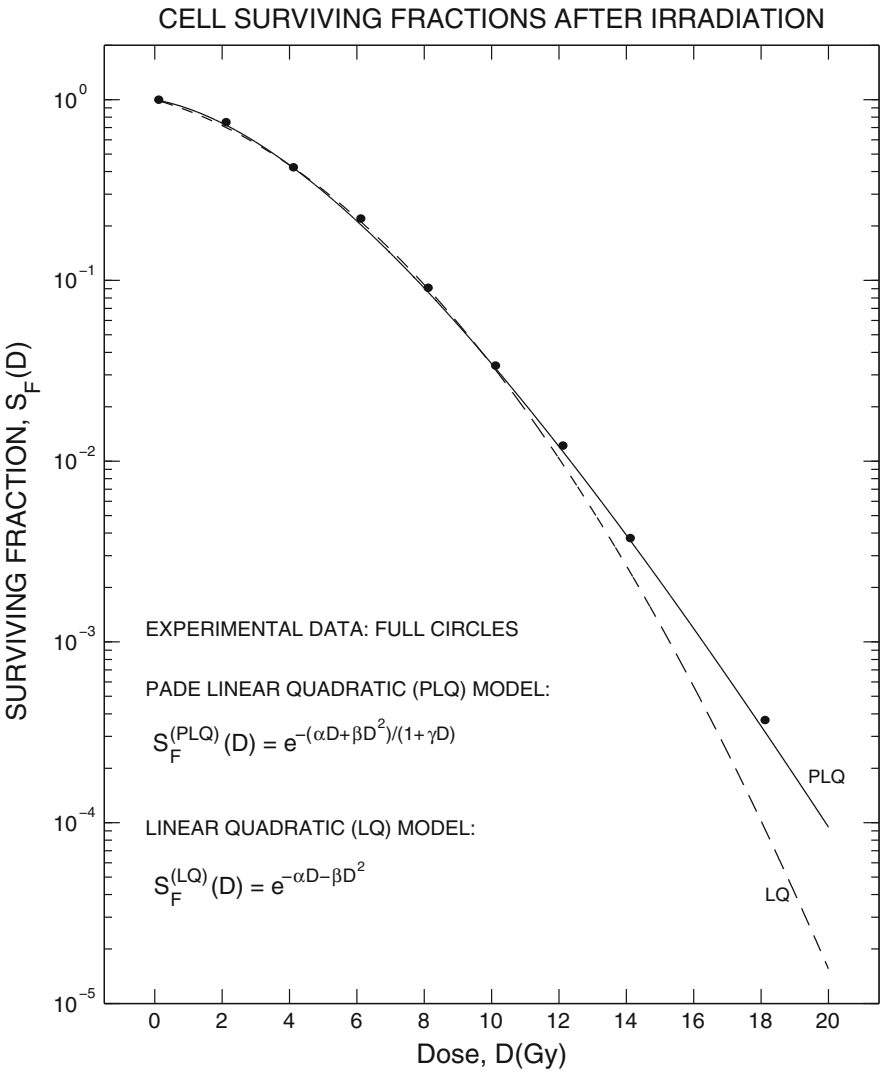

Fig. 1 Cell surviving fractions $S_F(D)$ as a function of radiation dose D in Gy. Experimental data (*symbols*) [23]: the mean clonogenic surviving fractions $S_F(D)$ for Chinese hamster V79 cells irradiated by 250 kVp X-rays. Theories; *full line*: Padé linear-quadratic (PLQ) model and *dashed line*: linear-quadratic (LQ) model.

ordinates are either logarithmic or linear for the surviving $S_F(D)$ or the full effect $-(1/D)\ln S_F(D)$, respectively.

It can be seen from Figs. 1 and 2 that throughout the entire dose range (0–18 Gy) the cell surviving fractions $S_F^{(PLQ)}(D)$ and the Fe-plot $-(1/D)\ln S_F^{(PLQ)}(D)$ from the PLQ model are in excellent agreement with the corresponding experimental data $S_F^{(exp)}(D)$ and $-(1/D)\ln S_F^{(exp)}(D)$, respectively. By contrast, as evidenced in Fig. 1, the LQ model for cell surviving fractions $S_F^{(LQ)}(D)$ is valid only at low-to-intermediate

