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ORIGINAL PAPER

Survival of radiation-damaged cells via mechanism of repair by pool molecules: the Lambert function as the exact analytical solution of coupled kinetic equations

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Abstract Repair of radiation damaged cells can be carried out through their interactions with intracellular substances that can supply the needed energy for repair. These substances may be viewed as forming a pool of repair molecules that through chemical reactions with lesions can lead to cell recovery from the initial radiation insult by deposition of dose D. Presently, time evolution of mean concentrations of interacting substances is obtained by solving the corresponding rate equations given by a coupled system of second-order non-linear differential equations that are imposed by the mass action law. For cell surviving fractions after irradiation, the most important quantity is the time-dependent concentration of lethal lesions. Our main working hypothesis is that pool substances are capable of repairing the inflicted injury to any cell molecules, including deoxyribonucleic acid which is generally viewed as the most critical target of radiation. The previous solution of these rate equations is only formal as it is expressed by yet another equation of an implicit, transcendental form. In the earlier applications, this formal solution has only been tackled by numerical means that, however, have no connection with any of the myriad of the usual explicit forms of cell surviving fractions. This drawback effectively discouraged researchers from further explorations of the otherwise attractive pool methodology. Such a circumstance is unfortunate in light of a clear and advantageous radiobiological interpretation of the parameters of this theoretical formalism of chemical kinetics.The present study is aimed at rescuing the pool methodology by solving the underlying transcendental equation for lethal lesions uniquely, exactly and explicitly in terms of the principal value Lambert W_0 function. This is a single-valued and dose-dependent function, which can be readily and accurately computed either from the available fast numerical algorithms or by employing the existing simple closed expressions with a quotient of

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elementary, logarithmic functions. Another distinct advantage of this analytical result is the known behaviors of W_0 at small and large doses. This permits an easy and immediate identification of the final D_0 (or D_{37}) dose and the extrapolation number n. Such a circumstance offers new possibilities within the presently proposed "Pool Repair Lambert" (PRL) model for analysis of problems encountered in assessing cell survival after exposure to various modalities of radiation, including different schedules (acute, fractionated) for the same radiation quality. Importantly, the PRL model is universally applicable to all doses with a smooth passage from low through intermediate to high doses. As to applications in radiotherapy, this feature is particularly important for treatment schedules with high-doses per fraction as in stereotactic radiosurgery and stereotactic body radiotherapy.

Keywords Radiobiological models · Repair pool molecules · Lambert function · Chemical kinetics · Rate equations · Dose planning systems · Hypofractionated radiotherapy

1 Introduction

This study is on the theory of chemical kinetics for cell repair after irradiation. In cellular radiobiology, the principal targets are deoxyribonucleic acid (DNA) molecules because of their central role in the genetic makeup of the cell, cell reproductivity through division, etc. The biological end-point of analyzing the impact of radiation can be very different e.g. chromosome aberration, clonogenic activity, etc. Radiation damage or lesion could also be multifaceted, such as single- and double-strand breaks (SSB, DSB) of DNA molecules, etc. Throughout the present work, potentially lethal lesions will be defined as repairable SSBs and DSBs of DNA molecules.

By contrast, one of the formulations of the linear-quadratic (LQ) model based on a molecular description of cell survival assumes that DSBs cause cell death [1–4]. However, many experiments over the last four decades have confirmed that DSBs can be repaired [5–9]. Various repair systems exist within and outside the cell. Repair is considered as being successfully completed within a definite time interval if the reproductive capacity of the cell could be restored. In radiobiology, cell death is understood in a restricted sense to mean cell reproductive death or mitotic death, which is loss of the cell's ability to divide i.e. to generate clones and, thus, to form colonies. Reproductively dead cells could still perform some metabolic functions even for a long time after irradiation.

Among the most important effects of radiation at the cellular level is reduction of the clonogenic ability relative to the unirradiated portion of the cell population. This can be quantified by the dose-effect relationship through a survival curve, which expresses the fraction of the cell population with the retained clone-forming capability. The related observable is cell surviving fraction which is denoted by $S_{\mathrm{F}}(D)$ and graphed on a semi-logarithmic plot as a function of the absorbed physical dose D. Cell survival curves and/or some other related quantities derived from $S_{\mathrm{F}}(D)$, e.g. biological effect, biologically effective dose or relative effectiveness, are very useful in radiotherapeutic treatment of cancer.

Discrepancies among various shapes of function $S_F(D)$ are connected with the differences between the effects of radiation on tumor and normal cells. This offers the possibility of modifying the shapes of the cell surviving fractions and the treatment regimens (e.g. a larger number of smaller fractions, a smaller number of larger fractions, etc.) so as to increase the therapeutic ratio and thus achieve the best clinical outcomes. Conventional fractionated radiotherapy with the total dose D split as 2 Gy per fraction for 5 days per week during 1 month permits cellular recovery or repair. This implies that, while attempting to find a scientifically-based justification of the preferential modification of the shape of $S_F(D)$ for optimal fractionation schedule, the focus should be placed on shoulders of survival curves and on the physical as well as biochemical processes governing cell repair.

The concept of repair by way of a metabolic pool is helpful for studying cell survival from the viewpoint of chemical kinetics. The notion of a pool refers to a pool or a reservoir of molecules that are unspecified chemical compounds (constituents or states) capable of undoing radiation-induced damage to the cell by counter-reactions [10–15]. In other words, these pool molecules from the cell environment (which is also irradiated) can induce metabolic processes involving the irradiated cell with the outcome of having repaired cells. In addition to a direct injury, cells can also be damaged indirectly by radicals created by radiation from surrounding water molecules. One of the ways in which a pool molecule can partially protect cells from radiation is to counteract this indirect effect of radiation by donating hydrogen atoms to radicals so as to neutralize their affinity for deleterious binding to DNA. The pool concept suggests that an increase in the dose yields a decreased ability of the irradiated organism or a single cell to cope with injuries i.e. damages. Such a diminished ability is assumed to arise whenever a pool of repair molecules has been either used up i.e consumed for recovery or was destroyed by radiation.

With these assumptions, it is easy to imagine how this pool notion would yield a cell surviving fraction exhibiting a shouldered response curve. Here, with an augmented dose, an increased fraction of the irradiated cell population at risk would eventually lose all its repair capacity. This implies that the cell survival curve at high doses should reduce to a single exponential. At low doses many lesions would be repaired, whereas as soon as the pool becomes depleted i.e. when the last molecule from the pool is either used up for repair or destroyed by radiation, any subsequent irradiation could lead to cell death. Cell death, nevertheless, need not occur, since the pool could be replenished through metabolic refilling by synthesis and thus again become available for the subsequent round of recovery. Such a replenishment of the pool effectively restores the shoulder in the radiation survival curve. This pattern is reminiscent of the Elkind–Sutton repair for the regimen of fractionated irradiation [16,17]. Overall, the pool concept reflects the effect of the changes in the environment of the irradiated cell. The essence of these changes is that they are capable of modifying the biological end-point of radiation which is presently taken to be cell survival i.e. the cell's capacity to divide and thus proliferate. The significance of the shoulder in the cell response curve is that it truly represents a measure or degree of reversing radiation damage through cell repair by pool molecules, enzyme catalysis or any other recovery pathways. The concept of cell repair mediated by pool molecules has originally been proposed by Powers [10] on a descriptive level, without any specified kinetic rate equations.

Subsequently, similarly to the development of various versions of the hit-target model, Orr and colleagues [11–15] formalized the Powers' pool concept [10] using certain first- and second-order rate equations from chemical kinetics to introduce three variants of different levels of sophistication.

Repair cannot occur without an energy supplier. One of the most versatile energy supplier to endergonic reactions (reactions that absorb energy) in the cells is adenosine triphosphate (ATP). In fact, all that was said about the repair capabilities of some unspecified pool molecules could equally be re-stated in terms of any other energy reservoir or an energy pump, which might furnish energy to the cell for repair. In such a case, cell repair would be re-activated as soon as the energy pumping systems has been refilled. In the pool methodology, it is not necessary to specify the type of pool molecules nor to clarify whether the energy pumping systems are directly or indirectly connected to radiation.[1] Rather, it is necessary to assess the importance of the effect of saturation and/or exhaustion of a generic repairing pool or energy pump as a result of the time development of some chemical processes that lead to certain metabolic changes in the irradiated cell. This is an alternative mechanism to the hit-target models [23,24] or to any of the existing interpretations of LQ model [1–4,25–31].

2 Chemical kinetics, rate constants and reaction velocities

Chemical kinetics, as a very important branch of chemistry, deals with rates at which chemical reactions proceed. This versatile research field describes interactive dynamics in systems comprised of separate molecules or molecular compounds that can react with each other. In such processes, the interacting species are called reactants. There might be more than two reactants in a given chemical reaction.

Interactions among the reactants can transform all or some of the reactants into entirely different species. Some of the reactants can emerge unaltered from chemical reactions in which, however, they could play a key role. An example is enzyme catalysis, in which enzyme molecules can interact with other reactants (one or more substrates). The outcome of such interactions can be one or more products, that are different from any of the substrates. Yet, the enzymes themselves complete the entire reaction chain emerging intact i.e. without undergoing the slightest change in their structure, concentration, etc.

Concentrations of reactants vary with time. Thus, all chemical reactions develop with a certain speed. As such, rates are the quantities that represent a measure of the efficiency of transformations from reactants to products. This is quantified by expressing a reaction rate k or a reaction velocity v as the quotient of an infinitesimal change in the concentration $\mathrm{d}[p](t)$ of the given product $[p](t)$ and an infinitesimal increment $\mathrm{d}t$ in time t :

$$v \propto \frac{\mathrm{d}[p](t)}{\mathrm{d}t}. \tag{2.1}$$

[1] Radiation itself is an energy supplier which, as such, could invoke some metabolic changes in the cell, including repair of radiation-inflicted damage. This pathway represents radiation-induced recovery which was extensively investigated in Refs. [18–22].

In other words, the reaction velocity is proportional to the first derivatives of concentration with respect to time (velocity $\propto \mathrm{d}[p](t)/\mathrm{d}t$). Such derivatives for each participant involved in a path of a given chemical reaction are equated to a combination (linear or non-linear) of concentrations of reactants. This gives rate equations, where the coefficients multiplying every concentration in these linear or non-linear superpositions are called the rate constants. For n reactants, there will be n rate equations that are coupled together.

From the mathematical viewpoint, given that only the first derivatives are involved with regard to the unknowns, these rate equations represent coupled first-order ordinary non-linear differential equations. In general, the rate equations are non-linear because the mentioned superpositions may involve the unknown concentrations raised to a power different from 1. Rate equations can be of the mth order, if the given concentration is raised to the mth power in the said superposition of concentrations. Most frequent are the zero-, first- and second-order rate equations in which the reaction velocities are proportional to the zero, first and second power of concentrations of the involved molecules denoted by X , Y , Z, etc. For example, second-order kinetics also refer to those chemical reactions with a product [X][Y] of two different concentrations. The special case Y = X of equal molecules corresponds to second-order kinetics involving $[\mathrm{X}][\mathrm{X}] = [\mathrm{X}]^2$.

Terminology of the mixed-order kinetics is also used for cases involving different powers of concentrations in linear or non-linear combinations of concentrations equated to the given velocities in rate equations. Similarly, the rate constant can be of e.g. the second-order if it multiplies either the term $[\mathrm{X}]^2$ or [X][Y]. Accordingly, the units of e.g. the first- and second-order rate constants are different, the former being e.g. in units $(\mathrm{M/g})^{-1}$, whereas the latter in $(\mathrm{M/g})^{-2}$, where M/g denotes mole per gram (mol/gram). Rate equations are set up by using the mass action law. This law dictates that the rate at which a chemical reaction proceeds is directly proportional to the product of the concentrations of the reactants.

3 Rate constants for lesion production, recovery and cell death

We shall introduce this notation for concentrations of various types of lesions per cell:

$[a](t)$ = concentration of potentially lethal lesions,
$[b](t)$ = concentration of lethal lesions,
$[c](t)$ = concentration repaired lesions,
$[p](t)$ = concentration of non-lethal lesions of pool molecules.

The rate constants of different transformations governed by chemical processes induced by radiation-cell interactions are:

k_0 = rate constant of increase in type $''a''$ lesions per unit dose at time $t = 0$,
k_1 = rate constant of the cell kill reaction $[a](t) \rightarrow [b](t)$,
k_2 = rate constant for the cell repair reaction $[a](t) \rightarrow [c](t)$.

Equivalently, rate k_0 can be defined through the reciprocal of the "final D_0 dose" via:

$$k_0 = \frac{1}{D_0}. \tag{3.1}$$

The final D_0 dose represents the dose at which the survival fraction $S_F(D)$ is reduced by a factor of $1/e \approx 0.37$, or by $\sim$37 % on the final, terminal portion of the dose-effect curve dominated by the purely exponential inactivation $S_F(D) \sim e^{-D/D_0}$. It is for this reason that D_0 is equivalently denoted by D_{37}. Such a reduction refers to any part of the terminal straight line in the semilogarithmic plot of $S_F(D)$ versus D e.g. from 0.1 to 0.037 or from 0.01 to 0.0037, etc. The notion of D_{37} is associated with the assumption of the exponential decay law specifically at high doses for the cell survival probability, $S_F(D) = e^{-D/D_0}$, where at $D = D_0$ we have $S_F(D_0) = 1/e \approx 0.37$. The same operational or geometrical meaning of D_0 is also used within the hit-target models [25–28] and indeed throughout cell radiobiology. A hit is a radiation event (e.g. ionization in collisions of the given particle beam with DNA molecules), whereas a target is a radiation-sensitive part of the cell. The simplest version of the hit-target theory is the single-target and single-hit (ST-SH) model [25], where the surviving fraction is given by $S_F^{(ST-SH)}(D) = e^{-D/D_0}$ at *all* doses. This model takes no account of cell repair so that every single direct hit is assumed to be recorded by the cell as lethal. Thus, the ST-SH model describes the cell as a counting detector with no dead time. In other words, within the classical hit-target theory lesions proportional to dose D are viewed as irrepairable. By contrast, as will be shown in Sect. 5.4, lesions proportional to dose D are repairable in the description by the PRL model.

Hereafter, concentrations of molecules as functions of time t will interchangeably be denoted by:

$$y(t) \equiv [y(t)] \equiv [y](t) \equiv [y]_t \equiv [y] \qquad (y = a\,,\ b\,,\ c\,,\ p). \tag{3.2}$$

Pool substances $''p''$ represent both repair molecules and lesions. This is because pool molecules can also be damaged by radiation. Moreover, we shall assume that all the $''p''$ lesions are repairable. Further, it will be supposed that whenever the pool of intracellular molecules is exhausted, it can subsequently be replenished by e.g. synthesis and thus become again available for repair of radiation-induced damage. The restriction to the non-lethal $''p''$ lesions alone and the limitation to a single repair system (i.e. one repair pathway) could readily be relaxed, but with the price of significantly increasing the number of parameters. However, the aim of the present mechanistic study is to deal with the minimal number of parameters that can be measured experimentally so as to acquire a clear biological as well as clinical meaning, interpretation and, hopefully, usefulness. While furthering a mechanistic radiobiological model based upon chemical kinetics and rate equations, we will still retain the goal of having a relatively small number of parameters (3 in the present work). This is in accordance with the general principle of parsimony: the smaller the number of estimation parameters the better, within reason. More specifically, for any type of modeling, be it mechanistic or phenomenological (empirical, fitting), the larger the set of parameters $\{p_1, p_2, p_3, \ldots\}$ to be estimated from experimental data, the more demands on computation for eventually achieving an acceptable accuracy of $\{p_1, p_2, p_3, \ldots\}$, the more stringent imposition on measurements for validation of $\{p_1, p_2, p_3, \ldots\}$ or related quantities.

The rate constant k_2 for transformation $a \to c$ is the rate at which $''a''$ is reduced to $''c''$ per unit of $''a''$. The rate k_1 of decrease of $''a + p''$ will be assumed to be a dose-independent constant throughout the time development of the type $''a''$ lesions. Further,

for convenience, we shall assume that a single dose D is delivered instantaneously at time $t = 0$. These are the so-called acute doses as opposed to fractionated dose delivery. The rate constant k_2 could be obtained by considering all lesions on which the recovery process can act. These are the type $''a''$ and $''b''$ lesions.

A generic working hypothesis of all pool-based models is that every increment of dose D yields more new $''a''$ and $''p''$ lesions. Moreover, it is assumed here that the rate for the transformation $a \to b$ is dependent solely on the concentration of the type $''a''$ lesions. This gives the following linear first-order rate equation for time evolution of concentration $[b](t)$:

$$\frac{\mathrm{d}[b](t)}{\mathrm{d}t} = k_1[a](t). \tag{3.3}$$

These are general remarks that are independent of the order of chemical kinetics for lesion production, cell repair and cell death. They will be supplemented by certain specific features in the next section which explicitly deals with the second-order kinetics for rate equations for time development of concentrations of molecules and chemical compounds.

4 Second-order kinetics for cell repair by pool molecules

Here, we shall make use of the second- or mixed-order kinetics to establish a mechanistic basis of lesion repair by means of a pool of molecules from the cell environment. This formalism employs Eq. (3.3) together with the assumption that with every increment of dose D, new lesions $''a''$ and $''p''$ will be produced. Additionally, during the conversion $''a'' \to ''b''$ (creation of lethal lesions), a realistic possibility will be allowed by which the rate for the competitive reaction $a \to c$ (formation of repaired lesions) could decrease even when the amount of $''a''$ is kept fixed. Such a decrease is due to the consumption of the pool molecules that are needed for repair of potentially lethal lesions $''a''$. Thus, more and more of the radiation-induced lesions $''a''$ (and eventually all of them if the pool $''p''$ is completely depleted by consumption in repair) will be converted to the lethal lesions $''b''$. Consequently, the rate of production of lethal lesions per unit dose will rise to a maximal value with increased dose, thus yielding the final straight-line segment of the logarithmic survival curve as a continuation of the initial shoulder at lower doses. Overall, a description of the branching by which the repaired lesions $''c''$ can be independently produced from both the $''a''$ and $''p''$ states, in fact, necessitates an explicit introduction of the product $[a](t)[p](t)$ of the corresponding concentrations into the rate equations for the mean number $[a](t)$ and $[c](t)$. This will give the second-order kinetic equations for $[a](t)$ and $[c](t)$.

4.1 Kinetic rate equations involving lesions and pool molecules

Using the mass action law, which governs the mass balance i.e. mass conservation in a chemical reaction, we can set up the following system of mixed-order kinetic rate equations:

$$\frac{\mathrm{d}[a](t)}{\mathrm{d}t} = -k_2[p](t)[a](t) - k_1[a](t)\,, \tag{4.1}$$

$$\frac{\mathrm{d}[b](t)}{\mathrm{d}t} = k_1[a](t)\,, \tag{4.2}$$

$$\frac{\mathrm{d}[c](t)}{\mathrm{d}t} = k_2[p](t)[a](t)\,, \tag{4.3}$$

$$\frac{\mathrm{d}[p](t)}{\mathrm{d}t} = -k_2[p](t)[a](t)\,, \tag{4.4}$$

with the initial conditions at $t = 0$:

$$[a]_0 = k_0 D, \quad [b]_0 = 0, \quad [c]_0 = 0, \quad [p]_0 = p_0\,, \tag{4.5}$$

where p_0 is the initial concentration of pool molecules that are available for repair at time $t = 0$. Dose D plays the role of a parameter for system (4.1)–(4.4) where time t is the independent variable. In analogy with (3.3), we can cast Eq. (4.1) into the form:

$$\frac{\mathrm{d}[a](t)}{\mathrm{d}t} = -k(t)[a](t), \tag{4.6}$$

where,

$$k(t) = k_1 + k_2[p](t). \tag{4.7}$$

In the first-order kinetics with pool repair molecules from earlier studies [11,13–15], the rate coefficient $k(t)$ in Eq. (4.6) was a material constant $k = k_1 + k_2$, i.e. a time-independent parameter. By contrast, in the present second-order kinetics of cell repair by pool molecules, the rate coefficient $k(t) = k_1 + k_2[p](t)$ in Eq. (4.1), rewritten as Eq. (4.6), is not a constant, as it explicitly depends on time t through concentration $[p](t)$ of pool molecules [12].

