Received:
14 January 2018

Revised:
12 February 2018

Accepted:
14 February 2018

<https://doi.org/10.1259/bjr.20180070>

Cite this article as:

Dale RG. Radiation repair models for clinical application. *Br J Radiol* 2019; **92**: 20180070.

PUSHING THE FRONTIERS OF RADIOBIOLOGY: A SPECIAL FEATURE IN MEMORY OF SIR OLIVER SCOTT AND PROFESSOR JACK FOWLER: REVIEW ARTICLE

Radiation repair models for clinical application

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ABSTRACT

A number of newly emerging clinical techniques involve non-conventional patterns of radiation delivery which require an appreciation of the role played by radiation repair phenomena. This review outlines the main models of radiation repair, focussing on those which are of greatest clinical usefulness and which may be incorporated into biologically effective dose assessments. The need to account for the apparent “slowing-down” of repair rates observed in some normal tissues is also examined, along with a comparison of the relative merits of the formulations which can be used to account for such phenomena. Jack Fowler brought valuable insight to the understanding of radiation repair processes and this article includes reference to his important contributions in this area.

INTRODUCTION

Effective modelling of radiation repair mechanisms is relevant to several aspects of fractionated radiotherapy and in the assessment of low dose-rate (LDR) brachytherapy, pulsed brachytherapy, biologically targeted radiotherapy and permanent seed implants. In this review there is particular emphasis on how repair effects may be incorporated within the concept of biologically effective dose (BED), a measure which allows relatively straightforward inter-comparison between different forms of radiation therapy.^{1,2} The discussion thus focuses more on “high level” modelling descriptions of repair, *i.e.* those capable of direct application to clinical problem solving, rather than on detailed consideration of the underlying mechanisms which might be involved.

The author’s interest in this area was a consequence of his early-career experience working under the guidance of Bill Liversage. In the mid-1960s high dose-rate (HDR) after-loaders were being introduced to replace existing LDR brachytherapy treatments and Liversage was engrossed with the problem of how to match the known biological effects of LDR with those of the emerging HDR treatments. A ground-breaking publication was the result,¹ in which Liversage derived the conditions for radiobiological equivalence between LDR and HDR schedules. It was that paper which stimulated the author’s own interest in radiobiological modelling, in turn leading to a number of fulfilling interactions with Jack Fowler.

LETHAL AND SUBLETHAL DAMAGE

Radiotherapy can be envisioned as creating both lethal and sublethal damage (SLD), both damage types resulting from a complex chain of events initiated by radiation interactions at the DNA level. Lethally damaged cells eventually die from their injury, but SLD leaves cells in an intermediate state from which full repair (or recovery) is potentially possible. However, if, prior to its complete repair, sublethal injury is compounded by further radiation damage then the cell may be converted from a sublethal to lethal state. For modelling purposes it is thus useful to consider two types of lethal damage²: Type A (proportional to dose and resulting from directly lethal ionising events) or Type B damage (proportional to dose² and resulting from complementary interactions between the SLD created by smaller ionising events). Type A and Type B damages are both ultimately lethal, but the processes which give rise to them are different.

BIOLOGICALLY EFFECTIVE DOSE AND RELATIVE EFFECTIVENESS (RE)

In terms of the linear-quadratic model, the BED for a conventional fractionated treatment (ignoring any repopulation effects) is:^{3–5}

$$BED = D \left[1 + \frac{D}{N(\alpha/\beta)} \right] \quad (1)$$

where D is the total dose, N is the number of fractions and α/β is the fractionation sensitivity of the tissue in question.

