A New Incomplete-repair Model Based on a 'Reciprocal-time' Pattern of Sublethal Damage Repair

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A radiobiological model for closely spaced non-instantaneous radiation fractions is presented, based on the premise that the time process of sublethal damage (SLD) repair is 'reciprocal-time' (second order), rather than exponential (first order), in form. The initial clinical implications of such an incomplete-repair model are assessed. A previously derived linear-quadratic-based model was revised to take account of the possibility that SLD may repair with time such that the fraction of an element of initial damage remaining at time t is given as $1/(1 + zt)$, where z is an appropriate rate constant; z is the reciprocal of the first half-time (τ) of repair. The general equation so derived for incomplete repair is applicable to all types of radiotherapy delivered at high, low and medium dose-rate in fractions delivered at regular time intervals. The model allows both the fraction duration and interfraction intervals to vary between zero and infinity. For any given value of z, reciprocal repair is associated with an apparent 'slowing-down' in the SLD repair rate as treatment proceeds. The instantaneous repair rates are not directly governed by total dose or dose per fraction, but are influenced by the treatment duration and individual fraction duration. Instantaneous repair rates of SLD appear to be slower towards the end of a continuous treatment, and are also slower following 'long' fractions than they are following 'short' fractions. The new model, with its single repair-rate parameter, is shown to be capable of providing a degree of quantitative explanation for some enigmas that have been encountered in clinical studies. A single-component reciprocal repair process provides an alternative explanation for the apparent existence of a range of repair rates in human tissues, and which have hitherto been explained by postulating the existence of a multi-exponential repair process. The build-up of SLD over extended treatments is greater than would be inferred using a single-exponential repair model and this has important implications in several areas of radiotherapy.

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A number of radiobiological models have been developed for application to the design and analysis of clinical and experimental data (1–5). The trend of recent years has been to use the linear-quadratic (LQ) model, the justification for this being that the LQ model has a biophysical base which relates clinically observed fractionation and dose-rate effects with first-order pair-wise repair, or mis-repair, of DNA strands. In all currently used LQ models the temporal progress of repair of sublethal damage is assumed to be exponential in form. However, a number of studies have indicated that repair after irradiation does not always proceed at a constant rate, suggesting that multi-exponential processes may exist (6–12) and LQ-based models have been revised to include this possibility (3, 4, 13, 14).

It has been postulated (15) that the biophysical process of sublethal damage (SLD) repair in DNA could follow a second-order (i.e. bi-molecular) process rather than a first-order (exponential) process. The implication of second-order repair is that the repair rate 'slows down' with increasing time, thus exhibiting similar properties to a multi-exponential pattern of repair. It also emulates the time-stretching characteristics of a 'square root of time' pattern of repair (16). A detailed analysis of several published data sets relating to DNA repair, and which suggest the presence of bi- or multi-exponential processes, has shown that none of them was inconsistent with the alternative (and simpler) hypothesis that repair is second-order (15). Using the latter approach, each data set required only a single parameter (the first half-life, τ) to define its entire course.

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In this article a single-component, second-order repair function is combined into the LQ model to develop incomplete repair equations which can be applied to the analysis of a wide range of radiotherapy. Some clinical implications of the new model are then assessed.

MATERIAL AND METHODS

Basis of the model

If it is assumed that the rate of repair of damaged lesions is proportional to the square of their number, the rate of disappearance of unrepaired lesions is given by:

$$\frac{dn}{dt} = -Cn^2 \quad [1]$$

where C is the rate constant. Integrating Eq. (1) from $t = 0$ to t, and rearranging, leads to:

$$\frac{n_t}{n_o} = \frac{1}{1 + n_o C \cdot t} \quad [2]$$

where n_t is the number of unrepaired lesions remaining at time t from an initial population of n_o such lesions. At the time point (the *first* half-time of repair, τ) at which the number of unrepaired lesions has fallen to half the initial number, it follows from Eq. (2) that:

$$\tau = \frac{1}{n_o C} \quad [3]$$

Combining Eqs. (2) and (3) suggests that, following a given dose of radiation, plotting the reciprocal proportion (n_0/n_t) of unrepaired lesions will yield a straight line of slope $1/\tau$, i.e.

$$\frac{n_0}{n_t} = 1 + n_0 C t = 1 + \frac{t}{\tau} \quad [4]$$

This is the hypothesis which has been extensively tested by Fowler (15) using DNA repair data, with no obvious contradiction to its validity.

A significant feature of Eqs. (2) and (3) is the suggestion that the amount of damage remaining at any time point is inversely related to the initial amount of damage, n_0, i.e. repair rate increases with initial damage and hence, dose. This seems to contradict almost all experimental evidence, which overwhelmingly shows no apparent change in repair rate with dose. For example, in the analysis by Fowler (15), Eq. (4) was found to give a similar fit to the double-strand repair data of Wlodek & Hittelman (17) measured at both 4 and 10 Gy, i.e. the repair process followed a second-order process in both cases and with a single value of τ, regardless of the initial dose. There is no experimental evidence to show that repair is *faster* after higher doses, as expected from Eq. (2) if the interaction rate (C) were constant. Since $\tau = 1/n_o C$, the observed dependence of τ on dose or amount of damage will of course define the relationship between C and n_o, the latter value of which is set at the end of each irradiation. The observations are predominantly that repair rates are independent of dose, a possible exception being at doses below 1 Gy (18). This independence implies that, as n_o increases, the rate C must decrease in direct proportion. This is consistent with the condition of enzyme saturation. After higher doses, the expected slower rate of repair due to enzyme saturation (19) is not observed because the enzymes have a higher probability of reaching the more numerous, more closely spaced, lesions, thus maintaining a near-constant repair rate. This point is covered further in the Discussion.