4.2 Analytical solution of the system of kinetic equations by means of the Lambert function

The coupled system of differential equations (4.1)–(4.4) can be solved exactly in the analytical form by first expressing $[a](t)$ from Eq. (4.2) as:

$$[a](t) = \frac{1}{k_1}\frac{\mathrm{d}[b](t)}{\mathrm{d}t}. \tag{4.8}$$

Then by inserting (4.8) into Eq. (4.4), we have:

$$\frac{\mathrm{d}\ln[p](t)}{\mathrm{d}t} = -\rho\frac{\mathrm{d}[b](t)}{\mathrm{d}t}, \tag{4.9}$$

where ρ is the quotient of the rates for the repair process and the development of a lethal lesion:

$$\text{Repair capacity or RC}: \quad \rho = \frac{k_2}{k_1} = \frac{\text{Rate of cell repair}}{\text{Rate of cell kill}}. \tag{4.10}$$

Constant ρ is a measure of the repair capacity (RC) of a repairing system, which is presently taken to be a pool of intracellular molecules. Conversely, the reciprocal of ρ denoted by η can be interpreted as the repair incapacity (RI) of the repairing system: the smaller η, the smaller capacity of intracellular pool molecules to repair damage of the irradiated cell:

$$\text{Repair incapacity or RI}: \quad \eta = \frac{1}{\rho} = \frac{k_1}{k_2} = \frac{\text{Rate of cell kill}}{\text{Rate of cell repair}}. \tag{4.11}$$

The rate constants k_1 and k_2 appearing in the relative radiosensitivity ρ from (4.10) are usually not measured experimentally in a direct way. However, by using the identity $k_2/k_1 = (k_2/k_0)/(k_1/k_0)$, we can rewrite (4.10) and (4.11) as:

$$\rho = \frac{g_\mathrm{r}}{f_\mathrm{u}}, \qquad \eta = \frac{f_\mathrm{u}}{g_\mathrm{r}}, \tag{4.12}$$

where f_u and g_r are the experimentally measurable fractions of unrepaired (u) i.e. lethal and repaired (r) lesions, respectively:

$$\left.\begin{aligned} f_\mathrm{u} &= \frac{k_1}{k_0} \quad \text{(Fraction of unrepaired or lethal lesions)} \\ g_\mathrm{r} &= \frac{k_2}{k_0} \quad \text{(Fraction of repaired lesions)} \end{aligned}\right\}. \tag{4.13}$$

Here, radiosensitivity k_0 can equivalently be conceived as the total inactivation probability, which is given by the sum of the two partial probabilities for cell repair (k_2) and cell death (k_1) as follows:

$$k_0 = k_1 + k_2 \qquad \therefore \qquad f_\mathrm{u} + g_\mathrm{r} = 1. \tag{4.14}$$

Maximal probability is equal to unity which upon division of both sides of equation $k_0 = k_1 + k_2$ is decomposed into its two fractions f_u and g_r according to $f_\mathrm{u} + g_\mathrm{r} = 1$, as in (4.14). Overall, irrespective of whether using k_2/k_1 or its identical counterpart $g_\mathrm{r}/f_\mathrm{u}$ for the same quantity in (4.10) or (4.12), respectively, ρ has a clear meaning of a branching ratio for the two underlying processes involving the cell repair and cell kill mechanisms.

By integrating differential equation (4.9), we obtain the result:

$$\ln[p](t) = -\rho[b](t) + \ln C_1, \tag{4.15}$$

where the integration constant C_1 can be determined by substituting the initial conditions (4.5) into (4.15), so that:

$$C_1 = p_0. \tag{4.16}$$

Inserting this constant into Eq. (4.15), it follows:

$$[p](t) = p_0 \mathrm{e}^{-\rho[b](t)}. \tag{4.17}$$

Further, with the help of (4.8) and (4.17), we can write Eq. (4.3) for $[c](t)$ as:

$$\frac{\mathrm{d}[c](t)}{\mathrm{d}t} = \rho p_0 \left\{\mathrm{e}^{-\rho[b](t)}\right\} \frac{\mathrm{d}[b](t)}{\mathrm{d}t}. \tag{4.18}$$

Acting upon both sides of this equation by the operator $\int \mathrm{d}t$ gives:

$$\left.\begin{array}{c} \int \mathrm{d}[c](t) = \rho p_0 \int \mathrm{e}^{-\rho[b](t)} \mathrm{d}[b](t) + C_2 \\ \therefore\ [c](t) = -p_0 \mathrm{e}^{-\rho[b](t)} + C_2 \end{array}\right\}, \tag{4.19}$$

where C_2 is the integration constant. Using the initial condition $[c]_0 = 0$ from (4.5), it follows:

$$C_2 = p_0, \tag{4.20}$$

so that,

$$[c](t) = p_0 \left\{1 - \mathrm{e}^{-\rho[b](t)}\right\}. \tag{4.21}$$

The relationship (4.8) is also useful when (4.8) and (4.17) are inserted into the rhs of Eq. (4.1) and integrated to yield:

$$\left.\begin{array}{c} \int \mathrm{d}[a](t) = -\int \left\{1 + \rho p_0 \mathrm{e}^{-\rho[b](t)}\right\} \mathrm{d}[b](t) + C_3 \\ \therefore\ [a](t) = p_0 \mathrm{e}^{-\rho[b](t)} - [b](t) + C_3 \end{array}\right\}. \tag{4.22}$$

With the initial conditions $[a]_0 = k_0 D$ and $[b]_0 = 0$ from (4.5), the integration constant C_3 becomes:

$$C_3 = k_0 D - p_0, \tag{4.23}$$

and, therefore,

$$k_0 D = [b](t) + p_0 \left\{1 - \mathrm{e}^{-\rho[b](t)}\right\} + [a](t), \tag{4.24}$$

where $k_0 D \geq 0$ and the rhs is positive or 0 for $t \geq 0$. Using (4.21), the result from (4.24) can be written as:

$$[a](t) = k_0 D - [c](t) - [b](t). \tag{4.25}$$

On the other hand, by adding together Eqs. (4.1), (4.2) and (4.3), we are led to:

$$\frac{\mathrm{d}}{\mathrm{d}t}\{[a](t) + [b](t) + [c](t)\} = 0. \tag{4.26}$$

Integration of (4.26) with the initial conditions from (4.5) yields:

$$[a](t) + [b](t) + [c](t) = k_0 D, \tag{4.27}$$

in agreement with (4.25). According to (4.17), the exponential $p_0 \mathrm{e}^{-\rho[b](t)}$ on the rhs of Eq. (4.21) is equal to $[p](t)$ so that:

$$[c](t) = p_0 - [p](t). \tag{4.28}$$

This shows that the concentration of repaired lesions $[c](t)$ is equal to the difference between the concentrations of pool molecules at the onset of the repair reaction ($t = 0$) and that at the subsequent time t. Of course, this does not mean that $[c](t)$ is independent of $[a](t)$ and $[b](t)$. Quite the contrary, $[p](t)$ is determined by both $[a](t)$ and $[b](t)$. This can be seen by inserting $[c](t) = a_0 - [a](t) - [b](t)$ from the mass balance expression (4.27) into the lhs of Eq. (4.28) to arrive at $[p](t) = p_0 - \{(a_0 - [a](t)) - [b](t)\}$, where $a_0 \equiv [a]_0 = k_0 D$ so that:

$$[p](t) = p_0 - [p'](t), \quad [p'](t) = [a'](t) - [b](t), \quad [a'](t) = a_0 - [a](t). \tag{4.29}$$

Here, the formal difference $[p'](t) = [a'](t) - [b](t)$ can be identified in another way by inserting the increment $[p](t) = p_0 - [p'](t)$ of the concentration of pool molecules into the rhs of Eq. (4.28) with the result $[p'](t) = [c](t)$. Thus, the auxiliary quantity $[p'](t)$ from (4.29) is, in fact, equal to the concentration of repaired lesions $[c](t)$ at time t. Moreover, relation $[p'](t) = [c](t)$ maps expression $[p](t) = p_0 - [p'](t)$ from (4.29) into formula $[p](t) = p_0 - [c](t)$, which coincides with Eq. (4.28).

As they stand, formulae (4.17), (4.21) and (4.24) for $[p](t)$, $[c](t)$ and $[a](t)$, respectively, are all expressed in terms of concentration $[b](t)$ of lethal lesions. However, $[b](t)$ is unknown. Moreover, it is precisely $[b](t)$ which is the sought main result of the analysis. Therefore, it would be advantageous to turn these relationships around and express $[b](t)$ through $[a](t)$. With this goal, we consider the following general transcendental equation of the type (4.24):

$$z - q_1 - q_2 \mathrm{e}^{-q_3 z} = 0. \tag{4.30}$$

Multiplication of this equation by $q_3 \mathrm{e}^{-q_1 q_3}$ and rearranging yields:

$$Z\mathrm{e}^{Z} = q_2 q_3 \mathrm{e}^{-q_1 q_3}, \qquad Z = q_3(z - q_1). \tag{4.31}$$

This implicit equation can be solved exactly first for Z as:

$$Z = W\left(q_2 q_3 \mathrm{e}^{-q_1 q_3}\right), \tag{4.32}$$

and subsequently for z with the result,

$$z = q_1 + \frac{1}{q_3} W\left(q_2 q_3 \mathrm{e}^{-q_1 q_3}\right). \tag{4.33}$$

Here, W is the Lambert function [32,33] defined as the multivalued solution of a transcendental equation:

$$W(z)\mathrm{e}^{W(z)} = \eta, \tag{4.34}$$

where η is a known i.e. given quantity. Another equivalent transcendental equation for W is obtained by taking the natural logarithm of both sides of (4.34):

$$\ln W(z) + W(z) = \ln \eta. \tag{4.35}$$

One of the explicit representations of $W(z)$ is this power series which converges for $|z| \leq 1/\mathrm{e}$:

$$W(z) = z - z^2 + \frac{3}{2} z^3 - \cdots = \sum_{m=1}^{\infty} \frac{(-m)^{m-1}}{m!} z^m, \quad |z| \leq \frac{1}{\mathrm{e}}. \tag{4.36}$$

For $z = x$, where x is real, only two branches, denoted by $W_0(x)$ and $W_{-1}(x)$, are real-valued. All the other branches or roots $W_k (k = 1, \pm 2, \pm 3, \ldots)$ of Eq. (4.34) are complex-valued. The Lambert function $W_0(x)$ is the principal branch among all the possible solutions $W_k (k = 1, \pm 2, \pm 3, \ldots)$ of Eq. (4.34). Specifically, for $x \in [-1/\mathrm{e}, +\infty]$, we have $W(x) \geq -1$, in which case $W(x)$ becomes the principal branch $W_0(x)$:

$$W(x) = W_0(x) \quad \text{if} \quad W(x) \geq -1 \quad \text{and} \quad x \in [-1/\mathrm{e}, +\infty], \tag{4.37}$$

and, furthermore:

$$W_0(x\mathrm{e}^x) = x \qquad \text{if} \qquad x \geq -1. \tag{4.38}$$

Comparing (4.24) and (4.30) and identifying:

$$\left.\begin{array}{c} z = [b](t) \\ q_1 = k_0 D - p_0 - [a](t) \\ q_2 = p_0 \\ q_3 = \rho \end{array}\right\}, \tag{4.39}$$

it follows:

$$[b](t) = k_0 D - p_0 - [a](t) + \frac{1}{\rho} W_0\left(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D + [a])}\right). \tag{4.40}$$

Here, the principal branch W_0 is taken for W because $\rho p_0 \mathrm{e}^{\rho(p_0-k_0+[a])} \geq 0$ for any time t. In this relation, we have $[a](t) \geq 0$ because all the physical concentrations are non-negative quantities. The corresponding time-dependent concentrations of pool molecules $[p](t)$ and repaired lesions $[c](t)$ are obtained by inserting (4.40) into Eqs. (4.17) and (4.21) with the results:

$$[p](t) = p_0 \mathrm{e}^{-\rho(k_0 D - p_0 - [a]) - W_0(x)}, \tag{4.41}$$

and,

$$[c](t) = p_0 \left\{1 - \mathrm{e}^{-\rho(k_0 D - p_0 - [a]) - W_0(x)}\right\}, \tag{4.42}$$

where,

$$x \equiv x(t) = \rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D + [a])} \geq 0. \tag{4.43}$$

Due to the randomness of ionizing radiation events, it is customaryto assume that the distribution of lethal lesions $[b](t)$ in individual cells obeys the Poisson statistics, so that:

$$S_{\mathrm{F}}(D, t) = \mathrm{e}^{-[b](t)}. \tag{4.44}$$

In other words, we suppose that the surviving fraction $S_{\mathrm{F}}(D, t)$ of the cell population with no lethal lesions $[b](t)$ is given by the Poisson probability law. Upon inserting the result for lethal lesions $[b](t)$ into (4.44), it follows:

$$S_{\mathrm{F}}(D, t) = \mathrm{e}^{p_0 - k_0 D + [a](t) - (1/\rho) W_0(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D + [a])})}, \tag{4.45}$$

or equivalently, by way of (4.43),

$$S_{\mathrm{F}}(D, t) = \mathrm{e}^{p_0 - k_0 D + [a](t) - (1/\rho) W_0(x)}. \tag{4.46}$$

Using (4.44) and $[b](t) = -\ln S_{\mathrm{F}}(D, t)$, we can equivalently rewrite Eq. (4.24) as:

$$k_0 D = [a](t) - \ln S_{\mathrm{F}}(D, t) + p_0 \left\{1 - S_{\mathrm{F}}^{\rho}(D, t)\right\}. \tag{4.47}$$

To solve this transcendental equation, we denote the term $p_0 S_{\mathrm{F}}^{\rho}(D, t)$ by Y/ρ with:

$$Y = \rho p_0 S_{\mathrm{F}}^{\rho}(D, t). \tag{4.48}$$

Equivalently, the surviving fraction $S_{\mathrm{F}}(D, t)$ can be expressed in terms of Y as follows:

$$S_{\mathrm{F}}(D, t) = \left(\frac{Y}{\rho p_0}\right)^{1/\rho}. \tag{4.49}$$

Employing (4.43), we can cast Eq. (4.47) into the following form:

$$\ln Y + Y = \ln x. \tag{4.50}$$

By reference to (4.35), the explicit solution of the implicit equation (4.50) becomes:

$$Y = W_0(x). \tag{4.51}$$

Returning to the cell surviving fraction by passing from Y to $S_{\mathrm{F}}(D, t)$ using (4.49), we have:

$$S_{\mathrm{F}}(D, t) = \left\{ \frac{W_0(x)}{\rho p_0} \right\}^{1/\rho}, \tag{4.52}$$

or equivalently,

$$S_{\mathrm{F}}(D, t) = \left\{ \frac{1}{\rho p_0} W_0 \left(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D + [a])} \right) \right\}^{1/\rho}. \tag{4.53}$$

Formally, the two derived solutions (4.45) and (4.52) for the same surviving fraction S_{F} look very different, especially regarding the way in which W_0 appears. However, since the lhs of Eqs. (4.45) and (4.52) represent the same S_{F}, the rhs of these latter equations ought to be identical, as well, and this gives the condition:

$$\left\{ \frac{W_0(x)}{\rho p_0} \right\}^{1/\rho} = \mathrm{e}^{p_0 - k_0 D + [a] - (1/\rho) W_0(x)}. \tag{4.54}$$

When both sides of Eq. (4.54) are raised to the power ρ, the following relation is obtained:

$$\frac{W_0(x)}{\rho p_0} = \mathrm{e}^{\rho(p_0 - k_0 D + [a]) - W_0(x)}. \tag{4.55}$$

The term $\mathrm{e}^{\rho(p_0 - k_0 D + [a]) - W_0(x)}$ in the rhs of this equation is identified as $x\mathrm{e}^{-W_0(x)}/(\rho p_0)$ by way of (4.43). This maps Eq. (4.55) to $W_0(x)/(\rho p_0) = x\mathrm{e}^{-W_0(x)}/(\rho p_0)$, which after multiplication by $\rho p_0 \mathrm{e}^{W_0(x)}$ reads as:

$$W_0(x)\mathrm{e}^{W_0(x)} = x, \tag{4.56}$$

where x is given by (4.43). Expression (4.56) is the definition the Lambert function. Thus, by assuming that condition (4.54) is fulfilled, the identity (4.56) is obtained. This shows that the two forms (4.45) and (4.52) of surviving fraction S_F are, in fact, identical to each other, as they must be, and this was set to prove.

As a check of the main result (4.40) for concentration of lethal lesions, we can employ the initial condition $[a]_0 = k_0 D$ from (4.5) to calculate the limiting value of $[b](t)$ as $t \to 0$:

$$\begin{aligned}\lim_{t\to 0}[b](t) &= k_0 D - p_0 - [a]_0 + \frac{1}{\rho} W_0\left(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D + [a]_0)}\right)\\ &= k_0 D - p_0 - k_0 D + \frac{1}{\rho} W_0\left(\rho p_0 \mathrm{e}^{\rho(k_0 D + p_0 - k_0 D)}\right)\\ &= -p_0 + \frac{1}{\rho} W_0\left(\rho p_0 \mathrm{e}^{\rho p_0}\right)\\ &= -p_0 + p_0 \cdot \left\{\frac{1}{\rho p_0} W_0\left(\rho p_0 \mathrm{e}^{\rho p_0}\right)\right\}\\ &= -p_0 + p_0 \cdot 1 = -p_0 + p_0 = 0,\end{aligned}$$

where (4.38) is used, so that:

$$\lim_{t\to 0}[b](t) = 0. \tag{4.57}$$

This is in agreement with the correct initial condition $[b]_0 = 0$ from (4.5), as it ought to be.