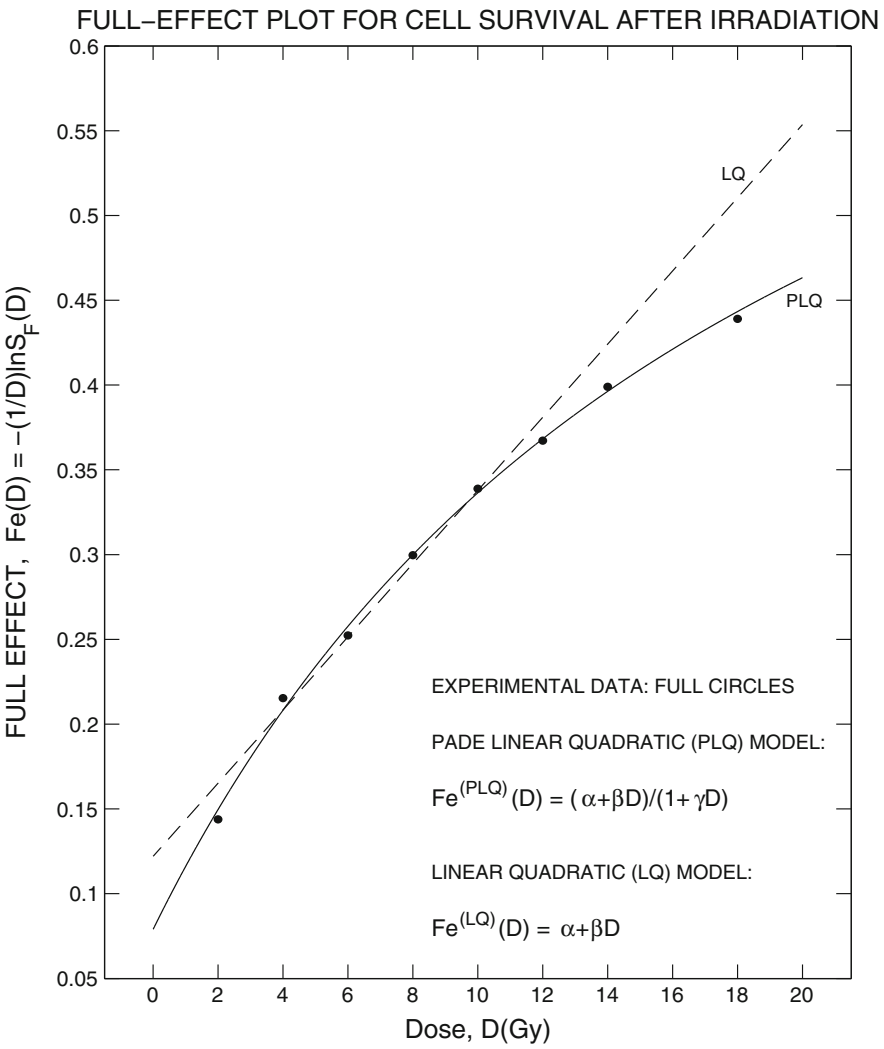

Fig. 2 The Full-effect (Fe) plot from the cell surviving fractions as given by the product of the reciprocal dose D^{-1} and the negative natural logarithm of $S_{\mathrm{F}}(D)$ on the ordinate versus D as the abscissa: $\mathrm{Fe}(D) \equiv -(1/D)\ln(S_{\mathrm{F}}) = R(D)$. Experimental data (*symbols*) [23]: the mean clonogenic surviving fractions $S_{\mathrm{F}}(D)$ for Chinese hamster V79 cells irradiated by 250 kVp X-rays. Theories; *solid curve*: Padé linear quadratic model and *dashed curve*: linear quadratic model (the *straight line* $\alpha + \beta D$).

dose $D \leq 10$ Gy. However, at higher doses shown in Fig. 1, the LQ model severely underestimates the experimental data that exhibit a characteristic exponential decline of the type $S_{\mathrm{F}}^{(\mathrm{exp})}(D) \sim \mathrm{e}^{-D/D_0}$ at very large values of D in sharp disagreement with the LQ-conceived Gaussian high-dose asymptote $S_{\mathrm{F}}^{(\mathrm{LQ})}(D) \sim \mathrm{e}^{-\beta D^2}$.

This breakdown of the LQ model is most prominently evidenced in the Fe-plot depicted on Fig. 2. Here, the reactivity or radiosensitivity $R^{(\mathrm{LQ})}(D) = \mathrm{Fe}^{(\mathrm{LQ})}(D) = -(1/D)\ln S_{\mathrm{F}}^{(\mathrm{LQ})}(D)$ from the LQ model predicts a straight line $\alpha + \beta D$. Geometrically