Eq. (2) may be re-written such that the probability (p) that a sublethally damaged component of DNA remains unrepaired at time t after its creation is given as:

$$p = \frac{1}{1 + zt} \quad [5]$$

where $z(= n_o C = 1/\tau)$ is a repair constant, with units of h^{-1}; z is the reciprocal of the first half-time of repair. Succeeding half-times become longer by simple arithmetic progression, i.e. the unrepaired component falls to 1/2 after a time lapse of $1 \times \tau$, to 1/3 after $2 \times \tau$, to 1/4 after $3 \times \tau$, etc. Thus, after an elapse of n half-lives the reciprocal time process will leave an unrepaired fraction of $1/(n + 1)$, rather than $1/2^n$ as occurs with mono-exponential repair. This effect is illustrated in Figs. (1) and (2), which compare mono-exponential and reciprocal time repair when plotted as a log-linear graph. Relative to the mono-exponential case the hyperbolic curves demonstrate the 'slowing-down' process which is characterized by Eq. (5)—for any given value of z the instantaneous repair rate will appear slower with increasing time after creation of the lesion. However, it will also be noted that there is an initial period over which the two lines are sufficiently close to each other for them to be indistinguishable by any experimental process. Over longer periods if recovery kinetics truly follow a

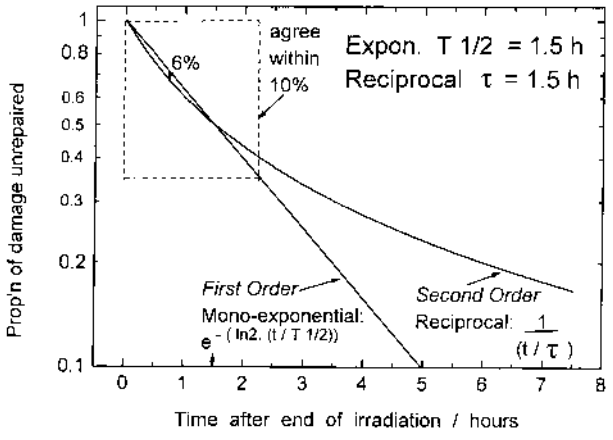

Fig. 1. Calculated repair curves plotted on a log-linear scale comparing exponential (striaght) with reciprocal repair with $T_{1/2}$ and τ both set at 1.5 h. The curves lie within 10% of each other ($\pm 5\%$) out to about $1.5 \times T_{1/2}$ or τ.

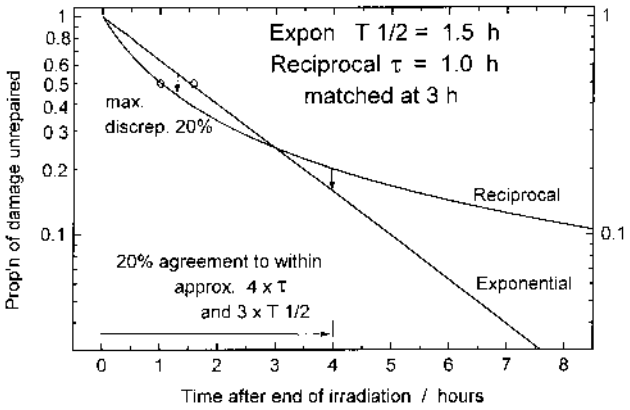

Fig. 2. As for Fig. 1, but with τ set as 2/3 the $T_{1/2}$ value, i.e. at 1 h. Here the discrepancy increases to 20%, ($\pm$ 10%), but remains within that margin until nearly 3 times τ or twice $T_{1/2}$.

second-order process, then the forced assumption of first-order kinetics would require that a more complex multi-exponential function be used to fit the data (9, 19).

As set out in Appendix A, Eq. (3) has been used as the basis for developing incomplete-repair equations for calculating the relative effectiveness (RE) for closely spaced fractions of finite duration. The method follows that previously used and involves separately formulating the Type A and Type B lethal damage in a regime (1, 2). Type A damage is that caused in a single ionization event; Type B damage is that caused by the interaction of two sublethal lesions which were created in separate ionizing events. Eqs. (A5), (A6) and (A7) can be used together for general situations. When it is known that the fractions are of short duration, as in fractionated high dose-rate (FHDR) radiotherapy, Eq. (A8) may be used. For continuous low dose-rate (CLDR) radiotherapy, Eq. (A9) can be used.

Method for determining repair rates at particular time points after irradiation

As Eq. (3) describes a repair process which slows down with increasing time elapsed since the initial damaging event, it is instructive to quantify how this is affected when non-instantaneous radiation delivery is used. With mono-exponential repair, the repair rate of SLD is fixed and is always the same irrespective of how long a particular lesion has remained unrepaired. In the reciprocal repair case, unrepaired lesions created early in the exposure period will be repairing more slowly at the cessation of irradiation than those lesions created near the end of the exposure. Thus the initial repair rate immediately after irradiation will appear to be slower for long exposures because there are more slow-repairing lesions present. Furthermore, instantaneous repair rates will appear to slow down during the irradiation period when reciprocal repair occurs, thereby increasing the likelihood that SLD will be compounded to be lethal damage. For these two reasons a given regime of CLDR may seem to be more potent (in terms of its RE and BED values) when analysed according to a reciprocal repair, rather than mono-exponential, repair model.

In Appendix B an equation is derived for determining the fraction of unrepaired damage which remains at any time (g) after cessation of an irradiation of duration T. From Eq. (B3) the apparent repair rates may be investigated.

RESULTS

Apparent repair rates

For non-instantaneous exposures the fraction of SLD remaining after cessation of irradiation is given by Eq. (B3). Using $z = 0.67\ h^{-1}$ (corresponding to a τ value of 1.5 h) the fractions of unrepaired damage remaining after exposures of varying duration are shown as a log-linear plot in Fig. 3. It will be noted that there are marked departures from mono-exponential repair, which would follow straight lines when plotted in this way. Also, in addition to the slowing-down effect discussed above, even the initial repair rates are slower after longer exposures, due to the greater proportion of 'slow-repairers' created earlier in the exposure. Table 1 summarizes the effect of this slowing-down process by listing the initial repair half-lives as determined from Fig. 1. Although the Table is based on $\tau = 1.5$ h, the principle is the same for any half-life value.

In any multi-fraction or extended radiotherapy treatment, be it CLDR, RHDR or PB, the effective repair rate of SLD at any particular time will depend on the duration of the individual exposures, the time elapsed since initiation of the treatment and (for FHDR or PB) the interfraction intervals. The repair rates influence the absolute amount of SLD that exists at any one time, which in turn governs how much of the SLD is compounded into Type B lethal damage. For these reasons the equations developed in Appendix A are relatively complex, despite the fact that a simple pattern of repair (Eq. (3)) has been assumed for the individual lesions. A significant aspect of this is that, for any first half-life of reciprocal time repair which is equated to a mono-exponential half-life, most radiotherapy regimes will appear to have higher RE values when analysed according to this new model. The differences in RE will be most pronounced in regimens involving closely spaced fractions and/or long fraction durations.