4.3 Asymptotic form of the solution at infinitely large times

Expressions (4.40), (4.41) and (4.42) represent the analytical, closed forms for concentrations $[b](t)$, $[p](t)$ and $[c](t)$, respectively, obtained as the exact solutions of the system of four coupled rate equations (4.1)–(4.4). These results for $[b](t)$, $[p](t)$ and $[c](t)$ are all expressed in terms of concentration $[a](t)$ of potentially lethal lesions. However, concentration $[a](t)$ itself cannot be obtained from the system (4.1)–(4.4). Nevertheless, for the present purpose all that is needed is the set of two particular values of $[a](t)$, one at $t = 0$ and the other at $t = \infty$. These are given by $[a]_0 = D/D_0$ and $[a]_\infty = 0$. The corresponding value $[b]_\infty$, which is of primary interest, signifies completion of the whole process after a sufficiently long time has elapsed i.e. when all the remaining potentially lethal lesions lead to cell death. Such a circumstance motivates consideration of the asymptotic limits of $[a](t)$, $[b](t)$, $[c](t)$ and $[p](t)$ at infinitely large times for a fixed dose D. The respective limiting values will be denoted by $[A]_D$, $[B]_D$, $[C]_D$ and $[P]_D$:

$$\lim_{t\to\infty}[a](t) = [a]_\infty \equiv [A]_D, \qquad \lim_{t\to\infty}[b](t) = [b]_\infty \equiv [B]_D\,, \tag{4.58}$$

and,

$$\lim_{t\to\infty}[c](t) = [c]_\infty \equiv [C]_D, \qquad \lim_{t\to\infty}[p](t) = [p]_\infty \equiv [P]_D\,, \tag{4.59}$$

where subscript D indicates that dose D is the independent variable. In analogy with convention (3.2), concentrations of molecules as functions of dose D will hereafter interchangeably be labeled as follows:

$$Y_D \equiv [Y_D] \equiv [Y]_D \equiv [Y] \qquad (Y = A\,,\ B\,,\ C\,,\ P). \tag{4.60}$$

Further, the limiting value of biological effect $\mathrm{E_B}(D,t)$ and surviving fraction $S_\mathrm{F}(D,t)$ for $t \to \infty$ will be denoted by $\mathrm{E_B}(D)$ and $S_\mathrm{F}(D)$, respectively:

$$\mathrm{E_B}(D) = \lim_{t\to\infty} \mathrm{E_B}(D,t), \tag{4.61}$$

and,

$$S_\mathrm{F}(D) = \lim_{t\to\infty} S_\mathrm{F}(D,t). \tag{4.62}$$

As stated, when time t tends to infinity ($t \to \infty$), all the potentially lethal lesions will disappear i.e. the asymptotic number $[a]_\infty$ of the type $''a''$ lesions will tend to zero:

$$[A]_D = 0. \tag{4.63}$$

By taking the limit $t \to \infty$ in the solution (4.40) alongside the relation $\lim_{t\to\infty}[a](t) = [a]_\infty \equiv [A](D) = 0$ from (4.58) and (4.63), we have:

$$[B]_D = k_0 D - p_0 + \frac{1}{\rho} W_0\left(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D)}\right). \tag{4.64}$$

The associated concentrations of pool molecules P_D and repaired lesions C_D can be deduced from (4.41) and (4.42) as:

$$[P]_D = p_0 \mathrm{e}^{-\rho[B]_D} = p_0 \mathrm{e}^{-\rho(k_0 D - p_0) - W_0(x_D)}, \tag{4.65}$$

and,

$$[C]_D = p_0\left\{1 - \mathrm{e}^{-\rho[B]_D}\right\} = p_0\left\{1 - \mathrm{e}^{-\rho(k_0 D - p_0) - W_0(x_D)}\right\}. \tag{4.66}$$

Variable x_D in the Lambert function $W_0(x_D)$ is the limit of $x(t)$ form (4.43) as $t \to \infty$:

$$x_D = \lim_{t\to\infty} x(t), \tag{4.67}$$

so that,

$$x_D \equiv x_0 \mathrm{e}^{x_0 - \rho k_0 D} \geq 0, \tag{4.68}$$

where,

$$x_0 = \rho p_0. \tag{4.69}$$

Further, it also appears that x_0 is the limiting value of $W_0(x_D)$ as dose D tends to zero:

$$\lim_{D\to 0} W_0(x_D) = x_0. \tag{4.70}$$

Likewise, the related surviving fraction $S_{\mathrm{F}}(D)$ is obtained from the Poisson probability (4.44) and (4.64) as:

$$S_{\mathrm{F}}(D) = \mathrm{e}^{-[B]_D}\,, \tag{4.71}$$

so that,

$$S_{\mathrm{F}}(D) = \mathrm{e}^{p_0 - k_0 D - (1/\rho) W_0(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D)})}, \tag{4.72}$$

or more succinctly,

$$S_{\mathrm{F}}(D) = \mathrm{e}^{-[B]_D} = \mathrm{e}^{p_0 - k_0 D - (1/\rho) W_0(x_D)}. \tag{4.73}$$

Alternatively, the limit $t \to \infty$ and the boundary condition $\lim_{t\to\infty}[a](t) = [a_\infty] \equiv [A]_D = 0$ could have also been used in the transcendental equation (4.24), which would then read as:

$$k_0 D = [B]_D + p_0 \left\{1 - \mathrm{e}^{-\rho[B]_D}\right\}. \tag{4.74}$$

This is of the form of Eq. (4.31) whose solution is given by (4.33). Therefore, with the appropriate specifications:

$$\left.\begin{array}{c} z = [B]_D \\ q_1 = k_0 D - p_0 \\ q_2 = p_0 \\ q_3 = \rho \end{array}\right\}, \tag{4.75}$$

the solution of (4.74) is identified to be:

$$[B]_D = k_0 D - p_0 + \frac{1}{\rho} W_0\left(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D)}\right), \tag{4.76}$$

in agreement with (4.64). Thus, the result (4.64), or equivalently, (4.76) for the final (asymptotic) concentration of lethal lesions $[B]_D$ is the same, irrespective of whether the limit $t \to \infty$ is taken in the implicit transcendental equation (4.74) or in its explicit solution (4.40), as it must be. The underlying biological assumption of the explicit final concentration $[B]_D$ is that all potentially lethal radiation injuries were transformed to lethal lesions $[A]_D = 0$ at asymptotic times $t \to \infty$.

Similarly to the analysis at arbitrary times t, we could have alternatively started directly from Eq. (4.47) for the surviving fraction and take the limit $t \to \infty$ therein. The pertinent limit $[a](t) \to 0$ for $t \to \infty$ reduces (4.47) to the following equation:

$$k_0 D = -\ln S_{\mathrm{F}} + p_0 \left\{1 - S_{\mathrm{F}}^{\rho}(D)\right\}, \tag{4.77}$$

which according to (4.52) has the solution,

$$S_{\mathrm{F}}(D) = \left\{\frac{1}{\rho p_0} W_0\left(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D)}\right)\right\}^{1/\rho}. \tag{4.78}$$

This expression is identical to (4.73) by reliance upon the relationship:

$$\left\{\frac{W_0(x_D)}{\rho p_0}\right\}^{1/\rho} = \mathrm{e}^{p_0 - k_0 D - (1/\rho) W_0(x_D)}, \tag{4.79}$$

which is the counterpart of (4.54) for $t \to \infty$. Here, we used expression (4.67).

5 The "Pool Repair Lambert" model for cell survival

Quantity $[B]_D$ represents the biological effect of radiation in the description of repair by a pool molecule or a pool energy. In the present derivation, we obtain the exact and explicit solution of chemical kinetics system (4.1)–(4.4) for the rate equations in terms of the Lambert transcendental function W_0. This formalism, which yields the biological effect (4.64), will hereafter be called the "Pool Repair Lambert" (PRL) model:

$$[B]_D \equiv \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)\,, \tag{5.1}$$

where,

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) = k_0 D - F_{\mathrm{B}}^{(\mathrm{PRL})}(D)\,, \tag{5.2}$$

and,

$$F_{\mathrm{B}}^{(\mathrm{PRL})}(D) = p_0 - \frac{1}{\rho} W_0(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D)}). \tag{5.3}$$

The biological effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ in (5.2) is the difference between the contributions from the two inactivation mechanisms: the direct cell kill given by the linear term $k_0 D$ and the molecular pool repair described by the non-linear function $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$, respectively. These two contributions are correlated. It is *a priori* expected that the repair mechanism itself is affected by the cell inactivation. Indeed, this is reflected in the cell recovery function $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ from (5.3), which correlates with the cell kill component $k_0 D$ through the exponential $\exp(\rho[p_0 - k_0 D])$ in (4.68) as the independent variable x_D of $W_0(x_D)$. Overall, the main significance of Eq. (5.2) is that the level of the biological effect of radiation is not simply equal to the initial direct damage $k_0 D$ predicted by the ST-SH model [25]:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{ST-SH})}(D) = k_0 D. \tag{5.4}$$

Rather, the administered physical dose D is modified by the cell response such that the starting number of lesions $k_0 D$ is reduced by activation of the pool repair system. The surrounding pool molecules protect the attacked cell by counteracting the radiation injury to yield the repair function $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$, which mitigates a part of damage $k_0 D$ as per (5.2).

As in (4.44), by assuming the Poisson distribution of maximized lethal lesions $[B]_D$, we can write the surviving fraction in the PRL model as follows:

$$S_{\mathrm{F}}^{(\mathrm{PRL})}(D) = \mathrm{e}^{-[B]_D} \equiv \mathrm{e}^{-\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}}. \tag{5.5}$$

This can be stated in a more explicit form:

$$S_{\mathrm{F}}^{(\mathrm{PRL})}(D) = \mathrm{e}^{p_0 - k_0 D - (1/\rho) W_0(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D)})}, \tag{5.6}$$

or equivalently, by way of (4.78),

$$S_{\mathrm{F}}^{(\mathrm{PRL})}(D) = \left\{ \frac{1}{\rho p_0} W_0 \left(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D)} \right) \right\}^{1/\rho}. \tag{5.7}$$

At the asymptotic times $t \to \infty$, the mean number of pool molecules $[P]_D$, repaired lesions, $[C]_D$, and lethal lesions $[B]_D$, are related to each other by:

$$[P]_D = p_0 + [B]_D - k_0 D, \qquad [C]_D = k_0 D - [B]_D. \tag{5.8}$$

If $\rho = 0$, there will be no repair by pool molecules, in which case we can deduce:

$$\begin{aligned} \lim_{\rho \to 0} \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) &= k_0 D - p_0 + \lim_{\rho \to 0} \left\{ \frac{1}{\rho} W_0 \left(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D)} \right) \right\} \\ &\approx k_0 D - p_0 + p_0 \cdot \lim_{\rho \to 0} \{ x_D / x_0 \} \\ &= k_0 D - p_0 + p_0 \cdot 1 \\ &= k_0 D - p_0 + p_0 = k_0 D = \frac{D}{D_0}, \end{aligned}$$

where we used the approximation $W_0(x_D) \approx x_D$ for $\rho \to 0$. The obtained result is the correct expression for $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)$, when only the exponential inactivation ($k_0 D = D/D_0$) acts on the cell, as expected:

$$\lim_{\rho \to 0} \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) = k_0 D = \frac{D}{D_0} \qquad \text{(No repair by pool molecules)}. \tag{5.9}$$

Inserting this expression into (4.17) and (4.21), we have:

$$\lim_{\rho \to 0} [P]_D = p_0, \tag{5.10}$$

and,

$$\lim_{\rho \to 0} [C]_D = 0. \tag{5.11}$$

With no recovery ($\rho = 0$) i.e. prior to activation of pool molecules in the process of lesion recovery, the number of these substances is equal to the initial number p_0, as in (5.10). Consequently, in the same limit $\rho \to 0$, the number of lesions by pool molecules is equal to zero i.e. $[C]_D = 0$, as in (5.11). Further, in the limit $p_0 \to 0$, we find from (4.64):

$$\begin{aligned}\lim_{p_0\to 0} \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) &= k_0 D - \lim_{p_0\to 0} p_0 + \lim_{p_0\to 0}\left\{\frac{1}{\rho} W_0\left(\rho p_0 \mathrm{e}^{\rho(p_0-k_0 D)}\right)\right\} \\ &= k_0 D - 0 + \frac{1}{\rho} W_0(0) = k_0 D + \frac{1}{\rho}\cdot 0 = k_0 D + 0 = k_0 D\end{aligned}$$

so that,

$$\lim_{p_0\to 0} \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) = k_0 D = \frac{D}{D_0}. \tag{5.12}$$

Similarly, it follows from (4.65) and (4.66) that:

$$\lim_{p_0\to 0} [P]_D = 0, \tag{5.13}$$

and,

$$\lim_{p_0\to 0} [C]_D = 0. \tag{5.14}$$

The limiting values (5.12), (5.13) and (5.14) are correct, since when repair is absent ($\rho = 0$), we have $[C]_D = 0$. Moreover, if no pool molecule is present at the onset of irradiation at $t = 0$, it follows that $p_0 = 0$. The case (5.14) is trivial, since if the initial concentration of pool molecules at $t = 0$ is zero i.e. $[p]_0 = p_0 = 0$, it would naturally be zero at any later time t, so that $[p]_0 = 0$, including $\lim_{t\to\infty}[p](t) = [P]_D = 0$.

5.1 The full-effect plot

In addition to the biological effect, there is another useful function which conveniently describes the influence of radiation on the cell. This function displays the so-named full-effect (Fe) plot [34,35], which shows a variation of $-(1/D)\ln S_{\mathrm{F}}(D)$ versus dose D :

$$\begin{aligned}\mathrm{Fe} &\equiv -\frac{1}{D}\ln S_{\mathrm{F}}(D) \quad \text{(Full effect)} \\ &= \mathrm{R}(D) \quad \text{(Reactivity)}.\end{aligned} \tag{5.15}$$

Function $\mathrm{Fe}(D)$ is also called the reactivity $\mathrm{R}(D)$ because it is one of the representations for description of the cell reaction to radiation [2,3]. The Fe-plot can convey important biological information for models that can transparently show the interplay of the direct cell kill and cell repair mechanisms. Definition (5.15) involves the product of the dose reciprocal $1/D$ and the biological effect $-\ln S_{\mathrm{F}}(D)$ via $-(1/D)\ln S_{\mathrm{F}}(D)$ in quantity $\mathrm{Fe}(D)$ or $\mathrm{R}(D)$.

In order to make the Fe-plot explicit in the PRL model, expression (5.6) for cell surviving fraction will be written in the following factorized form:

$$S_{\mathrm{F}}^{(\mathrm{PRL})}(D) = \left\{n\mathrm{e}^{-D/D_0}\right\} M(D), \tag{5.16}$$

with,

$$M(D) \equiv \mathrm{e}^{-(1/\rho)W_0(x_D)}, \tag{5.17}$$

where x_D is the auxiliary variable from (4.68) and n is the extrapolation number,

$$n \equiv \mathrm{e}^{p_0}, \tag{5.18}$$

or equivalently, $\ln n = p_0$. Parameter n, which is identified solely in terms of the initial concentration p_0 of the pool repair molecules, will be further discussed in Sect. 5.5 when considering the limit of the surviving fraction $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ at large doses D. Being a concentration, p_0 is always non-negative i.e. $p_0 \geq 0$, which also implies that $\ln n \geq 0$. This latter inequality will be satisfied if $p_0 \geq 1$:

$$\ln n = p_0 \qquad \Longleftrightarrow \qquad p_0 \geq 1. \tag{5.19}$$

By comparison with (5.16), it is pertinent to recall the functional form of the cell surviving fraction in the multi-target and single-hit (MT-SH) model:

$$S_{\mathrm{F}}^{(\mathrm{MT-SH})}(D) = \left(1 - \mathrm{e}^{-D/D_0}\right)^{n_{\mathrm{T}}}, \tag{5.20}$$

and,

$$S_{\mathrm{F}}^{(\mathrm{MT-SH})}(D) \underset{D\to\infty}{\approx} n_{\mathrm{T}}\mathrm{e}^{-D/D_0}. \tag{5.21}$$

We see that the term $n\mathrm{e}^{-D/D_0}$ in the curly brackets from (5.16) formally coincides with the asymptotic behavior of $S_{\mathrm{F}}^{(\mathrm{MT-SH})}(D)$ at large doses D. As mentioned, parameter D_0 is the mean lethal dose in the hit-target models where, n_{T} is the extrapolation number. We have already stated that in the present formalism D_0 is not the mean lethal dose, but only the reciprocal of the final slope k_0 of the cell survival curve. Further, unlike (5.18), the extrapolation number n_{T} in the MT-SH model from (5.21) is interpreted as the number of the sensitive sites (targets) in the cell, which is expected to be hit during the inactivation process. Further, as will be shown in Sect. 5.5, the modifying function $M(D)$ tends to unity as $D \to \infty$, so that the PRL and MT-SH models formally share the same type of the high-dose asymptotes $n\mathrm{e}^{-D/D_0}$ and $n_{\mathrm{T}}\mathrm{e}^{-D/D_0}$, respectively. Nevertheless, when inspecting $n\mathrm{e}^{-D/D_0}$ in (5.16) from the PRL model, given that the extrapolation numbers n and n_{T} have completely different biological interpretations, any reference to the MT-SH model should be descriptive and

qualitative as merely a way of a symbolic resemblance of the high-dose asymptotes of the two otherwise unequal descriptions of radiation-cell interaction.

Applying (5.15) to the cell surviving fraction (5.16) in the PRL model, we have:

$$\mathrm{Fe}^{(\mathrm{PRL})}(D) = -\frac{1}{D}\ln S_{\mathrm{F}}^{(\mathrm{PRL})}(D) = k_0 - \frac{1}{D}\left\{p_0 - \frac{W_0(x_D)}{\rho}\right\}. \tag{5.22}$$

or equivalently,

$$\mathrm{Fe}^{(\mathrm{PRL})}(D) = k_0 - \frac{F_{\mathrm{B}}^{(\mathrm{PRL})}(D)}{D}. \tag{5.23}$$

The curly brackets in (5.22) is the repair function $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ from (5.3). Since $1/D$ tends to infinity as $D \to 0$, the Maclaurin series expansion of the repair function $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ must not start with a constant term ($\sim D^0 = 1$). This is indeed the case, since the Maclaurin series for $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ contains only the powers D^m ($m = 1, 2, 3, \ldots$), such that its first term ($\sim D$) cancels D in the denominator from (5.23), so that the remainder of $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ is regular i.e. finite as $D \to 0$.