interpreted, the parameter α is the intercept of the latter straight line with the ordinate, whereas β is the slope of the same line $\alpha + \beta D$. Such a straight-line behavior of $\mathrm{Fe}^{(\mathrm{LQ})}(D)$ indicates that the full effect will continuously increase without limit by augmentation of dose D. Any departure of experimental data from this pattern would imply the inadequacy of the LQ model. This is precisely what is observed on Fig. 2, where the measured findings for $\mathrm{Fe}^{(\mathrm{exp})}(D) = -(1/D)\ln S_{\mathrm{F}}^{(\mathrm{exp})}(D)$ strongly deviate from the LQ-based straight line $\mathrm{Fe}^{(\mathrm{LQ})}(D) = \alpha + \beta D$ both at lower and higher doses. Simultaneously, it is clear from Fig. 2 that the pertinent prediction of the PLQ model for the Fe-plot via $R^{(\mathrm{PLQ})}(D) = \mathrm{Fe}^{(\mathrm{PLQ})}(D) = -(1/D)\ln S_{\mathrm{F}}^{(\mathrm{PLQ})}(D)$ is in excellent accord with the associated experimental data $\mathrm{Fe}^{(\mathrm{exp})}(D)$ at all doses. As opposed to the straight line $\mathrm{Fe}^{(\mathrm{LQ})}(D) = \alpha + \beta D$ in the LQ model, the Fe-plot in the PLQ model is given by the rectangular hyperbola $\mathrm{Fe}^{(\mathrm{PLQ})}(D) = (\alpha + \beta D)/(1 + \gamma D)$, which fully describes the experimental data $\mathrm{Fe}^{(\mathrm{exp})}(D)$, as per Fig. 2. While the LQ-based Fe-plot for the relative radiosensitivity is an ever increasing function with augmented dose, $\mathrm{Fe}^{(\mathrm{LQ})}(D) = \alpha + \beta D$, the PLQ-designed counterpart, $\mathrm{Fe}^{(\mathrm{PLQ})}(D) = (\alpha + \beta D)/(1 + \gamma D)$ saturates at asymptotically large D by attaining a constant value β/γ, which can be identified with the reciprocal of the mean lethal dose D_0.

The current practice in dose-planning system is to use the LQ model in determining the biologically effective dose, $\mathrm{BED}^{(\mathrm{LQ})} = 1 + (\beta/\alpha)D$. The BED is most useful in fractionation radiotherapy. In particular, the concept of the BED is envisaged to be of critical importance for prescribing the dose per fraction for non-conventional fractionations (larger doses per fraction) by extrapolating the abundant experience from conventional fractionation (smaller doses per fraction). In order to attain this planned goal, the BED must be consistently evaluated from one set of parameters that are material constants throughout the investigated dose-range. This is not the case with the LQ model, as can be inferred from Fig. 1. Namely, from the lack of agreement seen in Fig. 1 between $S_{\mathrm{F}}^{(\mathrm{LQ})}(D)$ and $S_{\mathrm{F}}^{(\mathrm{exp})}(D)$ beyond 10 Gy, it follows that $\mathrm{BED}^{(\mathrm{LQ})} = 1 + (\beta/\alpha)D$, based on only one fixed value of the ratio β/α, is inapplicable to the entire dose-range of interest, $D \in [0, 18]$ Gy. In other words, to obtain the BED which closely conforms to the experimental data at all doses from 0 to 18 Gy, the interval $D \in [0, 18]$ Gy could be split into 2 subranges $D \in [0, 10]$ Gy and $D \in [10, 18]$ Gy. This should subsequently be followed by 2 separate computations of the variance from $S_{\mathrm{F}}^{(\mathrm{LQ})}(D)$ and $S_{\mathrm{F}}^{(\mathrm{exp})}(D)$. The ensuing results might eventually give a reasonable agreement between the surviving fractions in the LQ model and the corresponding experimental data, with the price of having 2 sets of the quotients β/α, one for $D \in [0, 10]$ and the other for $D \in [10, 18]$. Such a dose-range dependence of the ratio β/α, automatically yields the associated dose-range dependence of the LQ-evaluated biologically effective dose, $\mathrm{BED}^{(\mathrm{LQ})} = 1 + (\beta/\alpha)D$. This latter dose-range dependence precludes any meaningful inter-comparisons of different fractionation regimens (e.g. small versus large doses per fraction) and, in fact, undermines the true concept as well as usefulness of the biologically effective dose.

The concept of the BED could be restored by having a single set of parameters that are dose-range independent, as is indeed the case in the PLQ model, $\mathrm{BED}^{(\mathrm{PLQ})} = (1 + \beta D/\alpha)/(1 + \gamma D)$. In this latter expression for the BED, the parameters α, β and γ are the same for the whole dose-range $D \in [0, 18]$ Gy. This is possible because these

parameters are reconstructed by the PLQ model in a single least-square minimization of the variance for $S_F^{(PLQ)}(D)$ and $S_F^{(exp)}(D)$ at all doses without dividing the whole dose-interval $D \in [0, 18]$ into 2 segments $D \in [0, 10]$ and $D \in [10, 18]$. Hence, rather than exclusively relying upon the LQ-based BED, as is currently the case, the biologically effective dose in the PLQ model should be used in dose planning systems as well as in inter-comparisons among different fractionation schedules in clinical practice. This suggested replacement of $BED^{(LQ)}$ by $BED^{(PLQ)}$ entails an additional parameter γ in the PLQ-envisaged BED, $(1 + \beta D/\alpha)/(1 + \gamma D)$. However, this is only a minor inconvenience, since the additional parameter γ is given by βD_0, where the mean lethal dose D_0 can readily be extracted by hand from the slope $k_0 = 1/D_0$ of the straight line for the terminal part of the analyzed experimental cell survival curve in a semi-logarithmic plot.