In the case of a single fraction, $N = 1$ and Equation (1) becomes:

$$BED = D \left[1 + \frac{D}{(\alpha/\beta)} \right] \quad (2)$$

The square bracketed components within BED equations are termed the Relative Effectiveness RE factors, the mathematical form of which depends on the type of treatment under consideration. In all cases, BED is given as the product:

$$BED = \text{Total Physical Dose} \times \text{RE}.$$

The RE expression in Equation (1) inherently assumes that the fraction delivery times are near-instantaneous (no more than a few minutes in duration) and that the inter-fraction spacings are long (several hours). As such there is no requirement for the RE factor to take account of incomplete-repair effects. For other types of irradiation (involving protracted dose delivery) the Type B damage is no longer proportional to the square of the dose—its magnitude will be reduced by an amount which depends on the repair kinetics of SLD and the precise pattern of radiation delivery. Conversely, in the case of closely spaced fractions Type B damage is increased on account of the compounding effect of successive fractions on any residual SLD. In all such cases the form of the RE factor is changed.

MONO-EXPONENTIAL REPAIR

To account for repair phenomena, the simplest modelling assumption is that the SLD following an acute exposure repairs exponentially with time, *i.e.* that the fraction (θ_t) of SLD remaining at time t after its creation is:

$$\theta_t = e^{-\mu t} \quad (3)$$

where μ is the exponential repair constant. Exponential repair can be considered as being first-order, meaning that, irrespective of the number of un-repaired lesions, the proportion of them that will repair in any given time interval is constant.

MULTIEXPONENTIAL REPAIR

It has been noted in several studies (*e.g.* Ang et al⁶ and others) that mono-exponential repair models do not provide a satisfactory explanation of all available data because the repair rate appears to reduce as time progresses. This difficulty is most easily circumvented by postulating the existence of two or more exponential repair components, each with a different repair rate. Two parameters are required to quantify each component: a repair rate and its relative preponderance. Thus, for an n -component model, $(2n-1)$ factors are required to fit the model to experimental data. In principle most data can be fit simply by the expedient of assuming as many exponential components as necessary, but empirically increasing the number of parameters lessens the credibility of the model.

For an n -component mono-exponential model, Equation (3) is modified to:

$$\theta_t = \sum_{i=1}^n f_i e^{-\mu_i t} \quad (4)$$

where μ_i and f_i are respectively the repair constants and their fractional proportion, with:

$$\sum_{i=1}^n f_i = 1$$

Ang et al⁶ showed that spinal cord repair data could be fitted to a two-component model with respective half-times of 0.7 h (approximately 40% proportion) and 3.8 h (approximately 60% proportion). Half-time is related to μ via $\mu = 0.693/\text{half-time}$, and the corresponding μ and f values to use in Equation (4) are thus $(0.99 \text{ h}^{-1}, 0.4)$ and $(0.182 \text{ h}^{-1}, 0.6)$. The presence of the long-lived repair component (half-time 3.8 h) may give rise to a significantly increased amount of un-repaired SLD at later times and which may be converted to additional lethal damage by subsequent fractions (via the Type B process), thereby increasing biological effect.

BEDS FOR CLOSELY SPACED FRACTIONS USING EXPONENTIALLY BASED MODELS

With mono-exponential repair the BED equation for closely spaced fractions combines Equations (1) and (3):⁷

$$BED = D \left[1 + \frac{D(1+h)}{N(\alpha/\beta)} \right] \quad (5)$$

where h is the “incomplete-repair” factor:⁸

$$h = \left(\frac{2}{N} \right) \cdot \frac{\theta_t}{(1-\theta_t)} \cdot \left[N - \frac{(1-\theta_t^N)}{(1-\theta_t)} \right] \quad (6)$$

and where t is the inter-fraction interval and θ_t Equation (3).

When there are several mono-exponential components, each with different repair half times, the corresponding BED for closely spaced equation is simply the total dose multiplied by the weighted addition of the respective RE factors,^{9,10} *i.e.*:

$$BED = D \sum_{i=1}^n f_i \left[1 + \frac{D(1+h_i)}{N(\alpha/\beta)} \right]$$

where the (f_i, h_i) combinations are the respective fractional and incomplete-repair factors for the i th component of repair. Thus, in the earlier example for spinal cord, the values to use in Equations (3), (6) and (7) would be $n = 2$, again with respective μ/f combinations of $(0.99 \text{ h}^{-1}, 0.4)$ and $(0.182 \text{ h}^{-1}, 0.6)$.