5.2 Differential equation for cell surviving fractions

The first derivative of the Lambert $W(z)$ function with any independent variable z (real or complex) is given by:

$$\frac{\mathrm{d}W(z)}{\mathrm{d}z} = \frac{W(z)}{z\{1 + W(z)\}}, \qquad z \neq 0. \tag{5.24}$$

In the present case, z is real-valued, $z = x_D$, where x_D is defined in (4.68). To pass from D to x_D variable, we make use of the differentiation chain rule $\mathrm{d}/\mathrm{d}D = (\mathrm{d}x_D/\mathrm{d}D)(\mathrm{d}/\mathrm{d}x_D)$, where $(\mathrm{d}/\mathrm{d}D)x_D = -\rho k_0 x_D$ and this yields:

$$\frac{\mathrm{d}W_0(x_D)}{\mathrm{d}D} = -\rho k_0 \frac{W_0(x_D)}{1 + W_0(x_D)}. \tag{5.25}$$

Thus, taking the first derivative of $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ with respect to D by employing (5.6) and (5.25), it follows that the surviving fraction in the PRL model satisfies the following first-order non-linear differential equation with a dose-dependent coefficient $k_0/\{1 + W_0(x_D)\}$:

$$\frac{\mathrm{d}S_{\mathrm{F}}^{(\mathrm{PRL})}(D)}{\mathrm{d}D} = -\frac{k_0}{1 + W_0(x_D)} S_{\mathrm{F}}^{(\mathrm{PRL})}(D), \tag{5.26}$$

for which the initial condition reads as:

$$S_{\mathrm{F}}^{(\mathrm{PRL})}(0) = 1. \tag{5.27}$$

If we are given Eq. (5.26) and the initial condition (5.27), the solution $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ could be found by integration, which gives $\int \mathrm{d}\ln S_{\mathrm{F}}^{(\mathrm{PRL})}(D) = -k_0 \int\{1 + W_0(x_D)\}^{-1}\mathrm{d}D$. This equation reduces to the following expression by using the relation $\mathrm{d}D = -(\rho k_0 x_D)^{-1}\mathrm{d}x_D$:

$$\ln S_{\mathrm{F}}^{(\mathrm{PRL})}(D) = \frac{I}{\rho} + C\,, \tag{5.28}$$

where C is the integration constant and I is this auxiliary integral:

$$I = \int \frac{1}{1 + W_0(x_D)}\frac{\mathrm{d}x_D}{x_D}. \tag{5.29}$$

With the help of the identity $1/\{1 + W_0(x_D)\} = 1 - W_0(x_D)/\{1 + W_0(x_D)\}$ alongside Eq. (5.24) via $(\mathrm{d}/\mathrm{d}x_D)W_0(x_D) = W(x_D)/\{x_D(1 + W(x_D))\}$, it follows:

$$I = \ln x_D - W_0(x_D), \tag{5.30}$$

so that,

$$\ln S_{\mathrm{F}}^{(\mathrm{PRL})}(D) = \frac{1}{\rho}\{\ln x_D - W_0(x_D)\} + C. \tag{5.31}$$

Constant C is determined by setting $D = 0$ in (5.31) together with using Eq. (5.27) and expression $W_0(\rho p_0 \mathrm{e}^{\rho p_0}) = \rho p_0$ from (4.38). The result is $C = (1/\rho)\ln(\rho p_0)$ which, combined with relation $\ln x_D = \ln(\rho p_0) + \rho(p_0 - k_0 D)$, casts the result (5.31) into the form:

$$\begin{aligned}\ln S_{\mathrm{F}}^{(\mathrm{PRL})}(D) &= p_0 - k_0 D - \frac{W_0(x_D)}{\rho} \\ &= p_0 - k_0 D - \frac{1}{\rho} W_0\left(\rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D)}\right),\end{aligned} \tag{5.32}$$

where (4.68) is utilized. This is in agreement with the natural logarithm taken of both sides of Eq. (5.6), showing that the final result (5.32) is the correct, exact solution of the non-linear differential equation (5.26) for the cell surviving fraction in the PRL model.

5.3 Initial and final slopes

Next, we shall derive the two important biological quantities that represent the initial and final slopes of the dose-response curve in the PRL model. The initial slope s_{i} for any surviving fraction $S_{\mathrm{F}}(D)$ is defined by the tangent to the dose-effect curve in the limit $D \to 0$:

$$s_{\mathrm{i}} \equiv -\lim_{D\to 0}\frac{\mathrm{d}S_{\mathrm{F}}(D)}{\mathrm{d}D}. \tag{5.33}$$

In the limit $D \to 0$, the lhs of Eq. (5.26) becomes equal to $-s_\mathrm{i}$ so that:

$$s_\mathrm{i} = \lim_{D\to 0} \frac{k_0}{1+W_0(x_D)} S_\mathrm{F}^{(\mathrm{PRL})}(D) = \lim_{D\to 0} \frac{k_0}{1+W_0(x_D)}, \tag{5.34}$$

where (5.27) is utilized. By reference to (4.70), we have:

$$\lim_{D\to 0} \frac{k_0}{1+W_0(x_D)} = \frac{k_0}{1+x_0}, \tag{5.35}$$

where x_0 is given in (4.69) as the maximal value of variable x_D from (4.68). This gives the initial slope from (5.26) as:

$$s_\mathrm{i} = \kappa_1, \quad \kappa_1 \equiv \frac{k_0}{1+\rho p_0} = \frac{1}{D_0}\frac{1}{1+\rho p_0} \qquad \text{(Initial slope)}. \tag{5.36}$$

The final slope s_f is the tangent to the terminal part of the cell survival curve. If the given surviving fraction S_F is going to exhibit a purely exponential inactivation at high doses, as in the experimental data, then the logarithmic derivative $(\mathrm{d}/\mathrm{d}D)\ln S_\mathrm{F}(D)$ must tend to a constant at $D \to \infty$. Hence, a constant s_f is defined by:

$$s_\mathrm{f} \equiv -\lim_{D\to\infty} \frac{\mathrm{d}\ln S_\mathrm{F}(D)}{\mathrm{d}D}. \tag{5.37}$$

By means of (5.26), this definition takes the following form in the PRL model:

$$s_\mathrm{f} \equiv -\lim_{D\to\infty} \frac{\mathrm{d}\ln S_\mathrm{F}^{(\mathrm{PRL})}(D)}{\mathrm{d}D} = -\lim_{D\to\infty} \frac{k_0}{1+W_0(x_D)}. \tag{5.38}$$

In the limit $D \to \infty$, variable $x_D = \rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D)}$ from (4.68) tends to zero:

$$\lim_{D\to\infty} x_D \equiv x_\infty, \qquad x_\infty = 0. \tag{5.39}$$

On the other hand, the Lambert $W_0(z)$ function is equal to zero for $z = 0$:

$$W_0(0) = 0. \tag{5.40}$$

Using (5.39) and (5.40), we can see that the limits $D \to \infty$ and $x_D \to 0$ are equivalent to each other, so that $\lim_{D\to\infty} W_0(x_D) = \lim_{D\to\infty} W_0(\rho p_0 \mathrm{e}^{\rho(p_0-k_0D)}) = \lim_{x_D\to 0} W_0(x_D) = W_0(0) = 0$ and, therefore:

$$\lim_{D\to\infty} W_0(x_D) = 0. \tag{5.41}$$

With this value at hand, Eq. (5.38) for the final slope becomes:

$$s_\mathrm{f} = \kappa_0, \quad \kappa_0 = k_0 = \frac{1}{D_0} \qquad \text{(Final slope)}. \tag{5.42}$$

Since $\rho > 0$ and $p_0 > 0$, we have $1 + \rho p_0 > 1$. Thus, comparing (5.36) and (5.42), we see that the initial slope is smaller than the final slope, as expected for a non-zero initial population of pool molecules ($p_0 \neq 0$) and for a still active pool repair system ($\rho \neq 0$) after the cell has absorbed dose D :

$$\text{Initial slope } (s_\mathrm{i}) \; < \; \text{Final slope } (s_\mathrm{f}). \tag{5.43}$$

Moreover, the difference between the final and initial slope is given by:

$$\Delta s_\mathrm{fi} \equiv s_\mathrm{f} - s_\mathrm{i} = \kappa_2 \,, \tag{5.44}$$

where,

$$\kappa_2 = \lambda \kappa_0, \qquad \lambda = \frac{\rho p_0}{1 + \rho p_0}, \qquad 0 \leq \lambda \leq 1. \tag{5.45}$$

Using the definitions of κ_1 and κ_2, it follows that their sum is equal to κ_0 :

$$\kappa_0 = \kappa_1 + \kappa_2. \tag{5.46}$$

Although $\kappa_1 \neq k_1$ and $\kappa_2 \neq k_2$, relation (5.46) is still of the same additive type as its counterpart $k_0 = k_1 + k_2$ from (4.14). Further, dividing both sides of Eq. (5.46) by κ_0 we have:

$$\lambda + \mu = 1, \tag{5.47}$$

where μ is defined by,

$$\mu \equiv \frac{1}{1 + \rho p_0}, \qquad 0 \leq \mu \leq 1. \tag{5.48}$$

It is illustrative to consider the biological significance of parameters κ_1 and κ_2 for $p_0 = 0$:

$$\{\kappa_1\}_{p_0=0} = k_0, \qquad \{\kappa_2\}_{p_0=0} = 0. \tag{5.49}$$

Thus, if pool repair molecules were not present at the onset of radiation-lesion interaction ($p_0 = 0$), constants κ_1 and κ_2 would be reduced to the final slope and zero, respectively. When repair is active ($p_0 \neq 0$), the proportionality constants between κ_j and k_j ($j = 1, 2$) can be expressed in terms of the measurable quantities $\{f_\mathrm{u}, g_\mathrm{r}\}$:

$$\kappa_1 = f_\mathrm{u} \frac{k_0}{h}, \qquad \kappa_2 = g_\mathrm{r} \frac{p_0 k_0}{h}, \tag{5.50}$$

where h is the partitioning or branching between the fractions of the unrepaired (f_u) and repaired (g_r) lesions,

$$h = f_\mathrm{u} + p_0 g_\mathrm{r}. \tag{5.51}$$

Using relation $k_0 = k_1 + k_2$ from (4.14), quantity h can be expressed exclusively through the repair-based parameters p_0 and g_r :

$$h = 1 + (p_0 - 1)g_r \geq 1\,, \tag{5.52}$$

where $p_0 \geq 1$ is used from (5.19). In particular, it is seen from (5.50) that even for the minute concentration p_0 of pool molecules, the cell kill rate k_1 would still be reduced by a factor of $h \geq 1$.

In most experimental data for mammalian cells, survival curves exhibit purely exponential behavior at both small and large doses. This occurs because of the absence of any appreciable activity of repair systems for two different reasons. In the low-dose limit, radiation damage is insufficient to trigger a significant activation of any repair pathway. At high doses, repair molecules are severely damaged and, moreover, the number of cell lesions is so large that repair systems become overwhelmed and, as such, are rendered inefficient. In these circumstances, the semilogarithmic surviving fraction versus D becomes a linear function of dose for small as well as large values of D. Consequently, in both limits $D \to 0$ and $D \to \infty$, the negative first derivative of the semilogarithmic surviving fraction with respect to D takes two different *constant* values that are, in fact, the initial and final slopes of the dose-effect curve:

$$s_i \equiv -\lim_{D\to 0} \frac{\mathrm{d}\ln S_F(D)}{\mathrm{d}D}, \qquad s_f \equiv -\lim_{D\to\infty} \frac{\mathrm{d}\ln S_F(D)}{\mathrm{d}D}. \tag{5.53}$$

This is the case for any radiobiological model with the correct i.e. purely exponential cell inactivation at small and large doses. In the PRL model, using Eq. (5.26), the relations from (5.53) are reduced to:

$$s_i = \lim_{D\to 0} \frac{k_0}{1 + W_0(x_D)}, \qquad s_f = \lim_{D\to\infty} \frac{k_0}{1 + W_0(x_D)}. \tag{5.54}$$

This immediately gives the end results (5.36) and (5.42) for the initial and final slopes on account of (5.35) and (5.41) for the limits $D \to 0$ and $D \to \infty$, respectively.

5.4 Asymptotic behavior of surviving fraction at the lowest doses

At extremely low doses ($D \to 0$), a negligible error is invoked by retaining only the first two terms in the Maclaurin expansion of $W_0(x_D)$ around $D = 0$. This leads to the approximation:

$$W_0(x_D) \underset{D\to 0}{\approx} \rho p_0 - \lambda\rho k_0 D\,, \tag{5.55}$$

where constant λ is given in (5.45). Inserting this result into Eq. (5.3) gives the first-order approximation $F_B^{(1)}(D)$ to the repair function $F_B^{(PRL)}(D)$ via:

$$F_B^{(PRL)}(D) \underset{D\to 0}{\approx} F_B^{(1)}(D)\,, \tag{5.56}$$

with,

$$F_{\mathrm{B}}^{(1)}(D) = \kappa_2 D, \tag{5.57}$$

where parameter κ_2 is defined in (5.45). To highlight that $F_{\mathrm{B}}^{(1)}(D)$ is valid only at low (L) doses, we can also use the alternative notation $F_{\mathrm{B,L}}^{(\mathrm{PRL})}(D)$ for $F_{\mathrm{B}}^{(1)}(D)$:

$$F_{\mathrm{B,L}}^{(\mathrm{PRL})}(D) = F_{\mathrm{B}}^{(1)}(D) = \kappa_2 D. \tag{5.58}$$

This yields the corresponding low-dose approximate formula for biological effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)$:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) \underset{D\to 0}{\approx} \mathrm{E}_{\mathrm{B,L}}^{(\mathrm{PRL})}(D)\,, \tag{5.59}$$

with,

$$\begin{aligned} \mathrm{E}_{\mathrm{B,L}}^{(\mathrm{PRL})}(D) &= k_0 D - F_{\mathrm{B,L}}^{(\mathrm{PRL})}(D) \\ &= \kappa_0 D - \kappa_2 D \\ &= (\kappa_0 - \kappa_2) D = \kappa_1 D, \end{aligned} \tag{5.60}$$

so that,

$$\mathrm{E}_{\mathrm{B,L}}^{(\mathrm{PRL})}(D) = \alpha D, \tag{5.61}$$

where,

$$\left.\begin{aligned} \alpha \equiv \kappa_1 = \kappa_0 - \kappa_2 \\ \alpha = \mu\kappa_0 = \frac{k_0}{1+\rho p_0} \geq 0 \end{aligned}\right\}. \tag{5.62}$$

Parameter α from (5.61) is, in fact, the relabeled initial slope s_{i} from (5.36) where $s_{\mathrm{i}} = \kappa_1$, so that:

$$\alpha = s_{\mathrm{i}}. \tag{5.63}$$

Therefore, at asymptotically low doses, the cell surviving fraction $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ behaves as:

$$S_{\mathrm{F}}^{(\mathrm{PRL})}(D) \underset{D\to 0}{\approx} S_{\mathrm{F,H}}^{(\mathrm{PRL})}(D), \tag{5.64}$$

where, biologically, $S_{\mathrm{F,L}}^{(\mathrm{PRL})}(D)$ is the lowest-dose approximation of $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$,

$$S_{\mathrm{F,L}}^{(\mathrm{PRL})}(D) = \mathrm{e}^{-\alpha D} \quad \text{(Surviving fraction at the lowest doses).} \tag{5.65}$$

Mathematically, this is also the first-order of the Maclaurin series of $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ and, as such, could equivalently be denoted by $S_{\mathrm{F}}^{(1)}(D)$:

$$S_{\mathrm{F}}^{(1)}(D) = S_{\mathrm{F,L}}^{(\mathrm{PRL})}(D) = \mathrm{e}^{-\alpha D}. \tag{5.66}$$

Overall, we see that in the PRL model the dominant mode of inactivation at very low doses is the exponential cell kill behavior of the response function, as also measured in the associated experiments. Of course, such an estimate cannot represent the whole dose-effect curve since the shoulder is missing at intermediate doses and, moreover, the high-dose exponential tail is absent with the final slope s_{f} which is different from α. As per derivation (5.60), parameter α in (5.62) is structured. It has two components, $\kappa_0 = k_0$ and $\kappa_2 = \lambda k_0$ that are the rate constant of potentially lethal and repaired first-step lesions, respectively. The ratio of these latter two rates can be expressed as the following alternative quotients:

$$\begin{aligned}\frac{\kappa_0}{\kappa_2} &= \frac{\text{Rate of potentially lethal lesions}}{\text{Rate of repaired first} - \text{step lesions}} \\ &= 1 + \frac{1}{p_0}\frac{k_1}{k_2} \\ &= 1 + \frac{1}{p_0}\frac{f_{\mathrm{u}}}{g_{\mathrm{r}}}.\end{aligned} \tag{5.67}$$

Here, f_{u} and g_{r} are the fractions of lethal and repaired lesions, whereas k_1 and k_2 are the rate constants of cell kill and cell repair, respectively. In (5.67), we used the defining relation $\rho = k_2/k_1$ from (4.10) for parameter ρ, as a measure of the repair capacity of a pool of intracellular molecules in the role of a repair system. As discussed, fractions f_{u} and g_{r} can be experimentally determined.

If we insert (5.55) into the rhs of Eq. (5.7), we obtain the result:

$$S_{\mathrm{F}}^{(\mathrm{PRL})}(D) \underset{D\to 0}{\approx} (1 - \alpha\rho D)^{1/\rho}\ , \tag{5.68}$$

which is a binomial expression raised to a non-integer power. However, this binomial tends to the Poisson law when $D \to 0$, on account of relation $\lim_{y\to 0}(1-\zeta y)^{-1/(\zeta y)} = \mathrm{e}^{-\zeta}$:

$$(1 - \alpha\rho D)^{1/\rho} \underset{D\to 0}{\approx} \mathrm{e}^{-\alpha D} = S_{\mathrm{F,L}}^{(\mathrm{PRL})}(D) = S_{\mathrm{F}}^{(1)}(D)\,, \tag{5.69}$$

where $S_{\mathrm{F,L}}^{(\mathrm{PRL})}(D)$ or $S_{\mathrm{F}}^{(1)}(D)$ from (5.65) or (5.66) is the lowest-dose asymptote of $S_{\mathrm{F,L}}^{(\mathrm{PRL})}(D)$.

5.5 Asymptotic behavior of surviving fraction at the highest doses

At high doses ($D \to \infty$), the Lambert function $W_0(x_D)$ reduces to zero according to (5.41) and, in this limit, repair function $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ becomes:

$$F_{\mathrm{B}}^{(\mathrm{PRL})}(D) \underset{D\to\infty}{\approx} F_{\mathrm{B,H}}^{(\mathrm{PRL})}(D)\,, \tag{5.70}$$

where,

$$F_{\mathrm{B,H}}^{(\mathrm{PRL})}(D) = p_0. \tag{5.71}$$

Recall that p_0, which is the initial concentration of pool molecules, is also the natural logarithm of the extrapolation number according to (5.18). The corresponding estimate of the biological effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ at high (H) doses reads as:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) \underset{D\to\infty}{\approx} \mathrm{E}_{\mathrm{B,H}}^{(\mathrm{PRL})}(D)\,, \tag{5.72}$$

where,

$$\mathrm{E}_{\mathrm{B,H}}^{(\mathrm{PRL})}(D) = k_0 D - p_0. \tag{5.73}$$

Thus, the surviving fraction $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ at high doses acquires the shape:

$$S_{\mathrm{F}}^{(\mathrm{PRL})}(D) \underset{D\to\infty}{\approx} S_{\mathrm{F,H}}^{(\mathrm{PRL})}(D)\,, \tag{5.74}$$

where,

$$S_{\mathrm{F,H}}^{(\mathrm{PRL})}(D) \equiv n\mathrm{e}^{-k_0 D} = n\mathrm{e}^{-D/D_0} \quad \text{(Surviving fraction at the highest doses)}. \tag{5.75}$$

Here, parameter n is the extrapolation number defined by,

$$n \equiv \mathrm{e}^{p_0} \qquad \therefore \qquad \ln n = p_0 \qquad \text{(Extrapolation number)}, \tag{5.76}$$

as in (5.18). In a semilogarithmic graph of the investigated surviving fraction versus dose, n represents the intercept of the tangent to $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ with the ordinate where $D = 0$. With such a plot, this is a geometrical interpretation of n which, therefore, is the value obtained when the straight line $p_0 - k_0 D$ for the terminal part of the dose-effect curve is back-extrapolated to $D = 0$, according to $\{p_0 - k_0 D\}_{D=0} = p_0 = \ln n$. Multiplication of both sides of relation $\ln n = p_0$ from (5.76) by the final D_0 dose gives $D_0 \ln n = p_0 D_0$. Here, $D_0 \ln n$ can be recognized as the quasi-threshold dose D_{q}, so that:

$$D_{\mathrm{q}} = \frac{p_0}{k_0} \qquad \text{or} \qquad D_{\mathrm{q}} = p_0 D_0. \tag{5.77}$$

Thus, applying the PRL model to the given experimental data, the quasi-threshold dose D_{q} becomes available by reconstructing the initial pool size p_0 and the final slope $k_0 = 1/D_0$. We see from (5.74) and (5.75) that the surviving fraction in the PRL model predicts the exponential inactivation of the cell at the highest doses, as also measured experimentally.