7 Conclusion

The main targets for irradiation in the human body are DNA molecules from the treated tissue. The heterogeneity of tumors implies that normal and cancerous cells are highly intertwined. In order to allow repair of irradiated healthy cells, radiation is usually administered in relatively small fractions of 2 Gy/day during 5 days/week within 1 month. This is known as the conventional fractionated radiotherapy. It has been conjectured that the ultimate success of radiotherapy depends critically on the ability to comprehend the mechanisms of cell repair. Therefore, alongside the necessary dosimetric evaluations, dose planning systems must also include biophysical modeling to assess and predict the actual extent of cell survival and repair after irradiation by any particle or ray beams used in radiotherapy.

One of the fastest expanding non-conventional fractionated radiotherapeutic modalities is stereotactic radiosurgery which is carried out by the gamma knife systems with fewer, but considerably larger and highly focused doses per fraction delivered within a much shorter time. It is here that radiobiological models with the correct high-dose behavior are of utmost importance. In order to optimize non-conventional fractionation, in the sense of determining the proper dose per fraction, clinical oncologists rely upon the abundant experience with the conventional fractionated radiotherapy. However, all the dose planning systems for the conventional radiotherapy are based upon the biologically effective dose (BED) estimated by the LQ model. Since the LQ model is a low-dose approximation, the BED cannot be determined uniformly for all the doses of interest. In practice, the LQ-based BED is obtained in a sequential manner by fitting this model to the experimental data in a limited dose-range at a time. To cover all the investigated doses, the BED is computed thereby for several dose intervals. Such segmented fittings yield several sets of radiobiological parameters with the consequence that the resulting BED becomes dose-range dependent. This, in turn, precludes a meaningful comparison between fractions for the conventional and non-conventional fractionated radiotherapeutic modalities. Hence the need for more advanced biophysical descriptions that would go beyond the LQ model and apply to any dose. This could make the BED dose-range independent and, thus, enable reliable comparisons between conventional and non-conventional radiotherapy.

Therefore, the main focus of this study is in establishing a mechanistically-based universally applicable radiobiological model for cell survival after exposure to radiation. Here, universality means that the same model remains equally valid at all absorbed doses D, ranging from low through intermediate to high energy depositions. Starting from the most general principles that an adequate repair-based model must fulfill, we have derived the PLQ, or equivalently, the DMM model for cell surviving fractions in the form of a rational function in the argument of the Poissonian exponential: $S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) = \exp\left[-(\alpha D + \beta D^2)/(1 + \gamma D)\right]$. The main features of this new radiobiological model can be summarized as follows:

(i) An appealing and multifaceted mechanistic description with a direct relation to Michaelis–Menten kinetics of enzyme catalysis for repair of radiation-induced lesions,
(ii) The three positive-definite parameters $\{\alpha, \beta, \gamma\}$ with their clear biological meaning and clinical interpretation,
(iii) A straightforward connection with the well-known two component model from the MT-SH formalism with the familiar parameters $\{k_1, k_0, n\}$ = {initial slope, final slope, extrapolation number} and the underlying mean lethal dose D_0 as $D_0 = 1/k_0$,
(iv) The non-zero constants for the initial and final slopes of the cell surviving fraction,
(v) A smooth switch from the Gaussian term $\exp(-\beta D^2)$ in the LQ model $S_{\mathrm{F}}^{(\mathrm{LQ})}(D) = \exp(-\alpha D - \beta D^2)$ to the purely exponential asymptote $\exp(-\beta D/\gamma) = \exp(-D/D_0)$ in the PLQ model at high doses, in accordance with the same pattern $S_{\mathrm{F}}^{(\mathrm{exp})}(D) \sim \exp(-D/D_0)$ of the terminal part of most of the experimentally measured dose-effect curves, and
(vi) The dose-range independence of the BED stemming from a single set of parameters $\{\alpha, \beta, \gamma\}$ for any given experimentally measured cell surviving fraction $S_{\mathrm{F}}^{(\mathrm{exp})}(D)$.

In several recent applications, including the present work, it has been found that the PLQ model systematically outperforms the LQ model by exhibiting excellent agreement with the available experimental data on cell surviving fractions and the related full-effect plots at all doses. This finding alongside the expounded mechanistic basis and the ease in computations should constitute an incentive for using the PLQ model in clinical dose-planning systems with the purpose of optimizing both conventional and non-conventional fractionated radiotherapy.

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