In practice hyperfractionated treatment fractions are rarely evenly spaced, the more usual pattern being two or more quite closely spaced daily fractions followed by relatively long over-night gaps. This is potentially difficult to handle numerically but an approximate approach is to calculate the BED for just one day of treatment using the relevant daily inter-fraction time spacings, the BED for the whole treatment then being

considered as being the daily BED multiplied by the total number of treatment days. The assumption here is that complete repair is able to take place overnight between the various daily treatment “blocks”. This may not always be the case, but the simplified approach is still better than making no allowance at all for incomplete repair.

PROTRACTED EXPOSURE AND THE LEA-CATCHESIDE MODEL

The discussion thus far relates to the repair that occurs following delivery of acute doses, *i.e.* those lasting a few minutes or less. When dose delivery is itself protracted the SLD repair can take place during the irradiation period, making the dose less effective than in the case of acute-exposure. This case was first examined by Lea and Catcheside¹¹ who were influenced by earlier observations¹² which had noted that lowering the radiation intensity produced a reduction in the number of chromosome and chromatid breaks. This led Lea and Catcheside to postulate that the damage created in the Type B process (to use the more modern terminology) was no longer proportional to dose,² but was proportional to a lower value given by (dose)² G, G being a time-dependent fractional number.

The derived form for G (again, when expressed using current symbolism) is:

$$G = \frac{2}{\mu T} \left\{ 1 - \frac{1 - e^{-\mu T}}{\mu T} \right\} \quad (8)$$

where T is the duration of the exposure and μ is the exponential rate constant for aberration repair. For short, acute, exposures T is close to zero and G is equal to unity. As T progressively increases the fractional value of G decreases and approaches zero at large values of T . Thus, as radiation exposure is protracted, Type B lethality becomes decreasingly influential.

The associated BED equation for a protracted dose delivered in time T , utilising Equation (8), is:²

$$BED = D \left[1 + \frac{2D}{\mu T (\alpha/\beta)} \left(1 - \frac{1 - e^{-\mu T}}{\mu T} \right) \right] \quad (9)$$

Interestingly, equating the RE expressions contained within Equations (2) and (9) leads to exactly the same conditions for LDR/HDR equivalence as had been earlier obtained by Liversage using an approach which also assumed mono-exponential repair kinetics but which did not involve the linear-quadratic model.¹

For multicomponent exponential repair, using the weighted addition of REs:

$$BED = D \sum_{i=1}^n f_i \left[1 + \frac{2D}{\mu_i T (\alpha/\beta)} \left(1 - \frac{1 - e^{-\mu_i T}}{\mu_i T} \right) \right] \quad (10)$$

For small values of T , Equations (9) and (10) are identical to Equation (2), and provide the BED for a single, acute dose delivery.

Equations (8–10) all consider repair to be a mono-exponential process. This is consistent with the first-order assumption Lea and Catcheside chose to use; they did consider that an alternative (second-order) process might be more appropriate but concluded that, for their purposes, the predictive differences between the two would be insignificant.

The conceptual difference between first-and second-order processes is now discussed.

FIRST- OR SECOND-ORDER REPAIR?

There is no *a-priori* reason for supposing that SLD repair should follow an exponential pattern. As noted above, whilst bi-exponential models can provide acceptable fits to clinical data that appear to show a “slowing down” of the repair process with time, this is not evidence that the contributing processes are indeed exponential; the associated equations may provide no more than good empirical descriptions of the data behaviour.