A similar derivation can also be made by using the alternative formula (5.7) for cell surviving fraction in the PRL model. To this end, given that $x_D \to 0$ when $D \to \infty$,

we can use the Maclaurin expansion of $W_0(x_D)$ around $x_D = 0$. In such a case, by retaining only the first z for $z = x_D$ in series (4.36), it follows:

$$S_{\mathrm{F}}^{(\mathrm{PRL})}(D) \underset{D\to\infty}{\approx} \left(\frac{x_D}{\rho p_0}\right)^{1/\rho} = \mathrm{e}^{p_0 - k_0 D} = n\mathrm{e}^{-D/D_0} = S_{\mathrm{F,H}}^{(\mathrm{PRL})}(D)\,, \quad (5.78)$$

in accordance with (5.75), as it should be.

Combining (5.16) and (5.75), the surviving fraction $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ in the PRL becomes:

$$S_{\mathrm{F}}^{(\mathrm{PRL})}(D) = S_{\mathrm{F,H}}^{(\mathrm{PRL})}(D) M(D)\,, \quad (5.79)$$

where $M(D)$ is from (5.17). Since the correct high-dose behavior of $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ is already secured by $S_{\mathrm{F,H}}^{(\mathrm{PRL})}(D)$ from (5.79), the remainder $M(D)$ should be inconsequential at $D \to \infty$. Indeed, by virtue of relation $\lim_{D\to\infty} W_0(x_D) = 0$ from (5.41), it follows:

$$\lim_{D\to\infty} M(D) = 1. \quad (5.80)$$

However, this does not imply that literally infinite doses are mandatory to ensure that $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ has reached its asymptote $S_{\mathrm{F,H}}^{(\mathrm{PRL})}(D)$. The reason for this is in the fact that the Lambert function $W_0(x_D)$ from $M(D)$ in (5.79) has quantity x_D as its independent variable, which itself decays exponentially with increasing dose D according to $x_D = \rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D)}$ as in (4.68). This makes the contribution from the modifying function $M(D)$ negligibly small as soon as the irradiation dose reaches the terminal, exponential part $\mathrm{e}^{p_0 - D/D_0}$ of the dose-effect curve $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$. This terminal part is, in fact, equal to $S_{\mathrm{F,H}}^{(\mathrm{PRL})}(D)$ according to (5.75). With the high-dose component $S_{\mathrm{F,H}}^{(\mathrm{PRL})}(D)$ already factored out in the full function $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ from (5.79), the modifying component $M(D)$ is anticipated to contribute significantly only at low doses and in the intermediate region around the shoulder. These features of the PRL model match precisely the biophysical conditions by which repair of radiation damage is important at lower and intermediate doses, with no appreciable influence on reversing the effect of radiation at large doses.

5.6 The asymptotes of biological effect at the lowest and highest doses without using the Lambert function

In Sects. 5.4 and 5.5, the exact expression for biological effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ from (5.2) and (5.3) in terms of the Lambert $W_0(x_D)$ function is used to derive the asymptotic behaviors $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) \approx \alpha D$ and $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) \approx D/D_0 - p_0$ at the lowest and highest doses, respectively. Here, we shall check these findings by two different and more direct derivations. With this goal, we shall bypass the exact explicit solution from (5.2) and (5.3) focusing on employing solely the transcendental equation $k_0 D =$

$[B]_D + p_0(1 - \mathrm{e}^{-\rho[B]_D})$ from (4.74), which in the PRL model takes the form:

$$k_0 D = \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) + p_0 \left\{1 - \mathrm{e}^{-\rho \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)}\right\}$$
$$= \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) + p_0 - p_0 \left\{1 - \rho \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) + \cdots\right\}, \tag{5.81}$$

where the Maclaurin series for $\mathrm{e}^{-\rho \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)} = \mathrm{e}^{-\rho[B]_D}$ is everywhere convergent. At the lowest doses, concentration of lethal lesions $[B]_D$, or equivalently, the biological effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)$, is small. Therefore, for $D \to 0$ it suffices to retain only the first two terms in the Maclaurin series from (5.81) to obtain the approximate expression:

$$k_0 D \approx (1 + \rho p_0) \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D), \qquad D \to 0. \tag{5.82}$$

Dividing both sides of (5.82) by $1 + \rho p_0$ and identifying the resulting constant $k_0/(1 + \rho p_0)$ as α according to (5.62), we have:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) \underset{D \to 0}{\approx} \alpha D, \tag{5.83}$$

which is the correct lowest-dose asymptote $\mathrm{E}_{\mathrm{B,L}}^{(\mathrm{PRL})}(D)$ from (5.59) and (5.61).

On the other hand, at the highest doses, concentration $[B]_D$ of lethal lesions is large, so that $\mathrm{e}^{-\rho[B]_D}$ tends to zero, or equivalently, $p_0 \mathrm{e}^{-\rho[B]_D} \ll [B]_D$. In such a case, by neglecting $p_0 \mathrm{e}^{-\rho \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)}$ relative to $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ in (5.81), it follows:

$$k_0 D \approx \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) + p_0, \qquad D \to \infty, \tag{5.84}$$
$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) \underset{D \to \infty}{\approx} k_0 D - p_0 = k_0 D - \ln n. \tag{5.85}$$

As per (5.73), this is the proper highest-dose asymptote $\mathrm{E}_{\mathrm{B,H}}^{(\mathrm{PRL})}(D)$ of the exact biological effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ in the PRL model.

6 Connections among different radiobiological models

Overall, the initial idea on the pool modeling from 1962 is due to Powers [10] in terms of a descriptive and qualitative argument. He did not provide any quantitative data for the cell evolution dynamics nor any equation or expression for a pool-based cell response to radiation. A quantitative analysis was given in 1972 by Laurie et al. [12] who, after stating Eqs. (4.1)–(4.4), immediately gave the asymptotic implicit solution (4.74) at $t \to \infty$ with no details of the derivation. Using the Poisson statistics according to (5.5), Laurie et al. [12] employed various graphs of the equivalent implicit, transcendental equation (4.77) for the cell surviving fraction $S_{\mathrm{F}}(D)$ to approximately estimate the parameters $\{k_0, p_0, \rho\}$. Subsequently, they computed dose D from Eq. (4.77) for a comprehensive set of survival levels [12].

Such an indirect and rough approach should be contrasted to the present analytical solution (4.76) of the transcendental equation (4.74) for $[B]_D$, or equivalently, (4.77) for $S_F(D)$ in terms of the single-valued Lambert $W_0(x_D)$ function. This automatically gives the single-valued surviving fraction in the PRL model according to (5.5) or (5.6). A clear benefit is due to the existing important properties of the Lambert W_0 function, including the asymptotic behaviors at small and large doses. This permits an easy extraction of the main three biological quantifying parameters, such as the extrapolation number, initial and final slopes of the dose-effect curves as done presently in the PRL model. Moreover, the numerical algorithms for generating the Lambert W_0 function are well established and readily available for fast generation of numerical tables at any value of the independent variable [36–39]. These algorithms have recently been supplemented by simple and very accurate analytical expressions for the Lambert function [40,41]. Such formulae are of great practical importance not only for the PRL model, but also for the recently suggested "Integrated Michaelis–Menten" (IMM) model [42]. The lack of an implicit formula for $S_F(D)$ from the work of Laurie et al. [12] was presumably the major reason for the fact that their version of the pool-based cell survival has not subsequently been used in the literature. Instead, thus far, only two greatly simplified versions of the repair pool concept were employed in computations from Refs. [11,13,15]. It is hoped that the advances achieved in the present study will spur further research using the PRL model in cellular radiobiology.

6.1 Link to the "Linear-Quadratic" model

6.1.1 Repair in the conventional "Linear-Quadratic" model

The biological effect, surviving fraction and full effect in the LQ model are given by:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}(D) = \alpha_{\mathrm{u}} D + \beta_{\mathrm{r}} D^2, \tag{6.1}$$

$$S_{\mathrm{F}}^{(\mathrm{LQ})}(D) = \mathrm{e}^{-\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}(D)} = \mathrm{e}^{-\alpha_{\mathrm{u}} D - \beta_{\mathrm{r}} D^2} \quad \text{or} \quad S_{\mathrm{F}}^{(\mathrm{LQ})}(D) = \left\{\mathrm{e}^{-\alpha_{\mathrm{u}} D}\right\}_{\mathrm{lethal}} \left\{\mathrm{e}^{-\beta_{\mathrm{r}} D^2}\right\}_{\mathrm{repair}}, \tag{6.2}$$

$$\mathrm{Fe}^{(\mathrm{LQ})}(D) \equiv -\frac{1}{D} \ln S_{\mathrm{F}}^{(\mathrm{LQ})}(D) = \alpha_{\mathrm{u}} + \beta_{\mathrm{r}} D\,, \tag{6.3}$$

where subscript "u" and "r" refer to unrepairable (lethal) and repairable lesions, respectively. Specifically in the LQ model, there is also another pair of quantities derived from (6.1). These are the biologically effective dose $\mathrm{BED}^{(\mathrm{LQ})}(D)$ and relative effectiveness $\mathrm{RE}^{(\mathrm{LQ})}(D)$:

$$\mathrm{BED}^{(\mathrm{LQ})}(D) \equiv \frac{\mathrm{E}_{\mathrm{B}}^{(\mathrm{LQ})}(D)}{\alpha_{\mathrm{u}}} = D + \rho_0 D^2 = D + D^2/\eta_0, \tag{6.4}$$

and,

$$\mathrm{RE}^{(\mathrm{LQ})}(D) \equiv \frac{\mathrm{BED}^{(\mathrm{LQ})}(D)}{D} = 1 + \rho_0 D = 1 + D/\eta_0, \tag{6.5}$$

where $\alpha_u \geq 0$ and $\beta_r \geq 0$ are the fitting constants and,

$$\rho_0 = \frac{\beta_r}{\alpha_u}, \quad \eta_0 = \frac{\alpha_u}{\beta_r}, \quad \eta_0 = \frac{1}{\rho_0}. \tag{6.6}$$

The observables $\mathrm{BED}^{(\mathrm{LQ})}(D)$ and $\mathrm{RE}^{(\mathrm{LQ})}(D)$ find their most frequent applications in fractionated radiotherapy, where e.g. ratio β_r/α_u represents a measure of tissue sensitivity to the size of dose d given in each treatment. Here, $d = D/N$ where D is the total dose administered in N fractions. In comparing biological models with measurements, any departure of experimental data for the Fe-plot from a straight of the type (6.3) would indicate the breakdown of the LQ model. In fact, such departures are expected to be the rule rather than the exception from the rule. Indeed, it is hardly physical that the cell reaction to radiation would never cease to occur no matter how large the absorbed dose could be. Namely, the Fe-plot (6.3) from the LQ model shows that reactivity $\mathrm{Fe}^{(\mathrm{LQ})}(D)$ increases without limit or bound with augmentation of dose D. However, quite the contrary is anticipated to occur on biophysical grounds, suggesting that sufficiently high doses would cause a complete desensitization of the cell to radiation. In other words, after a certain large threshold dose, any further exposure of the cells to irradiation would provoke no cell reaction whatsoever. In such a case, the repair system itself would either be exhausted or depleted by radiation, so that absorption of any subsequent quanta would lead straight to cell death. This situation corresponds to a kind of a saturation effect, which is observed in the related measurements and also predicted by the PRL model, as will be discussed in Sect. 7.

The interpretation of the LQ model from formula (6.2) has recently been reviewed in Ref. [4] where parameter $\alpha_u \geq 0$ is defined to be the cellular intrinsic radiosensitivity showing how many natural-log-cell-inactivations (killings) occur per gray (Gy) in an *unrepairable* manner. In other words, lesions $\alpha_u D$ are irrepairable. In the same formulation (6.2), parameter $\beta_r \geq 0$ represents the natural logarithm of the number of cells (per Gy^2) that are *repairable*. Thus, from the total biological effect $\alpha_u D + \beta_r D^2$ in expression (6.1), only portion $\beta_r D^2$ of lesions is viewed as being associated with repair. As such, ratios $\beta_r/\alpha_u = \rho_0$ and $\alpha_u/\beta_r = 1/\rho_0 = \eta_0$ are the measures of the repair capacity and repair incapacity of the cell, respectively. However, when repair is included, the total number of lesions must be *smaller* than the unrepaired portion ($\alpha_u D \geq 0$) of the whole radiation-induced damage. In other words, repair must *increase* the surviving fraction. This is not the case in (6.2) since $\alpha_u D \geq 0$ and $\beta_r D^2 \geq 0$ in the surviving fraction $\mathrm{e}^{-\alpha_u D - \beta_r D^2}$ are repairable and irrepairable lesions, respectively. Here, the total number of lesions $\alpha_u D + \beta_r D^2$ from (6.1) is *larger* than $\alpha_u D$. Consequently, the repair-related contribution $\beta_r D^2 \geq 0$ *decreases* the total probability for survival, since $\{\mathrm{e}^{-\alpha_u D - \beta_r D^2}\}_{\text{with repair}} \leq \{\mathrm{e}^{-\alpha_u D}\}_{\text{without repair}}$. Therefore, conceiving cell repair in the LQ model with $\alpha_u D$ and $\beta_r D^2$ taken as non-repairable and repairable damage [4], respectively, is inconsistent with the meaning of total number of lesions $\alpha_u D + \beta_r D^2$, which is the biological effect (6.1). The inconsistency is in the plus sign in front of $\beta_r D^2$ for $\beta_r \geq 0$. Repair must reduce portion $\alpha_u D$ and this would occur for $\beta_r < 0$. However, this would be unphysical since β_r is a rate, which must be positive. Moreover, a negative β_r would yield divergence of the surviving fraction $\mathrm{e}^{-\alpha_u D + |\beta_r| D^2}$ at doses $D > \alpha_u/|\beta_r|$ located after the

shoulder of the curve for the cell surviving fraction. This obstacle is eliminated in Sect. 6.1.2.

The discussed inconsistency is not an issue in the two of the alternative interpretations of the LQ model without repair having the surviving fraction $e^{-\alpha_0 D-\beta_0 D^2}$ with $\alpha_0 \geq 0$ and $\beta_0 \geq 0$, such as the molecular formalism [1] or the dual action model [2,3]. For example, according to the concept of dual action, radiation-caused lesions accumulate. In particular, lesions $\alpha_0 D$ and $\beta_0 D^2$ are considered as being produced by one and two tracks of traversing particles, respectively. Both $\alpha_0 D$ and $\beta_0 D^2$ can be SSBs and DSBs of DNA molecules. The overall cumulative biological effect of lesions $\alpha_0 D \geq 0$ and $\beta_0 D^2 \geq 0$ is manifested in summing the separate positive-valued contributions from these two cell killing modes, as per $\alpha_0 D + \beta_0 D^2$. This, in turn, decreases the cell surviving fraction because $e^{-\alpha_0 D-\beta_0 D^2}$ is smaller than the contributions from either of the individual probabilities $e^{-\alpha_0 D}$ or $e^{-\beta_0 D^2}$.

The important question which emerges from the outlined discussion is: whether repair could be consistently introduced in a conceptually modified linear-quadratic model and still preserve the same mathematical form of the surviving fraction $e^{-\alpha' D-\beta' D^2}$ with certain non-negative constants $\alpha' \geq 0$ and $\beta' \geq 0$? We shall see in Sect. 6.1.2 that this is indeed possible by using a low-dose second-order approximation to the Maclaurin series of $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ where, however, as opposed to Ref. [4], both the linear $(\alpha' D)$ and quadratic $(\beta' D^2)$ portions of radiation damage are repairable.

6.1.2 A new way of introducing repair in the "Linear-Quadratic" model via the second-order perturbation approximation to the "Pool Repair Lambert" model

If in the response $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ from (5.3), the Lambert function $W_0(x_D)$ is developed around $D = 0$ as the Maclaurin series and subsequently truncated by neglecting all the terms D^m $(m \geq 3)$, the following form is obtained:

$$W_0(x_D) \underset{D\to 0}{\approx} \rho p_0 - \lambda \rho k_0 D + \frac{\rho}{2}\lambda \mu^2 k_0^2 D^2 , \tag{6.7}$$

where λ and μ are defined in (5.45) and (5.48), respectively. Relative to (5.55), expression (6.7) explicitly displays the quadratic term (D^2). This yields radiation lesions with the linear (D) and quadratic (D^2) dose dependence both of which are, however, subject to repair. The resulting approximation of $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ denoted by $F_{\mathrm{B}}^{(2)}(D)$:

$$F_{\mathrm{B}}^{(\mathrm{PRL})}(D) \underset{D\to 0}{\approx} F_{\mathrm{B}}^{(2)}(D) , \tag{6.8}$$

reads as,

$$F_{\mathrm{B}}^{(2)}(D) = \kappa_2 D - \beta' D^2 , \tag{6.9}$$

where,

$$\beta' = \frac{p_0}{2}\mu^3 (\rho k_0)^2 \geq 0. \tag{6.10}$$

The first term $\kappa_2 D$ is the repair function $F_{\mathrm{B}}^{(1)}(D)$ from (5.57). Further, the associate biological effect $\mathrm{E}_{\mathrm{B}}^{(2)}(D) = k_0 D - F_{\mathrm{B}}^{(2)}(D)$ is given by:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) \underset{D\to 0}{\approx} \mathrm{E}_{\mathrm{B}}^{(2)}(D)\,, \tag{6.11}$$

where,

$$\begin{aligned} \mathrm{E}_{\mathrm{B}}^{(2)}(D) &= k_0 D - F_{\mathrm{B}}^{(2)}(D) \\ &= \kappa_0 D - \left(\kappa_2 D - \beta' D^2\right) \\ &= (\kappa_0 - \kappa_2)\, D + \beta' D^2 \\ &\equiv \alpha' D + \beta' D^2, \end{aligned} \tag{6.12}$$

so that,

$$\mathrm{E}_{\mathrm{B}}^{(2)}(D) = \alpha' D + \beta' D^2, \qquad \alpha' = \alpha. \tag{6.13}$$

Here, constant α' is the same parameter α from (5.62) appearing in the first-order asymptote $S_{\mathrm{F}}^{(1)}(D)$ from (5.65). Therefore, denoting by $S_{\mathrm{F}}^{(2)}(D)$ the second-order in the Maclaurin series of $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ around $D = 0$, we have:

$$S_{\mathrm{F}}^{(\mathrm{PRL})}(D) \underset{D\to 0}{\approx} S_{\mathrm{F}}^{(2)}(D)\,, \tag{6.14}$$

where $S_{\mathrm{F}}^{(2)}(D)$ is the surviving fraction of the same form as in the LQ model (6.2), but with the parameters α' and β' of different biological meaning,

$$S_{\mathrm{F}}^{(2)}(D) \equiv \mathrm{e}^{-\mathrm{E}_{\mathrm{B}}^{(2)}(D)} = \mathrm{e}^{-\alpha' D - \beta' D^2} \qquad (\alpha' \geq 0\ ,\ \beta' \geq 0). \tag{6.15}$$