Clinical examples where reciprocal repair is important

i) External beam radiotherapy involving two fractions of 2 Gy per day. Several centres have discontinued two fractions per day of 2 Gy because of unfavourable complications (20, 21). Yet, from calculations of incomplete repair (IR) assuming the usual late-responding mono-exponential rate of repair with $T_{1/2} = 1.5$ h, that is an unexpected finding. For generic late complications with $\alpha/\beta = 3$ Gy

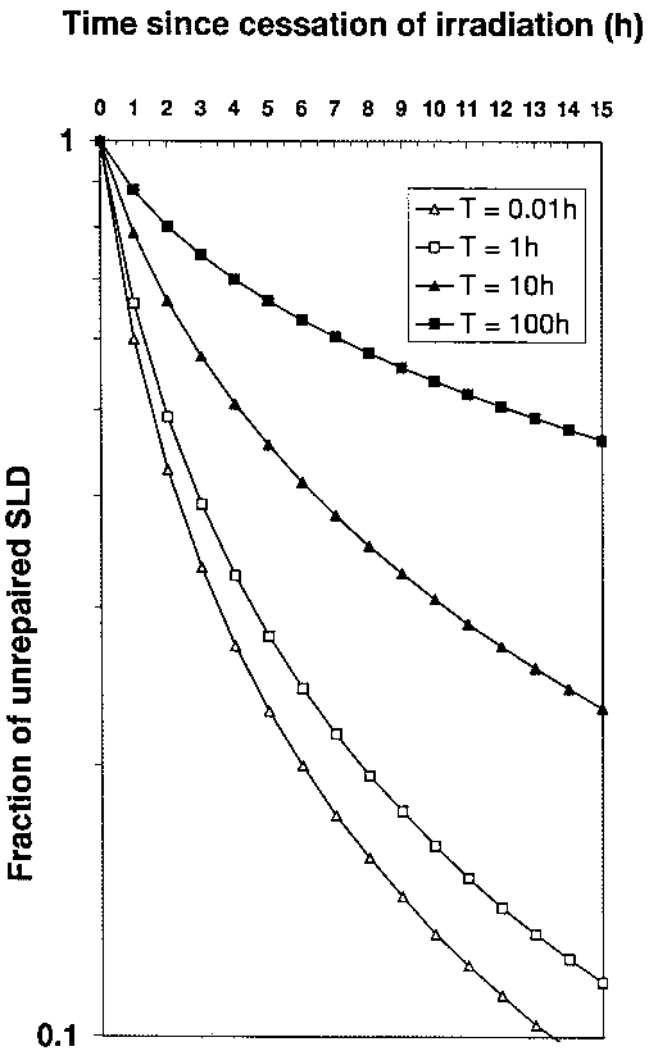

Fig. 3. The fraction of SLD remaining at any time (g) after cessation of irradiation is influenced by the duration (T) of the radiation exposure. All curves calculated using Eq. (B3) with $z = 0.67\ h^{-1}$, corresponding to a first repair half-life (τ) of 1.5 h for instantaneous irradiation.

there would be only 2.5% addition to the late BED in Gy_3 with the 6 h interval and less than 0.01% with the 18 h interval. Hence the overall schedule, with equal numbers of 6 h and 18 h intervals, experiences the average increase of these two BEDs, which is 1.25%. Thus, with mono-exponential repair, there would be negligible incomplete repair after the 18 h interval and no accumulation over the 4 days each week that are followed by treatment the next day.

Table 1

Initial repair half-lives immediately after a single exposure are influenced by the duration of the exposure. In all cases $z = 0.67\ h^{-1}$, corresponding to an initial repair half-life for individual lesions of 1.5 h. The first half-life values are determined directly from Fig. 1

Duration of irradiation (h)	Apparent first half-life (h)
0.01	1.5
1	1.9
10	4.1
100	12.4

Reference to Fig. 2 indicates how, in experimental data with realistic scatter, mono-exponential repair of longer $T_{1/2}$ could be mistaken for reciprocal repair with a shorter τ. If τ is longer than about 0.7 h there would be several percent of IR of late damage at 24 h after 2 Gy doses. This would accumulate over the 4 days of a standard week that are followed by another dose, and such an accumulation of IR would probably have been noticed. Therefore, assuming reciprocal repair (using Eqs. (A5)–(A7) with the reduced value of 1.0 h for τ suggests an IR of 5.7% for 6 h intervals and 2.1% for 18 h. This not only adds the mean of these values (3.9%) instead of 1.25% to the BED, but, more importantly, shows that 2.1% remains unrepaired at the time of the first fraction on the following day. This would be compounded to 8.6% additional BED each week (repair would be complete over the 72 h weekend interval), and hence to $8.6 + 3.9 = 12.5\%$ additional BED due to incomplete repair for the schedule. This is a relatively large margin, quite sufficient to increase late complications if maximum tolerable doses are being prescribed.

There is thus an explanation here for why schedules using 2×2 Gy per day can cause excessive normal tissue toxicity and are thus not in routine use.

ii) The myelopathies in the CHART pilot study. In this clinical study three doses per day of 1.5 Gy were given to the head and neck region, at precise 6-h intervals, for 11.5 days without a weekend break (22, 23). It is well known that myelopathy occurred in 5 patients in the pilot study, even though the spinal cord dose was restricted to 42 Gy by reducing to 28 the number of fractions which irradiated the cord (22). With the cord dose further reduced to 37.5 Gy in the main trial, no further cases occurred.

Ignoring incomplete repair, 42.0 Gy with 3 fractions a day of 1.5 Gy at 6-h intervals delivers a BED of 73.5 Gy_2 (with $\alpha/\beta = 2$ Gy). This figure can be obtained using the standard LQ equation for well-spaced high dose-rate fractions and is completely independent of repair half-life. As myelopathies would not be expected until at least 50 Gy and more probably 60 Gy in 2 Gy fractions (corresponding to a biological dose of between 100 and 120 Gy_2), we need to examine whether or not the new model of incomplete repair can explain an increase of 36 to 63% in Gy_2. The next two paragraphs provide a preliminary illustrative calculation.