An alternative approach is to assume that SLD repair follows a second-order process, for which the repair kinetics are determined, not just by the number of remaining un-repaired lesions, but additionally by the diminishing concentration of the agents which are facilitating (or “driving”) the repair process. Second-order processes are well known in chemistry (*e.g.* the law of mass action) and in physics (*e.g.* recombination of electrons and positive ions in semiconductors). In biological systems it would appear reasonable to think that second-order events are at least as likely as first-order processes because the latter rests on the questionable assumption that the “driving reactants” remain unlimited in extent. In contrast, the natural progress of second-order kinetics would continually reduce both the number of un-repaired lesions and the amount of reactant, causing the process to slow down more quickly than would a first-order reaction.

Jack Fowler demonstrated that a model based on second-order assumptions provides an excellent fit to a wide range of double- and single-strand DNA repair data, and has the practical advantage that it requires only one repair-rate parameter.^{13,14} Following Fowler’s reasoning, and using the terminology introduced earlier, the fraction of un-repaired SLD at any time t is given by:

$$\theta_t = \frac{1}{1 + zt} \quad (11)$$

Parameter z is the repair-rate constant which characterises the whole process and is equal in value to the reciprocal of the first half-time of repair (τ). (With second-order repair the repair half-time relevant to any time interval becomes longer with increasing time after exposure but, usefully, only the first half-time is required in the calculations.) Since the un-repaired damage at any point is proportional to the reciprocal of the time elapsed, Equation (11) may be said to be a “reciprocal-time” model.

Equation (11) suggests that, following a given acute dose of radiation, the reciprocal proportion of un-repaired lesions will increase linearly with time, *i.e.*:

$$\frac{1}{\theta_t} = 1 + zt$$

and this is the hypothesis which was extensively tested by Jack Fowler, no obvious contradictions being found. More recently, the Fowler model has been further developed and used to predict damage repair rates in therapeutic particle beams possessing a high linear energy transfer (LET).¹⁵

As Fowler showed in his derivation of Equation (11),¹⁴ a possible snag with a second-order model is that repair rates should increase with dose. This appears to contradict experimental evidence, which overwhelmingly shows no dose-dependence of damage repair rates. Fortunately, the end-point of the process [Equation (11)] was found to give a similar fit to the double-strand repair data measured at both 4 and 10 Gy, *i.e.* the repair process could be modelled with a single value of z , regardless of the initial dose.¹³

This apparent support for a second-order repair process is consistent with the condition of enzyme saturation previously suggested by Goodhead.¹⁶ Fowler pointed out that, in evolutionary terms, repair enzymes may be better suited to repairing damage from small environmental doses and could not cope with the large injury produced by therapeutic doses.^{13,17} After high doses, the expected slower rate of repair due to enzyme saturation may be off-set by the enzymes having a higher probability of reaching the more numerous, more closely spaced, lesions, thus maintaining a near-constant repair rate. This would have the effect of making repair rates unaffected by the magnitude of the delivered dose. Whatever the true explanation, Equation (11) appears entirely consistent with DNA repair data. Recently, other second-order repair models, involving two free parameters, have also been postulated.¹⁸

Figure 1 summarises the general characteristics of the mono-exponential, bi-exponential and reciprocal repair models when applied to spinal cord data. The assumed mono-exponential

repair parameter is $\mu = 0.46 \text{ h}^{-1}$, corresponding to a fixed repair half-time of 1.5 h, a generic value commonly assumed for late-responding normal tissues.^{1,2,8,14} For the reciprocal time plot the assumed value for z is 0.67 h^{-1} , corresponding to a first half-time of repair of 1.5 h.^{13,14} For the bi-exponential plot the above parameters for spinal cord have been used.

As will be noted, there is virtually no difference in the three models in the short interval 0–2 h, but thereafter the mono-exponential predictions dramatically diverge from the other two. The bi-exponential and reciprocal-time models are almost indistinguishable in the range 0–8 h, after which the long “tail” of the latter becomes more pronounced. This is because, unlike the case with the exponential-based models, the second-order model predicts that, with increasing time after irradiation, the proportion of SLD being repaired in any time interval is not constant, but is continually decreasing.