As mentioned in Sect. 5.4, radiosensitivity α, or equivalently, α' has two components that quantify the potentially lethal ($\kappa_0 D = k_0 D = D/D_0$) and repaired ($\kappa_2 D = \lambda k_0 D$) lesions. This is opposed to the LQ model [4] from (6.2) where lesions proportional to dose ($\alpha_{\mathrm{u}} D$) are irrepairable such that only the radiation damage $\beta_{\mathrm{r}} D^2$ can be repaired. By reference to (6.15), the characteristic α'/β' ratio is given by:

$$\frac{\alpha'}{\beta'} = \xi D_0, \qquad \xi = \frac{2}{p_0}\left(p_0 + \frac{k_1}{k_2}\right)^2. \tag{6.16}$$

The string of four successive equations in (6.12) for $\mathrm{E}_{\mathrm{B}}^{(2)}(D)$ details the answer to the question posed at the end of subsection (5.1). Therein, we inquired about the possibility of including repair in the linear-quadratic representation without encountering the inconsistency from Ref. [4] with a decreased cell survival. First, the biological

effect $\mathrm{E}_{\mathrm{B}}^{(2)}(D)$ from the repair-based linear-quadratic model via the second-order perturbation approximation to the PRL model is given by:

$$\mathrm{E}_{\mathrm{B}}^{(2)}(D) = k_0 D - F_{\mathrm{B}}^{(2)}(D)\,, \tag{6.17}$$

where $k_0 D$ is a potentially repairable lesion and $F_{\mathrm{B}}^{(2)}(D)$ is the repair function. Then, repair is seen as being applicable to lesions proportional to D and D^2 according to:

$$F_{\mathrm{B}}^{(2)}(D) = \kappa_2 D - \beta D^2. \tag{6.18}$$

Subsequently, when this latter twofold contribution from repair is *subtracted* from $k_0 D$, the total number of lesions is obtained through:

$$\mathrm{E}_{\mathrm{B}}^{(2)}(D) = \underbrace{\kappa_0 D}_{\text{initial lesions}} - \underbrace{(\kappa_2 D - \beta' D^2)}_{\text{repaired lesions}} \quad \text{(Consistent repair in linear}-\text{quadratics)}. \tag{6.19}$$

Here, to recall, $\kappa_0 D = k_0 D = a_0$ where a_0 is the initial concentration of potentially lethal lesions $''a''$. Finally, (6.19) gives:

$$\mathrm{E}_{\mathrm{B}}^{(2)}(D) = (\kappa_0 - \kappa_2) D + \beta' D^2 \equiv \alpha' D + \beta' D^2\,, \tag{6.20}$$

with $\alpha' = \kappa_0 - \kappa_2 = \alpha$ where α is in (5.62). This shows that it is possible to consistently include repair in the LQ-type modeling if both lesions proportional to dose and dose squared are repairable. Only the latter portion is repairable in (6.2) from Ref. [4]. In the linear-quadratic description (6.15), the survival probability $\mathrm{e}^{-k_0 D}$ based on potentially lethal lesions $k_0 D$ is *increased* by repair. The net result is a larger total probability $\mathrm{e}^{-k_0 D}\mathrm{e}^{k_2 D - \beta' D^2} = \mathrm{e}^{-\alpha' D - \beta' D^2}$, as per the discussed sequence of four equations in (6.12), or equivalently, (6.17)–(6.20) for $\mathrm{E}_{\mathrm{B}}^{(2)}(D)$.

In (6.16), quantity k_1/k_2 is the quotient of the rate constants for cell kill and cell repair mechanisms. Thus, because a portion of the linear inactivation $\alpha' D$ can be repaired via its component $\kappa_2 D$, quantity α'/β' is not simply in a direct proportion with the cell kill and cell repair ratio k_1/k_2. Rather, α'/β' is more involved since it is non-linearly dependent on k_1/k_2 by being proportional to $p_0^2 + 2p_0 k_1/k_2 + (k_1/k_2)^2$, as per (6.16). Of course, despite the relations between the sets $\{\alpha', \beta'\}$ and $\{k_0, p_0, \rho\}$, cell surviving fraction (6.15) could still retain the simplicity of the customary LQ model by extracting only two parameters α' and β' from the experimental data. However, the resulting α'/β' ratio cannot be interpreted as the quotient of the cell kill to cell repair. This is due to describing the lesions proportional to dose ($\sim D$) as repairable. Nevertheless, both the surviving fraction (6.2) and (6.15) suffer from continuous bending with augmentation of dose. This is not the case with the full PRL model (5.6) which can yield the most accurate numerical values for k_1/k_2. By contrast, any fitting of the truncated power series representation (5.6) from the PRL model, such as (6.15), to the given measured data would inevitably force the true k_1/k_2 ratio to acquire some altered and possibly unrealistic values as a direct consequence of minimization of the usual squared difference (Model − Experiment)^2.

6.2 Link to the "Padé Linear-Quadratic" model

The LQ model is known to be inadequate at large doses because of the continued bending of the cell surviving fraction $S_{\mathrm{F}}^{(\mathrm{LQ})}(D)$ with increased D. This failure is due to the Gaussian $\mathrm{e}^{-\beta_{\mathrm{r}} D^2}$, which dominates at large doses where for mammalian cells the purely exponential inactivation e^{-D/D_0} occurs, as confirmed by many measurements. This drawback has recently been overcome in a new repair-based mechanistic formalism called the Padé linear quadratic (PLQ) model [43–48]. The PLQ model consists of using a cell repair pathway for reducing the potentially lethal damage $k_0 D$ by subtracting the repaired lesions produced by a given repair system. In this model, the concentration of repaired lesions is obtained as the effective value, or equivalently, the halved harmonic mean of the low- and high-dose asymptotes of a repair function which has the correct behaviors at $D \to 0$ and $D \to \infty$. The PRL model has the repair function $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ with two such proper asymptotes at small and large doses. Therefore, the PLQ model can be deduced directly from such two asymptotic behaviors of $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$. To this end, we first write the biological effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}(D)$ in the PLQ model via the correct form of the type (5.2):

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}(D) = k_0 D - F_{\mathrm{B}}^{(\mathrm{PLQ})}(D). \tag{6.21}$$

Here, $F_{\mathrm{B}}^{(\mathrm{PLQ})}(D)$ is the repair function defined as the halved harmonic (or the effective value) of the respective low- and high-dose asymptotes $F_{\mathrm{B,L}}^{(\mathrm{PRL})}(D)$ and $F_{\mathrm{B,H}}^{(\mathrm{PRL})}(D)$ of $F_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ from (5.58) and (5.71), respectively:

$$F_{\mathrm{B}}^{(\mathrm{PLQ})}(D) = F_{\mathrm{B,eff}}^{(\mathrm{PRL})}(D) \equiv \frac{F_{\mathrm{B,L}}^{(\mathrm{PRL})}(D) F_{\mathrm{B,H}}^{(\mathrm{PRL})}(D)}{F_{\mathrm{B,L}}^{(\mathrm{PRL})}(D) + F_{\mathrm{B,H}}^{(\mathrm{PRL})}(D)}, \tag{6.22}$$

with,

$$F_{\mathrm{B,L}}^{(\mathrm{PRL})}(D) = \kappa_2 D, \qquad F_{\mathrm{B,H}}^{(\mathrm{PRL})}(D) = p_0, \tag{6.23}$$

where p_0 is the initial concentration of repair pool molecules and κ_2 is from (5.45). The resulting repair function in the PLQ model is:

$$F_{\mathrm{B}}^{(\mathrm{PLQ})}(D) = \frac{\kappa_2 p_0 D}{p_0 + \kappa_2 D}. \tag{6.24}$$

In this expression, component $1/(p_0 + \kappa_2 D)$ represents a hyperbola when graphed versus dose D. It behaves like constant $1/p_0$ at $D \to 0$ and it tends to zero for $D \to \infty$. When such a pure hyperbola is multiplied by $\kappa_2 p_0 D$, as in the rhs of Eq. (6.24), the so-called rectangular hyperbola $\kappa_2 p_0 D/(p_0 + \kappa_2 D)$ is obtained with a diametrically opposite pattern relative to $1/(p_0 + \kappa_2 D)$. Namely, rectangular hyperbola $\kappa_2 p_0 D/(p_0 + \kappa_2 D)$ tends to zero for $D \to 0$ as a linear term $\kappa_2 D$ and it levels off by attaining its plateau value p_0 at $D \to \infty$. This rectangular hyperbola is recognized

as the diagonal Padé approximant (PA) [49] given by the quotient of two first-degree polynomials $\kappa_2 p_0 D$ (numerator) and $p_0 + \kappa_2 D$ (denominator). Here, the denominator $(p_0 + \kappa_2 D)$ has its free constant non-zero term ($p_0 \neq 0$). By contrast, the numerator $(\kappa_2 p_0 D)$ does not have a free non-zero constant term since it begins with a linear dose ($\sim D$). In the general PA, the denominator polynomial is usually represented with a free constant equal to 1. This is achieved in (6.24) by factoring out constant $p_0 \neq 0$ from both the numerator and denominator and canceling it to write:

$$F_{\mathrm{B}}^{(\mathrm{PLQ})}(D) = \frac{p_0 \gamma D}{1 + \gamma D}, \tag{6.25}$$

where,

$$\gamma \equiv \frac{\kappa_2}{p_0}. \tag{6.26}$$

Using relation $\kappa_2 = \lambda k_0$ from (5.45) as well as parameter α from (5.62), we can cast (6.26) into the following form:

$$\gamma = \alpha \rho. \tag{6.27}$$

Expression $\gamma \equiv \kappa_2 / p_0$ from (6.26) represents the defining relation for constant γ, whereas its equivalent counterpart $\gamma = \alpha\rho$ from (6.27) is a derived equation. The important point to retain is that constant κ_2 is related to cell repair and, therefore, so is γ by way of relation $\gamma = \kappa_2 / p_0$ from (6.26).

Repair function (6.24) or (6.25) is of the form of the rectangular hyperbola encountered in the Michaelis–Menten [50] enzyme catalysis. In the present context, enzyme molecules and lesions interact to create an intermediate and unstable chemical compound, which after dissociation produces unaltered free enzymes and repaired lesions [46,47]. Thus, the Michaelis–Menten mechanism could be an alternative interpretation of the PLQ model with the pool of generic repair molecules being specified as enzyme molecules from the environment of radiation-damaged cell. In such a case, radiation-induced damage $k_0 D$ is diminished by a factor $p_0 \gamma D/(1 + \gamma D)$ due to the activated pool of repair enzyme molecules to yield the biological effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}(D) = k_0 D - p_0 \gamma D/(1 + \gamma D)$. Technically, reduction $p_0 \gamma D/(1 + \gamma D)$ is the dose-dependent repair rate or velocity of the type of the initial velocity v_0 from the Michaelis–Menten enzyme catalysis [50–52] and a further elaboration of this aspect of the PLQ model can be found in Refs. [46,47]. Repair velocity v_0 is a differential quantity in the sense of being defined by the first derivative with respect to time of the non-stationary concentration of substrate (lesion) $[S](t) \equiv [S]$ via $v_0 = \mathrm{d}[S]/\mathrm{d}t$. It is for this reason that the PLQ model is alternatively called the differential Michaelis–Menten (DMM) model [47]. Note that there is also the integrated Michaelis–Menten (IMM) model [42] which predicts the biological effect in terms of the Lambert $W_0(X)$ with $X \geq 0$.

Importantly, the Michaelis–Menten enzyme velocity v_0 can also be directly derived as the halved harmonic mean of the velocities for creation and destruction of the

intermediate complex without having to introduce any kinetic rate equation [42]. Rate equations (4.1)–(4.4) of the pool methodology are different from those of the Michaelis–Menten mechanism for enzyme catalysis in the quasi-steady state formalism of Briggs and Haldane [51]. This difference is most notably seen in the fact that unlike Refs. [50,51], the chemical reaction which obeys the system of rate equations (4.1)–(4.4) does not assume creation of an intermediate complex comprised of a pool molecule and a lesion. Yet the same type of the repair velocity is obtained as the corresponding typical expression for v_0 from the Briggs–Haldane [51] derivation of the Michaelis–Menten [50] formula. This occurrence is expected from the fact that we did not derive the PLQ model as e.g. a further approximation of the PRL model. Rather, we simply defined the PLQ model as the halved harmonic mean of the low- and high-dose asymptote of the biological effect from the PRL model. Therefore, it comes as no surprise that the repair function in the PLQ model coincides with the repair velocity v_0 given by the mentioned halved harmonic mean of the Michaelis–Menten enzyme rate [50] in the derivation from Ref. [42].

The corresponding biological effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}(D)$ in the PLQ model follows from (6.21) as:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}(D) = \frac{\alpha D + \beta D^2}{1 + \gamma D}\,, \tag{6.28}$$

with,

$$\alpha = \mu k_0, \qquad \beta = \gamma k_0, \qquad \gamma = \alpha\rho\,, \tag{6.29}$$

where ρ from (4.10) is the repair capacity and μ is in (5.48). Parameters α and γ are the same as in (5.62) and (6.27), respectively, and they are repeated in (6.29) for completeness. The corresponding Poissonian surviving fraction reads as:

$$S_{\mathrm{F}}^{(\mathrm{PLQ})}(D) \equiv \mathrm{e}^{-\mathrm{E}_{\mathrm{B}}^{(\mathrm{PLQ})}(D)} = \mathrm{e}^{-\frac{\alpha D + \beta D^2}{1+\gamma D}}. \tag{6.30}$$

We see that the PLQ model can be introduced either in terms of parameters $\{k_0, p_0, \rho\}$ from the PRL model or via the alternative set $\{\alpha, \beta, \gamma\}$ in (6.29). The defining relation of the extrapolation number n in the PLQ model [46,47] read as:

$$\ln n = \frac{\beta - \alpha\gamma}{\gamma^2}. \tag{6.31}$$

Inserting α, β and γ from (6.29) into (6.31), we can deduce the expression:

$$\ln n = p_0, \tag{6.32}$$

which is in agreement with the related formula (5.18) from the PRL model. The α/β ratio can now be extracted from (6.29) as:

$$\frac{\alpha}{\beta} = \eta D_0 \qquad \text{or} \qquad \frac{\alpha}{\beta} = \frac{k_1}{k_2} D_0\,, \tag{6.33}$$

where $\eta = k_1/k_2 = 1/\rho$ from (4.11) is the repair incapacity and D_0 or D_{37} is the reciprocal of the final slope k_0 of the dose-effect curve. Thus, unlike α'/β' from (6.16), expression (6.33) for the α/β ratio is directly proportional to the quotient of the cell kill to cell repair with the final D_0 dose as the proportionality constant. This is a much more transparent formula than its more involved counterpart from (6.16) in the repair-based LQ model. Further, the β/γ ratio can also be extracted from (6.29) to be:

$$\frac{\beta}{\gamma} = k_0 = \frac{1}{D_0} = s_\mathrm{f}\,, \tag{6.34}$$

where s_f is the final slope of the PRL model from (5.42). Moreover, using (5.48), it follows that all the three parameters α, β and γ of the PLQ model are embedded in the single constant μ :

$$\frac{\alpha\gamma}{\beta} = \mu. \tag{6.35}$$

Further, the initial slope of the PLQ model is calculated from (6.30) with the result α. This yields $\alpha = s_\mathrm{i}$ where s_i is the initial slope (5.36) in the PRL model. By using (6.29), we can cast the biological effect (6.28) into the form:

$$\mathrm{E}_\mathrm{B}^{(\mathrm{PLQ})}(D) = \frac{L(1+\rho L)}{\rho p_0 + (1+\rho L)}, \qquad L = k_0 D. \tag{6.36}$$

If the pool molecules were absent from the onset ($p_0 = 0$), all the potentially lethal lesions would be directly transformed to lethal radiation damage. In such a case $\mathrm{E}_\mathrm{B}^{(\mathrm{PLQ})}(D)$ from (6.36) would be equal to the biological effect $\mathrm{E}_\mathrm{B}^{(\mathrm{ST-SH})}(D)$ in the ST-SH model from (5.4):

$$\left\{\mathrm{E}_\mathrm{B}^{(\mathrm{PLQ})}(D)\right\}_{p_0=0} = \mathrm{E}_\mathrm{B}^{(\mathrm{ST-SH})}(D) = L = k_0 D. \tag{6.37}$$

Overall, the PLQ model solves the high-dose problem of the LQ model. In particular, the PLQ model predicts the correct exponential inactivations at both small and large doses with the asymptotes that coincide with their respective counterparts (5.65) and (5.75) from the PRL model:

$$S_\mathrm{F}^{(\mathrm{PLQ})}(D) \underset{D\to 0}{\approx} \mathrm{e}^{-s_\mathrm{i} D} = \mathrm{e}^{-\alpha D}\,, \tag{6.38}$$

and,

$$S_\mathrm{F}^{(\mathrm{PLQ})}(D) \underset{D\to \infty}{\approx} \mathrm{e}^{-s_\mathrm{f} D} = n\mathrm{e}^{-D/D_0}. \tag{6.39}$$

In between these two asymptotes, at intermediate doses, the PLQ model predicts shoulders in dose-effect curves as a direct consequence of inclusion of repair. Overall, the PRL and PLQ model share the identical extrapolation number, initial slope, final slope as well as the lowest- and highest-dose asymptotes of the cell surviving fractions. Such an outcome is, in fact, automatically prescribed by the construct (6.22). Note that,

in general, the halved harmonic mean, such as the one in the defining effective repair function (6.22) from the PLQ model, is known to be the truest average value (mean) for processes and phenomena whose development is characterized by kinetic rate equations. This fact together with the biological backing of parameters $\{\alpha, \beta, \gamma\}$, or equivalently, $\{k_0, p_0, \rho\}$ explains the systematic success of the PLQ model in detailed comparisons with experimental data [43–48].