Assuming a mono-exponential $T_{1/2}$ of 1.5 h, less than 4% of the total BED was expected to be added due to IR, but the 6 h minimum interval was insisted upon in the event of unexpected repair characteristics. Attempts have been made to explain the apparent biological overdose in terms of incomplete repair (24), but have not been satisfac-

tory, even using the bi-exponential repair data measured for rat spinal cord (8). These two exponential half-time were 3.8 h and 0.7 h with respective 48 : 62 partitioning. The bi-exponential model suggested a 9% increase in each day's BED but negligible IR after the 12 h overnight interval. A better explanation was found using the rat data from Landuyt et al. (25) with two exponential $T_{1/2}$ of 0.3 and 6 h.

Evidence has been presented elsewhere (26) that the τ for spinal cord from several sets of experiments in rats agreed on a range of 2.6 to 2.9 h, the slowest-repairing tissue recorded (7, 8, 10, 25). Using $\tau = 2.8$ h for 3×1.5 Gy fractions at 6-h intervals, reciprocal repair suggests around 23% additional BED within each day, making the daily BED as high as $73.5 \times 1.23 = 90$ Gy_2, but even that cannot explain the myelopathies. More importantly, there would be around 8% unrepaired SLD at the time of the first fraction on the next treatment day, 12 h after completion of the previous day's treatment. The accumulation of this 8% per day for 9 continuous days of treatment (the time required to deliver 27 fractions to the spinal cord) could lead to a 100% escalation of BED by the last day. The average increase throughout the entire treatment course resulting from this effect is therefore about half that figure, i.e. $\sim 50\%$, and this must be added to the 23% because of incomplete repair within each daily group of three fractions. The overall increase in spinal cord BED is thus $\sim 73\%$, taking it to a value of ~ 135 Gy_2, (equivalent to 67.5 Gy in well-spaced fractions of 2 Gy). This explanation is not sensitive to the actual values of τ, provided they are at least as long for human cervical as for rat cervical spinal cord.

It is clear from the above that residual unrepaired damage at the time of the first fraction on the next day could be an important source of additional effect, particularly in the spinal cord. It is doubtful whether anyone has looked for evidence of this in human radiotherapy, because the expectations from the conventional mono-exponential modelling are so different. (An extended model incorporating the effect of unequal time gaps between fractions has been developed by the authors and will be the subject of a future publication).

Conversion of low dose-rate brachytherapy regimes to medium and high dose-rate

Low dose-rate versus high dose-rate intercomparisons augment the suggestion that the reciprocal-repair τ value for a given tissue has a value lower than the mono-exponential $T_{1/2}$ of the same tissue. This would be expected if experimental measurements of $T_{1/2}$ employed time intervals of up to 2–3 times τ (Figs. 1 and 2). Figs. 4–7 demonstrate the effect of delivering a single boost dose of 10 Gy at varying dose-rates, analysed with the mono-exponential model (using $T_{1/2} = 1.5$ h) or the new model (with various values of τ). The curves show that at high dose-rates the

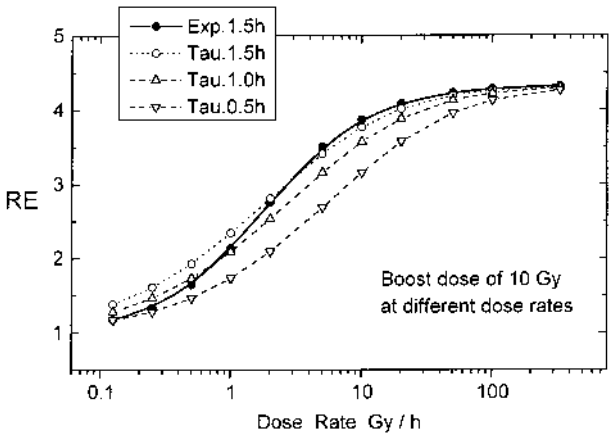

Fig. 4. Curves of RE vs. dose rate for a 10 Gy continuous irradiation delivered to a tissue with $\alpha/\beta = 3$ Gy. Full line: calculated assuming mono-exponential repair with $T_{1/2} = 1.5$ h, using Eq. (C) of Dale (1). Dashed and dotted curves: calculated using Eqs. (A5)–(A7) from the present paper, assuming reciprocal repair with τ values as indicated. Whilst the general changes of RE with dose rates are similar, there is significantly more damage predicted at low dose-rates to HDR by the reciprocal repair model, until a τ value smaller than 1/3 or 1.5 h is assumed (see also Table A). The curves all converge to RE = 1.0 at zero dose-rate and to RE = 4.33 at extreme HDR.

calculated values of RE are all in agreement, irrespective of the value of τ. This is to be expected, because repair has no effect in very short exposures. However, at low dose-rates of 0.3–0.5 Gy h^{-1}, equal REs are found for $T_{1/2} =$ 1.5 h and $\tau = 0.5$ h approximately. As discussed earlier, this is a natural consequence of reciprocal repair predicting more unrepaired damage, which has the largest effect on the longest irradiations. CLDR then appears much more damaging than we are accustomed to thinking, while HDR is relatively less changed. The effect is to make the conversion from LDR to HDR appear safer, using reciprocal repair, than previously thought when assuming mono-exponential repair. When conversion from CLDR to FHDR

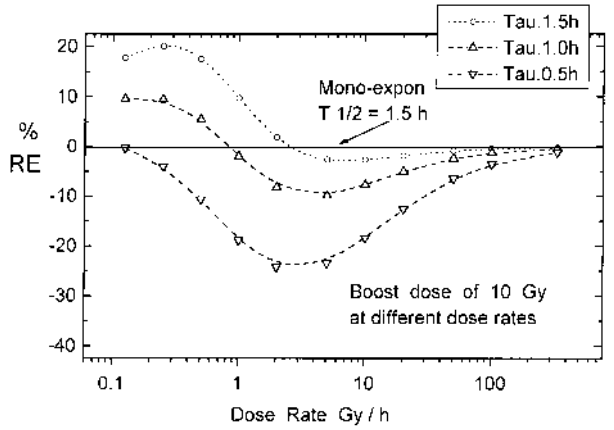

Fig. 5. The same data as in Fig. 4 but expressed as percentage deviation from the mono-exponential points.