This illustration helps make the point that, if reciprocal time repair is a viable explanation of the repair process, the build up of SLD in fractionated treatments may not always be negligible, perhaps not even in conventional case where the fractions are delivered at approximately 24 h intervals. Indeed, Jack Fowler was able to demonstrate that the BEDs calculated for closely spaced daily fractions could be as much as 50% higher than those calculated using the bi-exponential model, thereby providing a possible explanation for the unexpected cases of myelitis reported in the CHART pilot study.¹⁹

For a fractionated schedule of N closely spaced dose fractions the relevant second-order BED equation is:²⁰

$$\text{BED} = D \left(1 + \frac{D}{N(\alpha/\beta)} \right) \left\{ 1 + \left(\frac{2}{N} \right) \sum_{i=2}^N \frac{(N+1-i)}{[1+zt(i-1)]} \right\} \quad (12)$$

where t is the inter-fraction interval. More practical (but mathematically more complex) second-order equations for non-equally spaced fractions have also been derived.²¹

SECOND-ORDER REPAIR EQUATIONS FOR PROTRACTED DOSE DELIVERY

Equations (11) and (12) consider the case of acute dose delivery. When the delivery is itself more protracted the corresponding BED equation for a single dose of duration T is:^{17,20}

$$\text{BED} = D \left[1 + \frac{2D}{z^2(\alpha/\beta)} \left\{ \frac{(1+zT)\ln(1+zT)-zT}{T^2} \right\} \right] \quad (13)$$

As T becomes small Equation (13) simplifies to Equation (1), *i.e.* as noted earlier in the first-order case, at short dose delivery times the exact pattern of SLD repair becomes irrelevant in BED formulations.

A GENERAL OBSERVATION CONCERNING THE DOSE-RATE EFFECT

Figure 2 shows qualitatively how the RE of a given dose varies with its delivery time, *i.e.* over a wide dose-rate range. Irrespective of

Figure 1. Comparison of SLD repair characteristics following an acute radiation dose using three alternative models. SLD, sublethal damage.

Figure 2. General depiction of the dose-rate effect in terms of the variation of RE with irradiation time for a given dose of radiation. Although the precise shape and positioning of the curve is both model- and parameter-dependent, the sigmoid form of the relationship is a characteristic of both first-order (exponential) and second-order (reciprocal-time) models. The vertical extension of the curve is governed by dose (higher dose-higher maximum RE, and vice versa) and tissue α/β (lower α/β -higher RE, and vice versa). At very low dose the sigmoid is almost a horizontal line and there is very little dose-rate effect. The slope and lateral positioning of the curve is dominated by the repair rate(s): faster repair-curve shifted leftward; slower repair-curve shifted rightward. RE, relative effectiveness.

the assumed repair kinetics (mono-exponential, multiexponential or reciprocal-time) a general sigmoid-shaped RE relationship is predicted by all three models, [*i.e.* the square bracketed terms in Equations (9), (10) and (12)]. In all cases the RE maximises when delivery time is short and falls to unity when delivery time is long. Between these two extremes the RE decreases, at first slowly and then more abruptly, finally decreasing asymptotically to 1. The period over which the abrupt change occurs is a function of the repair rates (the μ values in the case of exponential repair; z -values in the case of reciprocal-time repair). When the delivery time is broadly comparable to the repair half-times associated with these rate constants (*i.e.* in the range of many minutes to a few hours) the RE is at its most unpredictable and this is when particular note needs to be taken of the possible clinical consequences. Some relevant examples are:

- (1) External beam fractions of extended duration^{22–24}
- (2) Some forms of pulsed brachytherapy^{25–27}
- (3) Medium dose-rate brachytherapy²⁸
- (4) Progressively extended treatment times in external beam ⁶⁰Co, Gamma Knife therapy or ¹⁹²Ir brachytherapy due to source decay.²⁹ (See also Jones and Hopewell in this Special Review).