6.3 Link to the "Hug–Kellerer–Haynes" saturable repair model

The PRL model can be connected with some other repair-based radiobiological models by further exploiting the known asymptotes of the Lambert function $W_0(x_D)$ from the biological effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ in (5.2). To this end, we first note that the implicit definition of this biological effect is given by the transcendental equation deduced from (5.2) and (4.74):

$$k_0 D = \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) + p_0 \left\{1 - \mathrm{e}^{-\rho \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)}\right\}. \tag{6.40}$$

The second part $p_0\{1 - \mathrm{e}^{-\rho \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)}\}$ of this expression has a form of a saturable repair function where in the exponential $\mathrm{e}^{-\rho \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)}$ one can make a linear approximation αD in $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)$ via $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) \approx \alpha D$ to have:

$$\mathrm{e}^{-\rho \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)} \approx \mathrm{e}^{-\alpha \rho D}. \tag{6.41}$$

With this approximation and by using relation $\gamma = \alpha\rho$ from (6.27), the saturable repair function from (6.40) becomes:

$$p_0 \left\{1 - \mathrm{e}^{-\rho \mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D)}\right\} \approx p_0 \left(1 - \mathrm{e}^{-\gamma D}\right). \tag{6.42}$$

Thus, if approximation (6.41) is used in the rhs of Eq. (6.40), its lhs would acquire the form:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) \approx k_0 D - p_0 \left(1 - \mathrm{e}^{-\gamma D}\right). \tag{6.43}$$

On the other hand, the biological effect $\mathrm{E}_{\mathrm{B}}^{(\mathrm{HKH})}(D)$ in the Hug-Kellerer-Haynes (HKH) model [53–56] is given by:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{HKH})}(D) = k_0 D - \tilde{\alpha} \left(1 - \mathrm{e}^{-\tilde{\beta} D}\right), \tag{6.44}$$

where $\tilde{\alpha} \geq 0$ and $\tilde{\beta} \geq 0$ are freely adjustable constants. Therefore, by reference to (6.43), it follows:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) \approx \mathrm{E}_{\mathrm{B}}^{(\mathrm{HKH})}(D), \tag{6.45}$$

provided that,

$$\tilde{\alpha} = p_0, \qquad \tilde{\beta} = \gamma. \tag{6.46}$$

Formula (6.44) together with the assumption of the Poisson distribution of lesions gives the surviving fraction $S_{\mathrm{F}}^{(\mathrm{HKH})}(D)$ in the pool-repair-based HKH model:

$$S_{\mathrm{F}}^{(\mathrm{HKH})}(D) = \mathrm{e}^{-\mathrm{E}_{\mathrm{B}}^{(\mathrm{HKH})}(\mathrm{D})} = \mathrm{e}^{-k_0 D + p_0\left(1-\mathrm{e}^{-\gamma D}\right)}. \tag{6.47}$$

In the context of population studies of species, including humans, the type of saturation function from (6.47) has first been proposed by Gompertz [57]. Employing the same procedure as in Sect. 5.6, it follows that the low- and high-dose asymptotes of $\mathrm{E}_{\mathrm{B}}^{(\mathrm{HKH})}(D)$ from (6.44) and (6.46) coincide with the corresponding asymptotic behaviors of the biological effect from the PRL and PLQ models:

$$S_{\mathrm{F}}^{(\mathrm{HKH})}(D) \underset{D\to 0}{\approx} \mathrm{e}^{-\alpha D}, \tag{6.48}$$

where α stems from $k_0 - \tilde{\alpha}\tilde{\beta} = k_0 - p_0\gamma = k_0 - p_0\alpha\rho = k_0 - p_0\mu k_0\rho = k_0(1 - \mu\rho p_0) = k_0\mu = \alpha$,

$$S_{\mathrm{F}}^{(\mathrm{HKH})}(D) \underset{D\to\infty}{\approx} n\mathrm{e}^{-D/D_0}, \; n = \mathrm{e}^{p_0}. \tag{6.49}$$

An alternative approximation of the same equation (6.40) can be generated by substituting the high-dose asymptote $\mathrm{E}_{\mathrm{B,H}}^{(\mathrm{PRL})}$ from (5.73) into the exponential with the result:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}(D) \approx k_0 D - p_0\left\{1 - \mathrm{e}^{\rho(p_0 - k_0 D)}\right\}. \tag{6.50}$$

If the dose-effect curve reached its terminal part, only the cell kill mechanism ($k_0 D$) would be active. In such a case, term $p_0\{1 - \mathrm{e}^{\rho(p_0 - k_0 D)}\}$ from (6.50) will be nearly zero,

$$p_0\left\{1 - \mathrm{e}^{\rho(p_0 - k_0 D)}\right\} \approx 0 \quad (\text{At the terminal part of dose} - \text{effect curve}). \tag{6.51}$$

The solution of this equation is given by:

$$D \approx \frac{p_0}{k_0} = D_{\mathrm{q}}, \tag{6.52}$$

where, by way of (5.77), quotient p_0/k_0 is identified as the quasi-threshold dose D_{q}.

Both approximations (6.43) and (6.50) use only the iterates of the transcendental equation (6.40) without any reference the exact explicit solution for $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}$ from (5.2) in terms of the Lambert function $W_0(x_D)$. Moreover, in estimates (6.43) and (6.50), the dose-dependent part of the initialization of iterations is the high-dose inactivation

$(k_0 D)$. Therefore, we could also carry out an alternative analysis by starting from the exact expression for $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}$ in (5.2) and therein develop $W_0(x_D)$ in the Maclaurin series around $D = \infty$ which corresponds to $x_D = 0$. Thus, according to (4.36), we have:

$$W_0(x_D) = \sum_{m=1}^{\infty} \frac{(-m)^{m-1}}{m!} x_0^m \mathrm{e}^{m\rho(p_0 - k_0 D)}, \tag{6.53}$$

where $x_0 = \rho p_0$, as per (4.69). The convergence circle of this series is given by $x_D = \rho p_0 \mathrm{e}^{\rho(p_0 - k_0 D)} \leq 1/\mathrm{e}$, which can be expressed in terms of dose as:

$$D \geq D_{\mathrm{T}}, \qquad D_{\mathrm{T}} = \frac{1 + \rho p_0 + \ln(\rho p_0)}{\rho k_0}. \tag{6.54}$$

At large doses, by keeping only the first term z for $z = x_D$ in series (6.53), it follows:

$$\frac{W_0(x_D)}{\rho} \underset{D \to \infty}{\approx} p_0 \mathrm{e}^{\rho(p_0 - k_0 D)}, \tag{6.55}$$

which upon insertion in the exact formula (5.73) for $\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})}$ gives the approximation:

$$\mathrm{E}_{\mathrm{B}}^{(\mathrm{PRL})} \underset{D \to \infty}{\approx} k_0 D - p_0 \left\{ 1 - \mathrm{e}^{\rho(p_0 - k_0 D)} \right\}, \tag{6.56}$$

in agreement with (6.50). Overall, this simplified consideration with account of high-dose asymptotes alone suffices to see that the PRL model adequately describes the biological course of the radiation event in the mechanism-switching region characterized by the condition $D \approx D_{\mathrm{T}}$. When dose D becomes equal to transition dose D_{T}, repair becomes ineffective and the surviving fraction is dominated by the linear response $k_0 D$, which signifies the onset of the terminal, exponential portion of the dose-effect curve. The transition dose D_{T} is the signature of a switch of the kinetics from the second-order (cell repair) to the first-order (cell kill) for description of interaction between pool molecules and lesions through the underlying chemical reaction. Such a switch corresponds to the passage from the shouldered part to the straight-line portion of the dose-effect curve in the semilogarithmic plot of cell surviving fraction $S_{\mathrm{F}}^{(\mathrm{PRL})}(D)$ as a function of dose D.

This examination shows that the transition dose D_{T} is born out naturally in the PRL model with the numerical value determined automatically by the already reconstructed parameters p_0, k_0 and ρ as per (6.54). In contrast to this, in the linear-quadratic-linear (LQL) [58–60] and the universal survival curve (USC) [61] models, D_{T} is introduced *ad hoc* as an independent fitting parameter to remove the Gaussian tail by hand from the LQ model at $D > D_{\mathrm{T}}$ in an attempt to force the exponential inactivation at high doses [43,44,46–48,62–71].

Although the transition dose is not explicitly needed in the PRL model, D_{T} can be reconstructed using three biological parameters p_0, k_0 and ρ. No condition is imposed within the PRL model to split apart the shouldered from the straight-line parts of the dose-effect curve. Instead, the properly-formulated kinetic rate equations in the

PRL model yield the unique solution whose power series expansion at large doses automatically gives the transition dose D_T as the convergence radius of this Maclaurin expansion.

7 Results and discussion

7.1 Measurable parameters of the "Pool Repair Lambert" model

In the PRL model, there is an explicit connection of parameters $\{\rho, p_0, D_0\}$ with the dynamics of evolution of lesion concentrations. For example, ρ is a quotient of the rate constants for cell repair (k_2) and cell kill (k_1) from (4.10), or equivalently, a ratio of experimentally measurable fractions of repaired (g_r) lesions and unrepaired i.e. lethal lesions (f_u) from (4.12). Biologically, constant ρ is the repair capacity of the pool of intracellular molecules. The other two quantities D_0 and p_0 from the triple $\{\rho, p_0, D_0\}$ in the PRL model can be graphically read off by way of the tangent to the terminal (exponential) part of the experimentally measured dose-effect curve $S_F^{(exp)}(D)$ versus D. Therein, the reciprocal $1/D_0$ of the "final D_0 dose" is the final slope k_0 of the said tangent and $n = e^{p_0}$ is the extrapolation number as the intercept of the same tangent with the ordinate $S_F^{(exp)}(D)$ at dose $D = 0$ of the abscissa.

Thus, even by a trivial (and, in fact, by hand) extraction of k_0 and n without any fitting, one could reconstruct the two important parameters of primary biological and clinical meaning and interpretation i.e. the final D_0 dose and the initial concentration p_0 of pool molecules available for repair. The substitution of such retrieved quantities $\{p_0, k_0\}$ into expression (5.6) for $S_F^{(PRL)}(D)$ would leave us with a single unknown parameter ρ in the PRL model. Finally, this latter constant could be either deduced via relation $\rho = g_r/f_u$ by using the measured fractions of the lethal and repaired lesions f_u and g_r or reconstructed from $S_F^{(exp)}(D)$ by minimization of the squared difference $\{S_F^{(PRL)}(D) - S_F^{(exp)}(D)\}^2$.

7.2 Comparisons of radiobiological models with measurements

Comparisons between the PRL and LQ models are presently performed relative to the experimental data for cell response to irradiation. Thus, Fig. 1 displays the dose-effect curves or cell surviving fractions, S_F, computed in these two models and measured experimentally. Figure 2 shows the full effect plot or the Fe plot, which is also called the reactivity or relative radiosensitivity plot and is given by the product of the reciprocal dose and the negative logarithmic surviving fraction, $-(1/D) \ln S_F$.

These figures show that the PRL model is in excellent agreement with the measurements throughout the considered dose range from low through intermediate to high radiation exposures. By contrast, it is clear from Figs. 1 and 2 that the LQ model is of limited usefulness, as it breaks down at high doses. As mentioned, in an Fe-plot, any departure of experimental data from a straight line indicates a failure of the LQ model. This is evident from Fig. 2 where the LQ model predicts the straight line $\alpha_u + \beta_r D$ which is not confirmed by the corresponding measurement. Here, the experimental

data are well described by the curved line of the PRL model. The numerical difference between the PRL and LQ model is substantial.

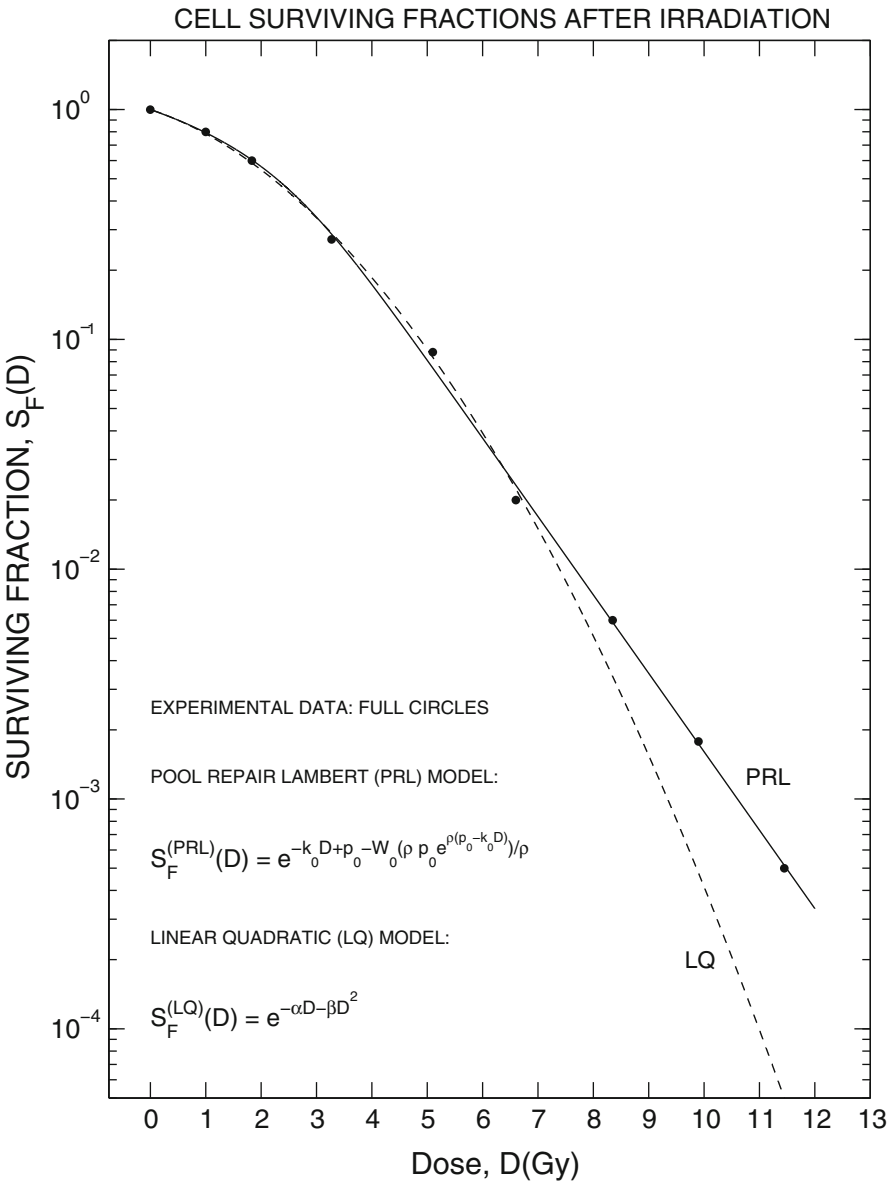

Fig. 1 Cell surviving fractions $S_F(D)$ as a function of radiation dose D in Gy. Experimental data (*symbols*) [17,72]: the mean clonogenic surviving fractions $S_F(D)$ for Chinese hamster V79 cells irradiated by 50 kVp X-rays. Theories: *full line*: PRL (pool repair Lambert) model and *dashed line*: LQ (linear quadratic) model

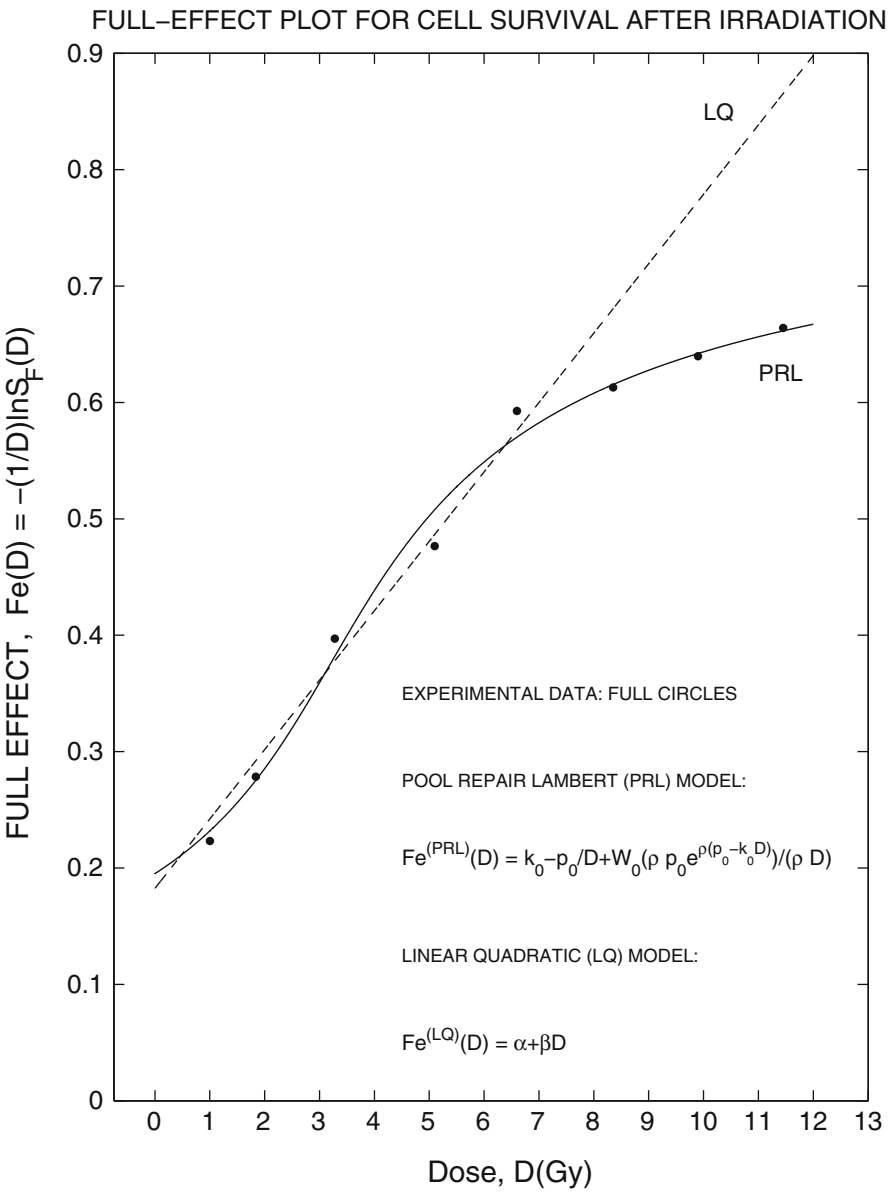

Fig. 2 The full-effect (Fe) plot from the cell surviving fractions as given by the product of the reciprocal dose $1/D$ and the negative natural logarithm of $S_{\mathrm{F}}(D)$ on the ordinate versus D as the abscissa: $\mathrm{Fe}(D) \equiv -(1/D)\ln(S_{\mathrm{F}}) = R(D)$. Experimental data (*symbols*) [17,72]: the corresponding values for Chinese hamster V79 cells irradiated by 50 kVp X-rays. Theories: *solid curve*: PRL model and *dashed curve*: LQ model

The straight line $\alpha_{\mathrm{u}} + \beta_{\mathrm{r}} D$ of the LQ model from Fig. 2 shows that the underlying observable, which is relative radiosensitivity, rises indefinitely with no limit as the administered dose D is increased. This is an utterly unphysical description which is

at variance with measurements that, however, exhibit a saturation effect at sufficiently high doses. As such, a realistic Fe-plot from an experiment usually has the form of a rectangular hyperbola, as also predicted by the PRL model in Fig. 2, rather than the straight line of the LQ model. The rectangular hyperbola from the PRL model implies that repair of radiation damage to the cell through pool molecules is equivalent to the Michaelis–Menten [50] chemical reaction of enzyme-lesion catalysis.

8 Conclusions

Notwithstanding the great importance of advances by physics and technology in radiotherapy, significant improvements must also rely upon the relevant aspects of biological effects of interactions between living cells and radiation. For example, within fractionated radiotherapy, which is overwhelmingly used in clinical practice, the most prominent biological aspect in the response of the cell to irradiation is repair of potentially lethal damage. The existence of repair or recovery mechanisms is evidenced by the appearance of a shoulder in a typical dose-effect curve and by the reduced radiation effectiveness with reduced dose rates. The present study has the primary focus on elucidating a special repair mechanism from the standpoint of chemical kinetics and the underling time evolution of radiation lesions. Within this topic, one of our major goals is to use the concept of cell repair to systematically develop the theoretically well-founded formalisms capable of providing quantitative explanation and interpretation of cell surviving curves and relative radiosensitivities that are among the principal signatures of dose-effect relations. The presently expounded novel strategy and the obtained results can further be exploited in radiotherapy e.g. for finding the optimal doses to be given to patients during various fractionation regimens with a particular advantage for high-dose per fraction schedules consisting of only fewer deliveries, as in stereotactic radiotherapy.