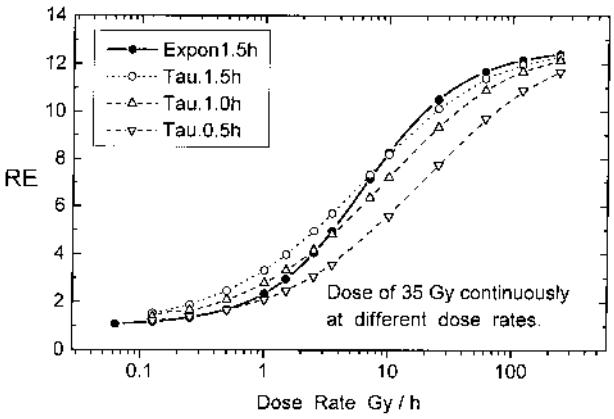

Fig. 6. Curves of RE vs. dose-rate as in Fig. 4 but for a continuous irradiation of 35 Gy.

are made using smaller $T_{1/2}$ values for tumour than for late-responding normal tissue, the conversion seems to carry less risk than when equal $T_{1/2}$ is assumed for both tissues (27–29). In this preliminary study we shall for simplicity consider only late-responding tissues with $\alpha/\beta =$ 3 Gy and a mono-exponential $T_{1/2}$ of 1.5 h. In gynaecological brachytherapy there is evidence that the probability of severe late complications increases rapidly above a rectal BED of about 125 Gy_3, whether delivered by LDR, MDR, or HDR brachytherapy (15, 30). Obtaining this same BED value from both the CLDR and FHDR regimens provides a mechanism for finding a representative value of τ. Assuming mono-exponential repair with $T_{1/2} = 1.5$ h, 70 Gy of CLDR delivered in 140 h (at 0.5 Gy/h) is calculated to be equivalent to 5 HDR brachytherapy treatments, each of 7.1 Gy. Both treatments deliver ~ 120 Gy_3 to late-responding tissues and may be considered clinically equivalent. This $T_{1/2}$ of 1.5 h might not be exactly the correct one to use, but it is commonly accepted and determines the BED of 120 Gy_3, which is also close to the expected tolerance dose from small-volume irradiation with external

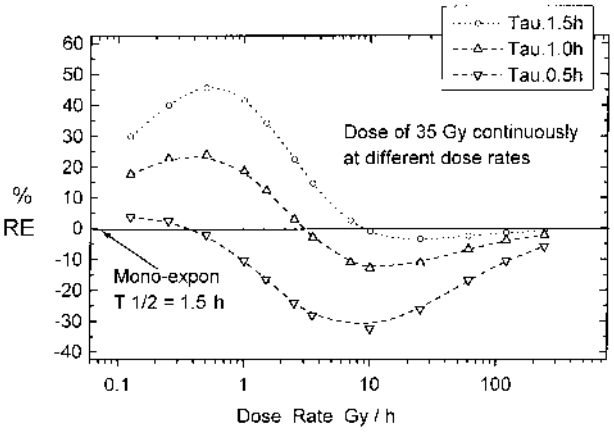

Fig. 7. The same data as in Fig. 6 but expressed as percentage deviation from the mono-exponential points.

beams (at HDR). Either schedule is equivalent to 71.8 Gy given in 2 Gy fractions at conventional HDR.

The corresponding calculation assuming reciprocal repair with $\tau = 1.5$ h yields a BED of 196 Gy_3, which is equivalent to 117.5 Gy given as 2 Gy fractions, and is clearly wrong. However, it is possible to select other values of τ in order to determine which will give a similar BED3 for the CLDR regime. The results of making this selection are shown in Table 2, from which it is clear that $\tau = 0.45$ h may be an appropriate choice in this context. It should be noted that the time required for the amount of unrepaired damage to fall from 50% to 25% is 0.9 h, so measurements of $T_{1/2}$ at longer times would yield a value of around 1–2 h.

The 'equivalent' mono-exponential half-life associated with reciprocal time decay can be determined by noting that, at any time (t) after initial irradiation the apparent exponential decay constant (μ_{app}) is related to z and t via:.

$$e^{-\mu_{app}} = \frac{1}{1+zt} \quad [6]$$

Eq. (9) may be re-written to find the apparent mono-exponential half-life ($T_{app} = \ln 2/\mu_{app}$) at time t, i.e.

$$T_{app} = \frac{0.693t}{\ln(1+zt)} \quad [7]$$

Using Eq. (7) with $z = 0.67\ h^{-1}$ ($\tau = 1.5$ h), the apparent half-lives of mono-exponential decay after lapses of 0.1, 1, 10 and 100 h are 1.1, 1.4, 3.2 and 16.4 h, respectively. This again indicates that if recovery kinetics truly follow a second-order process, then the forced assumption of first-order kinetics would require that a multi-exponential repair function be used in order to fit repair data derived from observations over extended time periods.

Both the mono-exponential repair and reciprocal repair model might be unreliable for medium dose-rates (MDR) as there is no means of knowing which might be better without further data. Figs. 5 and 7 indicate discrepancies of $\pm 20\%$ or more in total dose (or RE) between the two models for a CLDR boost of 10 Gy, and more than 30 or 40% for 35 Gy, with the major change occurring across the MDR range. Even the τ value of 0.45, shown to be a good match to the conventional mono-exponential $T_{1/2}$ of 1.5 h at low dose-rate, is a poor match in the MDR range. Overall these results would suggest that even more care may be necessary in changing from LDR to MDR than was previously thought because dose adjustments as great as 30% may be required in order to maintain a normal tissue isoeffect.