Outside this range, RE is less sensitive to changes in treatment duration and is either close to its maximum (short dose delivery time) or minimum (long dose delivery time). Again it is emphasised that this is a general trend to be expected from the three repair models considered here. The precise positioning and slope of the sigmoid will be model- and parameter-dependent but the sigmoidal variation of RE with changing dose delivery time is a characteristic in all cases.

The maximum RE attained is governed by the tissue α/β ratio, with lower α/β tissues possessing higher RE and vice versa. Thus the RE sensitivity to changes in dose-rate is expected to be more pronounced in late-responding tissues rather than tumours, in the same way that RE sensitivity to changes in external beam fractionation is usually greater in such structures. The maximum RE also increases with increasing delivered dose, similarly increasing the sensitivity to dose-rate changes. As a corollary, at low total dose the maximum RE is numerically close to unity and the curve becomes almost flat, *i.e.* there is very little variation with treatment time and hence, little dose-rate effect. Finally, the lateral positioning of the curve is governed by the repair half-times: faster repair leads to a leftward shift, and vice versa.

Figure 2 (which is a generalised form of a more restricted depiction discussed elsewhere)³⁰ thus provides a useful pictorial summary of several important aspects associated with the dose-rate effect which are generally true and not model-specific. It is informative to consider dose-rate phenomena as being essentially a time effect (since the influence of repair is fundamentally dependent on the time available for the repair to take place) rather than on dose-rate *per se*. HDR irradiation generally involves shorter treatment times and there is thus little opportunity for SLD repair during the dose delivery. This is the main reason why HDR is more effective than LDR.

Because the precise positioning of the sigmoid curve is dependent on delivered dose, tissue α/β and the assumed repair kinetics, the last two differing between tumours and late-responding normal tissues, care needs to be taken in attempting to define what is meant by high, medium and LDR. Thus the dose-rate definitions provided by, for example, ICRU38, should be seen as being no more than very general guidelines.³¹ Finally, the likelihood that some of the radionuclides employed in various types of brachytherapy may possess relative biological effectiveness values greater than unity will also have a significant influence on the associated dose-rate effect, and hence on the relationships between different types of therapy.^{32–34}

CONCLUSION

Repair considerations have traditionally been considered most relevant to LDR brachytherapy, but the emergence of newer radiotherapy techniques involving novel temporal patterns of radiation delivery means that allowance for the clinical consequences of incomplete-repair may be required on a wider scale. This article limits itself to discussing repair issues relating to closely spaced fractions and protracted, constant dose-rate

exposure, but the same modelling principles can be applied to pulsed brachytherapy,^{25,26,35} permanent implants,^{32,33,36,37} and biologically targeted radiotherapy.^{38–41}

Some summary points are: (a) The fractional amount of SLD repair occurring in successive time intervals is not always constant—the repair taking place in successive time intervals may reduce with increasing time after irradiation, particularly in some normal tissues. This is conventionally explained by assuming that there are two or more exponential components of repair. (b) Multiexponential (first-order) repair models require knowledge of several parameter values, which lessens their usefulness. The reciprocal-time (second-order) model emulates the “slowing down” characteristics of multiexponential models, yet requires just one parameter. (c) For some practical clinical applications there is often no clear justification for preferring either the first- or second-order approach, although the latter may be better founded. Both approaches can allow the likely clinical consequences of incomplete-repair to be assessed and

the best choice of model is often that which requires the simplest mathematics in the particular circumstances. In making the choice the principle of Occam’s razor remains valid, a point Jack Fowler often made in his lectures.¹⁴

Other, more complex, repair models have been developed for both low- and high-LET application^{42–45} but, although these have the potential to provide useful insights to phenomenological aspects, they are often difficult to apply easily in the clinical domain, largely on account of the number of parameters involved. The repair models discussed in this article allow quantification and treatment inter-comparisons to be made via the widely used BED methodology which, while not able to provide exact answers to all problems, is often capable of reducing the likelihood of serious clinical error.

ACKNOWLEDGEMENTS

To Jack Fowler and Oliver Scott, both of whom provided great inspiration.

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