With these goals, the mechanistic “Pool Repair Lambert” model, or PRL, is introduced in this work to describe survival of irradiated cells. It is derived from the second-order chemical kinetics for a quantitative description of interaction between radiation and lesions. Here, the term “second-order” implies that the product of two concentrations is present in the rate equations. Because of the appearance of such products, the ensuing evolution of concentrations of lesions (radiation-damaged DNA substrates) and repair pool molecules is nonlinear. We use the mass action law to set up the corresponding systems of coupled nonlinear differential rate equations. The direct cell kill mechanism by single radiation events is automatically included. We proceed in two parallel steps: (1) by implementing the concept of a pool of intracellular molecules for repair of potentially lethal lesions and (2) by simultaneously accounting for a competitive mechanism, which is transformation of potentially lethal radiation damage to lethal lesions.

The PRL model expresses the cell surviving fractions in a compact analytical form by means of the readily calculable transcendental Lambert W_0 function whose independent variable contains the physically absorbed dose D. The applicability domain of the PRL model extends over the entire dose range, from low through intermediate to high dose exposures. The ensuing cell surviving fractions in this model exhibit the exponential cell kill modes at both low and high doses with a repair-based shoulder

located in-between the latter two extreme intervals. Such characteristic patterns in these three dose-subregions are smoothly ingrained in the Lambert W_0 function and they are made apparent in the course of deriving the constant non-zero initial and final slopes of the dose-effect curves. The universal validity of the PRL model across the entire dose spectrum is rooted in the dynamics of the starting rate equations and their explicit solutions via the Lambert W_0 function. Moreover, at very small doses, the PRL model predicts the exponential cell kill mechanism.

At very high doses, the PRL model formally possess the asymptotic behavior of the multi-target and single-hit model, or MT-SH, by predicting the surviving fraction ne^{-D/D_0} as $D \to \infty$, where n is the extrapolation number and D_0 is the inverse of the final slope k_0. This similarity of the two models at asymptotically large doses D should not be taken too literally as the equivalence of these formalisms. Rather it should be viewed merely as a descriptive resemblance of the two very different approaches with unequal biological meaning of the parameters. Thus, the terminal, exponential parts of the dose-effect curve in both the PRL and MT-SH models are characterized by the final D_0 dose as the dose increment for which survival decreases by 37 %. However, the customary biological interpretation of D_0, as the mean lethal dose, is pertinent to the hit-target description, but not to the PRL model. This difference comes from the fact that radiation lesions proportional to dose D are repairable and irrepairable (lethal) in the PRL and hit-target model, respectively. Moreover, in the PRL model, the extrapolation number is related to the size of the pool of repair molecules prior to irradiation ($\ln n = p_0$). On the other hand, in the MT-SH model, the extrapolation number n is interpreted as the number of sensitive sites (targets) in the cell that all need to be inactivated to cause cell death. Very large extrapolation numbers (occasionally of the order of 1000 or larger) have been reported in the literature with cells grown in culture [73]. However, it is unlikely that thousands of sites need to be hit to inactivate a cell [74]. As such, the original meaning of the extrapolation number conceived as the number of targets is widely considered as unrealistic.

All these circumstances point to the essential advantage of expressing the solutions of the invoked rate equations by analytical functions of the known asymptotic behaviors. Such is the Lambert function W_0, which secures the experimentally observed shoulders in dose-effect curves, as well as the modality of exponential cell inactivations in the limit of very small and very large doses. This bypasses altogether the long-practiced empirical and phenomenological patching of the low-dose LQ model to the high-dose exponential tail of cell surviving fractions in the LQL and USC models [58–61]. Comparisons of the PRL model with experimentally measured cell surviving fractions show excellent agreement at all the investigated doses. In particular, strikingly improved is the PRL-based full-effect or the Fe plot, which shows a typical concave curvature, as also confirmed by measurements, in contrast to straight lines given by the LQ model.

The most significant practical usefulness of the PRL model is in the potential of providing the radiation oncologist with a realistic strategy for designing more effective fractionation schedules, especially in dose planning systems for fast and worldwide expanding hypofractionated radiotherapy, which is also known as stereotactic radiosurgery [75–77], where the LQ model fails to conform with measurements of cell responses to high-dose irradiations.

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References

1. K.H. Chadwick, H.P. Leenhouts, A molecular theory of cell survival. Phys. Med. Biol. **18**, 78–87 (1973)
2. A.M. Kellerer, H.H. Rossi, The theory of dual action. Curr. Top. Radiat. Res. **8**, 85–158 (1974)
3. A.M. Kellerer, H.H. Rossi, A generalized formulation of dual radiation action. Radiat. Res. **75**, 471–488 (1978)
4. J.F. Fowler, Practical time-dose evaluation or how to stop worrying and learn to love linear quadratics, in *Technical Basis of Radiation Therapy: Medical Radiology, Radiation Oncology*, 5th edn., ed. by S.H. Levitt, J.A. Purdy, C.A. Perez, P. Poortmans (Springer, Berlin, 2012), pp. 3–50
5. P.M. Correy, A. Cole, Double strand rejoining in mammalian DNA. Nat. New Biol. **245**, 100–101 (1973)
6. M. Frankenberg-Schwager, D. Frankenberg, R. Harbich, Repair of DNA double-strand breaks as a determinant of RBE of alpha particles. Br. J. Cancer **49**(Suppl. VI), 169–173 (1984)
7. N. Cheong, R. Okayasu, S. Shjah, T. Ganguly, P. Mamman, G. Iliakis, In vitro rejoining of double-strand breaks in cellular DNA by factors present in extract of HeLa cells. Int. J. Radiat. Biol. **69**, 665–677 (1996)
8. A. Asaithamby, N. Ueamatsu, A. Chaterjee, M.D. Story, S. Burma, D.J. Chen, Repair of HZE-particle-induced DNA double strand breaks in normal human fibroblasts. Radiat. Res. **169**, 437–446 (2008)
9. J.N. Kavanagh, K.M. Redmond, G. Schettino, K.M. Prise, DSB repair: a radiation perspective. Antioxid. Redox Signal. **18**, 2458–2472 (2013)
10. E.L. Powers, Consideration of survival curves and target theory. Phys. Med. Biol. **7**, 3–28 (1962)
11. J.S. Orr, C.S. Hope, S.E. Wakerley, A metabolic theory of cell survival curves. Phys. Med. Biol. **11**, 103–108 (1966)
12. J. Laurie, J.S. Orr, C.J. Foster, Repair processes and cell survival. Br. J. Radiol. **45**, 362–368 (1972)
13. J.F. Malone, *The Kinetics of Recovery of Cellular Proliferation After Irradiation*. PhD Thesis (unpublished), The National University of Ireland, Dublin (1972)
14. J.S. Orr, J. Laurie, J. Kirk, J.F. Malone, The "pool" and the initial slope of survival curves for high- and low-LET radiation, in *Cellular Survival after Low Doses of Irradiation* (The 6th L.H. Gray Conference, Bedford College, London, 16–21 September 1974), ed. by T. Alper (Wiley, The Institute of Physics Publishing, Bristol, 1975), pp. 86–87
15. J.F. Malone, I.A. Kinsella, J.H. Hendry, Prediction of the initial shape of survival curves when direct measurement is not possible, in *Cellular Survival After Low Doses of Irradiation* (The 6th L.H. Gray Conference, Bedford College, London, 16–21 September 1974), ed. by T. Alper (Wiley, The Institute of Physics Publishing, Bristol, 1975), pp. 313–318
16. B. Jacobson, Evidence of recovery from X-ray damage in Chlamydominas. Radiat. Res. **1**, 394–406 (1957)
17. M.M. Elkind, H. Sutton, Radiation response to mammalian cell growth in culture: I. Repair of X-ray damage in surviving Chinese Hamster cells. Radiat. Res. **13**, 556–593 (1960)
18. J. Calkins, An unusual form of response in X-irradiated protozoa and a hypothesis as to its origin. Int. J. Radiat. Biol. **12**, 297–301 (1967)
19. J. Calkins, Similarities in the radiation response of Escherichia coli and Tetrahymena pyriformis. Int. J. Radiat. Biol. **13**, 283–288 (1967)
20. J. Calkins, W. Todd, Evidence for a triggered or activated repair system in Saccharomyces cerevisiae. Int. J. Radiat. Biol. **14**, 487–491 (1968)
21. J. Calkins, The variation of radiation sensitivity of bacteria fed Tetrahymena pyriformis during the growth cycle and factors related to its origin. Photochem. Photobiol. **8**, 115–129 (1968)
22. J. Calkins, G. Griggs, Photoreactivation of UV reactivation in protozoa. Photochem. Photobiol. **10**, 445–449 (1969)
23. K.G. Zimmer, *Studies on Quantitative Radiation Biology* (Oliver and Boyd, London, 1961)
24. K.G. Zimmer, From target theory to molecular radiobiology. Phys. Med. Biol. **14**, 545–553 (1969)
25. D.E. Lea, A theory of action of radiations on biological materials: I. The time-intensity factor. Br. J. Radiol. **11**, 489–497 (1938)

26. D.E. Lea, A theory of action of radiations on biological materials: II. Delay in cellular division. Br. J. Radiol. **11**, 554–562 (1938)
27. D.E. Lea, D.G. Catcheside, The mechanism of induction by radiation by chromosome aberrations in transcedentia. J. Genet. **44**, 216–245 (1942)
28. D.E. Lea, *Actions of Radiations on Living Cells* (Cambridge University Press, London, 1947)
29. H.D. Thames, K.K. Ang, F.A. Stewart, E. van der Schueren, Does incomplete repair explain the apparent failure of the basic LQ model to predict spinal cord and kidney responses to low doses per fraction? Int. J. Radiat. Biol. **54**, 13–19 (1988)
30. D.J. Brenner, L.R. Hlatky, P.J. Hahnfeldt, Y. Huang, R.K. Sachs, The linear-quadratic model and most other common radiobiological models result in similar predictions of time-dose relationships. Rad. Res. **150**, 83–91 (1998)
31. R. Dale, Use of the linear-quadratic radiobiological model for quantifying kidney response in targeted radiotherapy. Cancer Biother. Radiopharmac. **19**, 363–370 (2004)
32. J.H. Lambert, Observationes variae in mathesin puram. Acta Helvetica, physico-mathematico-anatomico-botanico-medica. Basel **3**, 126–168 (1758)
33. R.M. Corless, G.H. Gonnet, D.E.G. Hare, D.J. Jeffrey, D.E. Knuth, On the Lambert *W* function. Adv. Comput. Math. **5**, 329–359 (1996)
34. B.G. Douglas, J.F. Fowler, J. Denekamp, S.R. Harris, S.E. Ayers, S. Fairman, S.A. Hill, P.W. Sheldon, F.A. Stewart, The effect of multiple small fractions of x-rays on skin reactions in the mouse, in *Cellular Survival After Low Doses of Irradiation* (The 6th L.H. Gray Conference, Bedford College, London, 16–21 September 1974), ed. by T. Alper (Wiley, The Institute of Physics Publishing, Bristol, 1975), pp. 351–361
35. B.G. Douglas, J.F. Fowler, The effect of multiple small doses of X rays on skin reactions in the mouse and basic interpretation. Radiat. Res. **66**, 401–426 (1976)
36. F.N. Fritsch, R.E. Shafer, W.P. Crowley, Solution of transcendental equation $we^w = x$, Algorithm 443: function $WEW(x)$. Commun. Assoc. Comp. Machin. **16**, 123–124 (1973)
37. D.A. Barry, P.J. Culligan-Hensley, S.J. Barry, Real values of the W-function. Assoc. Comp. Machin. Trans. Math. Softw. **21**, 161–171 (1995)
38. D.A. Barry, S.J. Barry, P.J. Culligan-Hensley, Algorithm 743: WAPR: a FORTRAN routine for calculating real values of the W-function. Assoc. Comp. Machin. Trans. Math. Softw. **21**, 172–181 (1995); [Web reference for free downloading both fortran (wapr.f) and matlab (wapr.m) programs: http://www.netlib.org/toms/743]
39. D. Veberič, Having Fun with Lambert $W(x)$ Function, arXiv:1003.1628v1 [cs.MS], 15 pp, Last updated: 8 March 2010
40. S. Winitzki, Uniform approximations for transcendental functions, in *Lecture Notes in Computer Science*, Nr. 2667, ed. by V. Kumar, M.L. Gavrilova, C.J.K. Tan, P. L'Ecuyer (Springer, Berlin, 2003), pp. 780–789
41. Dž. Belkić, Theory and practice with the transcendental Lambert *W* function in interdisciplinary research: introduction of a highly accurate single analytical formula. J. Math. Chem. (submitted) (2014)
42. Dž. Belkić, Repair of irradiated cells by Michaelis–Menten enzyme catalysis: the Lambert Function for integrated rate equations in description of surviving fractions. J. Math. Chem. (2013). doi:10.1007/s10910-014-0308-2
43. Dž Belkić, Parametric analysis of time signals and spectra from perspective of quantum physics and chemistry. Adv. Quantum Chem. **6**, 145–260 (2011)
44. Dž. Belkić, K. Belkić, Padé–Froissart exact signal-noise separation in nuclear magnetic resonance spectroscopy. J. Phys. B: At. Mol. Opt. Phys. **44**, 125003.1–125003.18 (2011)
45. Dž Belkić, K. Belkić, High-resolution signal processing in magnetic resonance spectroscopy for early cancer diagnostics. Adv. Quantum Chem. **62**, 243–347 (2011)
46. Dž Belkić, K. Belkić, Mechanistic repair-based Padé linear-quadratic model for cell response to radiation damage. Adv. Quantum Chem. **65**, 407–449 (2013)
47. Dž Belkić, K. Belkić, Mechanistic description of survival of irradiated cells: repair kinetics in Padé linear-quadratic or differential Michaelis–Menten model. J. Math. Chem. **51**, 2572–2607 (2013)
48. B. Andisheh, M. Edgren, Dž Belkić, P. Mavroidis, A. Brahme, B.K. Lind, A comparative analysis of radiobiological models for cell surviving fractions at high doses. Techn. Cancer Res. Treatm. **12**, 183–192 (2013)

49. Dž Belkić, *Quantum-Mechanical Signal Processing and Spectral Analysis* (Taylor & Francis, London, 2005)
50. L. Michaelis, M.L. Menten, Die kinetik der invertinwirkung. Biochem. Z. **49**, 333–369 (1913); [English translation by R.S. Goody and K.A. Johnson, The kinetics of invertase action. Biochem. **50**, 8264–8269 (2011); Supporting Information: The full text (34 pp) of the German to English translation of the original paper by Michaelis and Menten (1913, op. cit.) available at: http://pubs.acs.org]
51. G.E. Briggs, J.B.S. Haldane, A note on the kinetics of enzyme action. Biochem. J. **19**, 338–339 (1925)
52. D.D. van Slyke, G.E. Cullen, The mode of action of urease and of enzymes in general. J. Biol. Chem. **19**, 141–180 (1914)
53. O. Hug, A.M. Kellerer, Zur interpretation der dosiswirkungsbeziehungen in der strahlenbiologien. Biophysik **1**, 20–32 (1963)
54. A.M. Kellerer, O. Hug, Theory of dose-effect relations. Encycloped. Med. Radiol. **3**, 1–42 (1972)
55. R.H. Haynes, The interpretation of microbial inactivation and recovery phenomena. Radiat. Res. Suppl. **6**, 1–29 (1969)
56. K.E. Ekstrand, The Hug–Kellerer equation as the universal cell surviving curve. Phys. Med. Biol. **55**, N267–N273 (2010)
57. B. Gompertz, On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. Phil. Trans. B **1**, 513–583 (1825)
58. M. Scholz, G. Kraft, A parameter-free track structure model for heavy action cross section, in *Biophysical Modelling of Radiation Effects*, ed. by K.H. Chadwick, G. Moschini, M.N. Varma (Adam Hilger, Bristol, 1992), pp. 185–192
59. H. Paganetti, M. Goitein, Biophysical modelling of proton radiation effects based on amorphous track models. Int. J. Radiat. Biol. **77**, 911–928 (2001)
60. M. Astrahan, Some implications of linear-quadratic-linear radiation dose-response with regard to hypofractionation. Med. Phys. **35**, 4161–4172 (2008)
61. C. Park, L. Papiez, S. Zhang, M. Story, R.D. Timmerman, Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. **70**, 847–852 (2008)
62. M. Guerrero, X.A. Li, Extending the linear-quadratic model for large fraction doses pertinent to stereotactic radiotherapy. Phys. Med. Biol. **49**, 4825–4835 (2004)
63. L. Garcia, D. Wilkins, G. Raaphorst, α/β ratio, a dose range dependence. Int. J. Radiat. Oncol. Biol. Phys. **67**, 587–593 (2007)
64. C. Zhang, N.A. Mayr, S.S. Lo, L. Lu, K. Li, J.Z. Wang, The α/β ratio: dose-range dependent or model limitation? Int. J. Radiat. Oncol. Biol. Phys. **75**, S610–S611 (2007)
65. J.P. Kirkpatrick, J.J. Meyer, L.B. Marks, The linear-quadratic model is inappropriate to model high-dose per fraction effects in radiosurgery. Semin. Radiat. Oncol. **18**, 240–243 (2008)
66. J.P. Kirkpatrick, D.J. Brenner, C.G. Orton, The linear-quadratic model is inappropriate to model high-dose per fraction effects in radiosurgery. Semin. Radiat. Oncol. **18**, 3381–3384 (2009)
67. M.C. Joiner, S.M. Bentzen, Fractionation: the linear-quadratic approach, in *Basic Clinical Radiobiology*, 4th edn., ed. by M. Joiner, A. van der Kogel (Hodder Arnold, London, 2009), pp. 102–119
68. S.M. Bentzen, M.C. Joiner, The linear-quadratic approach in clinical practice, in *Basic Clinical Radiobiology*, 4th edn., ed. by M. Joiner, A. van der Kogel (Hodder Arnold, London, 2009), pp. 120–134
69. L.G. Hanin, M. Zaider, Cell-survival probability at large doses: an alternative to the linear-quadratic model. Phys. Med. Biol. **55**, 4687–4702 (2010)
70. J.Z. Wang, N.A. Mayr, W.T.C. Yuh, A generalized linear-quadratic formula for high-dose rate brachytherapy, and radiosurgery. Int. J. Radiat. Oncol. Biol. Phys. **69**, S619–S620 (2007)
71. J.Z. Wang, Z. Huang, S.S. Lo, W.T.C. Yuh, N.A. Mayr, A generalized linear-quadratic model for radiosurgery, stereotactic body radiation therapy and high-dose rate brachytherapy. Sci. Trans. Med. **2**(39), 39ra48 (2010)
72. M.M. Elkind, H. Sutton, X-ray damage and recovery in mammalian cells in culture. Nature, **184**, 1293–1295 (1959)
73. P.E. Bryant, LET as a determinant of oxygen enhancement ratio and slope of survival curve of Chlamydomonas. Int. J. Radiat. Biol. **23**, 217–226 (1973)
74. E.W. Emery, The associated inactivation model, in *Celullar Survival after Low Doses of Irradiation* (The 6th L.H. Gray Conference, Bedford College, London, 16–21 September 1974), ed. by T. Alper (Wiley, The Institute of Physics Publishing, Bristol, 1975), pp. 64–68

75. L. Leksell, The stereotactic method and radiosurgery of the brain. Acta Chirurg. Scand. **102**, 316–319 (1951)
76. I. Lax, H. Blomgren, I. Näslund, R. Svanström, Stereotactic radiotherapy of extracranial targets. Z. Med. Phys. **4**, 112–113 (1994)
77. R. Timmerman, An overview of hypofractionation. Semin. Rad. Oncol. **18**, 215–222 (2008)