Pulsed brachytherapy

The following facts are agreed among modellers who have computed values for RE or total equivalent dose for PDR schedules of 0.5, 1, 2 or more Gy per pulse repeated at 1, 2, 4 or more hours (31–33). There is little difference in the

Table 2

Determination of an approximate value of τ which will predict CLDR and FHDR regimes similar to those (70 Gy/140 h and 5× 7.1 Gy) found to be equivalent using a mono-exponential $T_{1/2}$ of 1.5 h. For both these regimes the BED is 119.7 Gy_3 and the equivalent total dose (for $\alpha/\beta = 3$ Gy) in 2 Gy fractions is 71.8 Gy. The table shows that $\tau = 0.45$ h gives a very close match

Reciprocal repair half-life (h)	BED (Gy_3) for CLDR delivered as 70 Gy/140 h	Total dose (Gy) when delivered as FHDR in 2 Gy fractions	Required dose/fraction (Gy) if given as 5 HDR fractions
1.5	195.8	117.5	9.44
1.0	163.0	97.8	8.50
0.5	124.4	74.6	7.27
0.45	120.0	72.0	7.12
0.4	115.5	69.3	6.96
0.3	106.1	63.7	6.62

REs or total doses required for a given level of biological damage between CLDR and PDR, unless:

(a) Dose per pulse rises above 1 Gy, or
(b) A substantial component of exponential half-time of repair is < 0.5 h, and/or
(c) Very high dose-rates, above 10 Gy/h are used on tissues with short $T_{1/2}$, so that
(d) The pulse duration approaches the $T_{1/2}$ value and both are short.

Where more than one of these conditions occur, RE values for PB can be about 40% above those for CLDR, assuming the mono-exponential model. As shown by the dotted line in Fig. 8 (taken from the central curve of Fig. 2 in Fowler & Van Limbergen (33)), this peak occurs only when a pulse of at least 2 Gy is delivered (at 4-h intervals) in about 0.2 h (12 min) or less and when the half-time of repair is less than 0.25 h. Fig. 9 shows that the RE values are less elevated ($\sim 20\%$ high) when 1 Gy pulses are used at 1-h intervals.

If the calculations are repeated using the equations in the present paper, assuming the same range of τ as previously for $T_{1/2}$, we obtain the solid curves in Figs. 8 and 9. These are similar in shape to the mono-exponential curves (dashed line) but are only about two-thirds as discrepant from equality with CLDR for the whole range. This preliminary calculation suggests that the problems with late complications from PDR may be somewhat less than currently believed, but a significant complication is the fact, mentioned above, that τ is probably smaller than $T_{1/2}$ for a given tissue by a factor between 1.5 and 3.

The effect of this may be determined from specific examples. The RE increment using the mono-exponential model with $T_{1/2}$-1 h is, as determined from Fig. 8, $\sim 16\%$. If the reciprocal repair τ value which corresponds to this $T_{1/2}$ is (say) 0.5 h, the RE increment (also from Fig. 8) is $\sim 18\%$, with the reciprocal repair model predicting a bigger overdose, by a large margin. However, if the respective $T_{1/2}$ and τ values are 0.6 h and 0.3 h, the respective elevations in RE are $\sim 26\%$ and $\sim 22\%$, i.e. reciprocal repair predicts a marginally smaller overdose. It is clear from this that the predictions of the two models will differ depending on the specific combination of treatment circumstance and radiobiological parameters. In the absence of hard information on the repair characteristics of tissues that are being treated with PB in place of CLDR, it remains prudent to attempt to avoid the circumstances outlines in a)–d) above, and which are generally relevant for both patterns of SLD repair.

DISCUSSION

The initial applications of the reciprocal model to the analysis of clinical data suggest that this may be a useful tool, with the potential for considerably wider application. Despite being associated with more complex formulae than are required for exponential-based analyses, the reciprocal repair model is easier to fit to clinical data as there is only one repair parameter (z or τ) involved. An exponential model with n components involves knowledge of $(2n - 1)$ parameters: n repair constants and $(n - 1)$ partitioning constants.

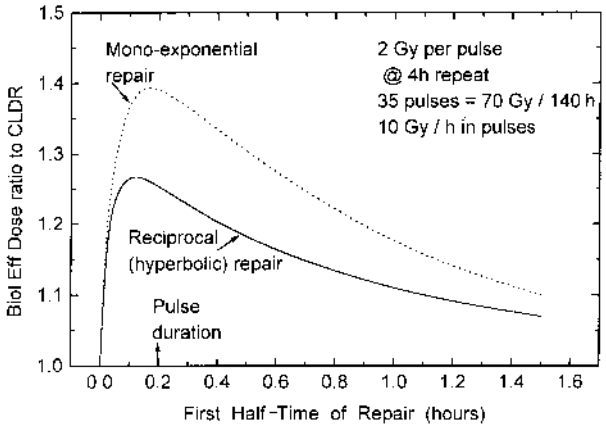

Fig. 8. Radios of BED (or RE) for PDR to those of CLDR for 70 Gy/140 h, as a function of assumed $T_{1/2}$ (mono-exponential) or τ (reciprocal repair), for 10 Gy h^{-1} dose-rate in each 2 Gy pulse with 4 h repeats. Dotted curve from Fig. 2 in Fowler & Van Limbergen (25) assuming mono-exponential repair. Full line: Reciprocal repair from Eqns. (A5)–(A7) in the present paper.

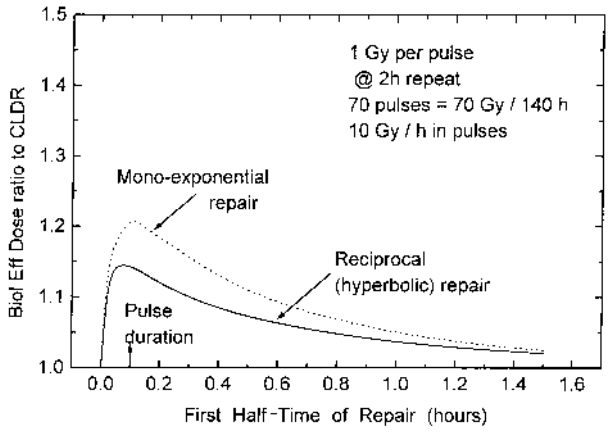

Fig. 9. As in Fig. 8, but with 1 Gy pulses and 2 h repeats.

An analysis of several experimental animal data sets has already demonstrated that there are no statistically significant exceptions to the hypothesis that radiation-induced damage follows a second-order process (15). The development of an LQ-based model which can accommodate an unlimited range of fraction durations and interfraction intervals offers the possibility of a reassessment of wise range of clinical data.

Which values of τ should be used? If the reciprocal repair τ value is taken to be identical to the mono-exponential $T_{1/2}$, then, irrespective to the value chosen, the new model will always predict a higher RE and BED for all types of treatment, the exception being well-spaced FHDR treatments. This is because, whenever radiation durations are non-instantaneous, or when fraction spacing is such that there is residual IR at the beginning of later fractions, the 'slowing down' effect allows more of the SLD to be compounded to Type B lethal damage than would occur with mono-exponential repair. Bentzen et al. (34) carefully analysed the results of clinical radiotherapy schedules using two fractions per day separated by 3–6 h and found $T_{1/2}$ values as long as 3–4 h for acute mucosal reactions. These results are different to explain unless there is a mechanism invoked to account for a slowing-down of repair. This implies that current models underestimate the toxicity of, for example, CLDR and PB treatments, but this may not be always be the case. The analyses of the CLDR/FHDR intercomparison presented above strongly suggests that the value of τ to use is considerably less than the mono-exponential $T_{1/2}$; indeed use of a smaller τ is essential if log cell kill (of which BED is a measure) is to be kept the same in order to facilitate the CLDR/FHDR intercomparison. On the other hand, the preliminary analysis here of the CHART myelopathies and of the rat spinal cord data (22) suggests that the τ value to use for the cord is of similar order to the longer repair half-time found from the crude average of a bi-exponential fit. However, the value of 2.7 h is much smaller than the $T_{1/2}$ s found in bi-exponential results from rat spinal cord (2, 20).

If reciprocal repair is indeed a better description of the overall repair process then it raises questions which must be addressed in the longer term. Second-order (hyperbolic) repair carries the implication that repair rates increase with increasing damage, and hence, dose. Thus, to be consistent with the observation that almost all measured and/or derived repair rates are independent of dose it is necessary to invoke the existence of an additional (rate-limiting) mechanism which effectively maintains the second-order repair rate at a constant figure.

Goodhead (35) has suggested that the constancy of repair rates with increasing dose implies that there is no saturation of repair enzymes. This is a justifiable requirement if it is assumed that first order (exponential) repair kinetics apply, ie that the repair-rate of damaged lesions is propotional to their number. With second-order repair kinetics, however, the repair-rate is proportional to the square of the number of lesions [Equation [1]], which would call into question the validity of the assumption of non-saturation of enzymes. The alternative postulation of enzyme saturation at higher doses would set a limit to the velocity of repair due to this agency and would help remove the implicit difficulty with the predictions of second order repair. The expected slowing down of repair due to the saturation process would be off-set by the increased likelihood that the extant enzymes will interact with the more densely spaced damage lesions. Thames (36) also has discussed the possibility of enzyme saturation in alternative models of repair.

Although the postulation of enzyme saturation helps remove a significant difficulty, Fowler (15) has speculated that rate-limited repair in a second-order model may be explainable even without enzyme saturation. The juxtapositioning into close proximity of damaged entities, a process which would have a lower probability with increasing concentration of damage (ie the rejoining rate would slow down), would also help maintain a constant repair rate due to the law of mass action. As dose increases the repair rate would be proportional to the product of the falling concentration of those lesions which are suitably positioned for repair and the (increasing) enzyme concentration. However, no specific mechanism is assumed in this article and it remains to be demonstrated whether or not a reciprocal repair model is a better reflection of the underlying processes which govern the repair phenomenon.

CONCLUSION

An incomplete-repair model based on reciprocal repair of sublethal radiation damage has been shown to be capable of emulating many of the characteristics previously ascribed to the presence of two or more repair components in a multi-exponential model. The two-event biophysical base from which the equations have been developed is common to other LQ formulations; it is only the assumption about the temporal pattern of repair that has been

changed. It is this step that leads to a theoretical description of a single-element, slowing-down process which does not involve several mono-exponential elements. A practical advantage of the reciprocal repair model is that it requires fewer parameters than its multi-exponential equivalent and is therefore preferred in cases where the two models seem to provide an equally plausible fit to clinical or experimental data (15).

The twin concepts of BED and RE remain unchanged with the new model, but the reciprocal repair phenomenon holds significant implications when intercomparing treatments, for which at least one involves closely spaced fractions (e.g. teletherapy with multiple fractions per day or pulsed brachytherapy) or continuous delivery of radiation (e.g. continuous or falling dose-rate brachytherapy). In such cases the numerical values attached to the BEDs and REs may well be different from those calculated even with a bi-exponential model, thus altering the conditions for equivalence between the compared treatments and changing some of the predictive bases when designing new treatments.

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APPENDIX A: *Derivation of equations for calculating relative effectiveness (RE) when there is reciprocal repair of sublethal damage (SLD)*

Apart from the changed assumption relating to the mathematical form of the repair rate of SLD, the steps followed here mirror those previously used elsewhere (1, 2).

Treatment consists of N fractions, each of duration T. The interfraction interval (time elapsed between end of one fraction and beginning of next) is x. R is the dose-rate, assumed constant throughout.

Consider the SLD created at time t into first fraction.

Prob. (either target hit in one radiation event) = 2pRdt.

The time elapsed (g) between this instant of time and a time point 't' into the ith fraction is:

$$g = (T - t) + (i - 1)x + (i - 2)T + t' = i(x + T) - t - T - x + t'$$

Therefore, on the assumption that repair follows a hyperbolic-type process in a form as given by Eq. (3), it follows that:

$$\text{Prob. (damage still exists at that time)} = 2pR\left(\frac{1}{1 + z[i(x + T) - t - T - x + t']}\right) \cdot dt$$

Thus, the probability that SLD created in the whole of the first fraction still exists at time t′ into the ith fraction is:

$$2pR \int_0^T \frac{1}{1 + z[i(x + T) - t - T - x + t']} \cdot dt = \frac{2pR}{z} \cdot \{\ln[1 + z(i(x + T) - T - x + t')] - \ln(1 + z(i(x + T) - 2T - x + t'))\} \quad [A1]$$

At any time, probability (2nd target is hit in time dt) = pRdt. Therefore, if there ar n target pairs and ε is the probability they interact together, the total Type B damage created in the ith fraction as a result of sub-lethal damage created in the 1st fraction is:

$$n\varepsilon pR \int_0^T [\text{Eq(A1)}] \cdot dt' = \frac{2n\varepsilon p^2R^2}{z} \cdot \int_0^T [\text{Eq(A1)}] \cdot dt' \quad [A2]$$
$$= \frac{2\beta R^2}{z} \cdot \int_0^T \{\ln[1 + z(i(x + T) - T - x + t')] - \ln[1 + z(i(x + T) - 2T - x + t')]\} \cdot dt'$$

where $\beta = n\varepsilon p^2$.

By similar reasoning, the total amount of Type B damage created within any one fraction due to interactions with sub-lethal damage created within that same fraction is:

$$\frac{r\beta R^2}{z} \int_0^T \ln(1 + zt')dt' \ldots \quad [A3]$$

For a whole treatment consisting of N fractions, there are N amounts of component A3 contributing to the total Type B damage. The total contribution of component A2 to the total Type B damage must additionaly take account of the influence of sub-lethal created in the 2nd, 3rd etc fractions on the ith fraction, and it may be shown that the summation to achieve this is of the form:

$$\sum_{i=2}^{N} (N + 1 - i) \times \text{Eq(A2)}$$

i.e. total Type B damage in N fractions is TB, where:

$$TB = \frac{2N\beta R^2}{z} \int_0^T \ln(1 + zt')\} \cdot dt' + \frac{2\beta R^2}{z} \sum_{i=2}^{N} (N + 1 - i) \cdot \int_0^T \{\ln[1 + z(i(x + T) - T - x + t')] - \ln[1 + z(i(x + T) - 2T - x + t')]\}\, dt'$$
$$= \frac{2N\beta R^2}{z^2}[(1 + zT)\ln(1 + zT) - zT] + \frac{2\beta R^2}{z} \sum_{i=2}^{N} (N + 1 - i) \cdot \int_0^T \{\ln[1 + z(i(x + T) - T - x + t')] - \ln[1 + z(i(x + T) - 2T - x + t')]\}\, dt'$$

$$= \frac{2\beta R^2}{z^2}$$

$$\left\{ \begin{array}{l} N[(1+zT)\ln(1+zT) - zT] \\ \\ +z\sum_{i=2}^{N}(N+1-i)\cdot\int_0^T \{\ln[1+z(i(x+T)-T-x+t')] \\ \\ -\ln[1+z(i(x+T)-2T-x+t')]\}\,dt' \end{array} \right\} \quad [A4]$$

For specific values of z, x and T, the integral in Eq. (A4) can be evaluated directly using mathematical software. Where this is not possible, the value of the integral (Int) can be determined from:

$$Int = \frac{1}{z}$$

$$\left[\begin{array}{l} A(ixz + iTz - 2Tz - xz + 1) + B(2Tz - 2 - 2ixz - 2iTz + 2xz) \\ +C(1 + ixz + iTz - xz) \end{array} \right]$$

where

$$A = \ln(1 - 2zT + zix + ziT - zx)$$

$$B = \ln(1 - zT + zix + ziT - zx)$$

$$C = \ln(1 + zix + ziT - zx)$$

In which case Type B damage can be calculate via:

$$TB = \frac{2\beta R^2}{z^2}\left\{ \begin{array}{l} N[(1+zT)\ln(1+zT) - zT] \\ \\ +z\sum_{i=2}^{N}(N+1-i)Int \end{array} \right\} \quad [A5]$$

The total Type A damage is TA, where:

$$TA = N\alpha RT \quad [A6]$$

$$\text{Thus, } RE = 1 + \frac{TB}{TA} \quad [A7]$$

In the case of closely spaced HDR fraction, each of magnitude d, $R = d/T$.

Substituting this into Eq. (A5) and noting the behaviour as $T \to 0$ we have:

$$TB \to \beta d^2\left\{N + 2\sum_{i=2}^{N}\frac{(N+1-i)}{[1+zx(i-1)]}\right\}$$

Thus, from Eq. (A7), the RE for closely spaced HDR fractions is:

$$RE = 1 + \frac{d}{(\alpha/\beta)}\left\{1 + \frac{2}{N}\sum_{i=2}^{N}\frac{(N+1-i)}{[1+zx(i-1)]}\right\} \quad [A8]$$

For a single fraction of extended duration (i.e. CLDR irradiation) $N = 1$ and, as there are no interactions between successive fractions, the summation term in Eqs. (A4) can be deleted. In such cases:

$$TB = \frac{2\beta R^2}{z^2}[(1+zT)\ln(1+zT) - zT]$$

and:

$$Re = 1 + \frac{2R}{z^2(\alpha/\beta)}\left[\frac{(1+zT)\ln(1+zT) - zT}{T}\right] \quad [A9]$$

Eq. (A9) may be derived independently from first principles. Taken together, Eqs. (A5–A7) are applicable to a range of clinical circumstances involving irradiations at any dose-rate and with small or large interfraction intervals. For FHDR and CLDR, respectively, they give the same numerical results as Eqs. (A8) and (A9), but are not restricted in their application as are the latter equations.

Note: Readers who wish to write computer programs based on the above equations are advised that, for numerical evaluation of Eqs. (A4) and (A5), it is necessary to specify double precision arithmetic).

APPENDIX B: The calculation of remaining fraction of sublethal damage (SLD) following irradiations of extended duration

Consider a single irradiation of duration T. At any (t) into the irradiation a certain amount (Δ) of SLD is created in elemental time dt. At time g after the end of irradiation, the amount (f) of the particular element of damage which still remains is:

$$f = \frac{\Delta}{1 + z(T - t + g)}$$

Thus, the amount of all the damage created in total time T which remains at time g after the cessation of irradiation is F(g), where:

$$F(g) = \int_0^T f \cdot dt = \frac{\Delta[\ln(1+z(T+g)) - \ln(1+zg)]}{z} \quad [B1]$$

Immediately after irradiation (when $g = 0$) the amount of remaining SLD is F(0), where:

$$F(0) = \frac{\Delta\ln(1+zT)}{z} \quad [B2]$$

The fraction of damage remaining at time g after cessation of irradiation, expressed relative to the amount which exists at the end of irradiation, is then given as:

$$\frac{F(g)}{F(0)} = \frac{\ln(1+z(T+g)) - \ln(1+zg)}{\ln(1+zT)} \quad [B3]$$