LETTER TO THE EDITOR

The modified linear-quadratic model of Guerrero and Li can be derived from a mechanistic basis and exhibits linear-quadratic-linear behaviour

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LETTERS TO THE EDITOR

The modified linear–quadratic model of Guerrero and Li can be derived from a mechanistic basis and exhibits linear–quadratic–linear behaviour

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The Editor,

Sir,

We would like to comment on the recent paper published by Guerrero and Li (2004). These authors have suggested a modification to the linear–quadratic (LQ) model in order to better describe the cellular dose response at large dose per fraction. Because the LQ model predicts a dose response whose slope increases with dose, cell lines that exhibit a constant final slope tend to have a poor fit to the LQ model at higher doses. The modification of the LQ model that Guerrero and Li have proposed is a welcome and useful progression of the LQ formalism. The manner in which Guerrero and Li introduced this modification, however, was without a mechanistic justification, and could appear to be arbitrary. The purpose of this letter is to show that Guerrero and Li’s modification to the LQ model does have a mechanistic justification, and to show that the mechanistic basis is where sublethal lesion interaction is not considered insignificant as compared to sublethal lesion repair, and further that sublethal lesion interaction is modelled as a linear process.

We have previously shown (Carlone 2004, Carlone et al 2003) that the LQ model can be derived using the compartmental model shown in figure 1. In this figure, the quantity \( A \) represents the number of potential target sites in a cell; \( B \) is the number of sites within the cell where sub-lethal damage has been created; and \( C \) is the number of sites where irreparable damage exists. When a cell is irradiated, the production of \( B \) lesions occurs at a rate of \( 2p \mu \), the dose rate. The constant \( p \) is defined as the yield per unit dose of sub-lethal lesions\(^1\) (Dale 1985). In figure 1, the depletion of sublethal lesions by interaction is considered to be small as compared to repair, and so lesion formation can be considered to be two separate components as shown in figure 1. Assuming exponential repair of sublethal lesions, as shown on the left of figure 1, the steady state value of \( B \) is determined by solving:

\[
\frac{dB}{dt} = \frac{d}{dt} (2pR - \mu B).
\]

The solution for \( B(t) \) is:

\[
B(t) = \frac{2pR}{\mu} \left[ 1 - \exp(-\mu t) \right].
\]

Next formation of irreparable lesions is considered. This is accomplished by either of the two pathways shown on the right of figure 1. Non-repairable lesions are directly produced at

\(^1\) The multiplier 2 is included because there are two potential target pairs required for sub-lethal lesions to interact. This factor was originally introduced when single strand lesions were thought to interact to form an non-repairable double strand lesion. Thus there were \( 2 \times A \) potential sites for a sublethal lesion. It could be omitted from the current derivation; however it is left here to preserve the derivation of Dale (1985).
Figure 1. A representation of the LQ model, which illustrates the assumptions necessary to derive the LQ equation based on the kinetics of lesion formation, repair and interaction. The quantity $A$ represents locations within a cell where a radiation event can occur, $B$ is the number of sublethal lesions, and $C$ is the number of irreparable lesions. The principle LQ assumptions are that repair of sublethal lesions occurs at a rate that is much greater than interaction of sublethal lesions, and that interaction of sublethal lesions is a linear process. As a result of the first assumption, the LQ equation can be modelled in two distinct steps. The first step, shown on the left, populates sublethal lesions in a cell, and allows exponential repair. Once a cell is populated with sublethal lesions, interaction of sublethal damage is considered.

A rate given by $\alpha R$, where $R$ is the dose rate. In the second pathway, the pre-existing sublethal lesions $B$ can interact with the formation of new $B$ lesions, with interaction probability $\varepsilon$. New $B$ lesions are produced at the rate $pR$, so the total rate of $C$ lesion production is the product of the new lesion production rate, $pR$, with the number of pre-existing lesions, $B$, and the probability of interaction, $\varepsilon$ (Dale 1985). The differential equation for $C$ is:

$$\frac{dC}{dt} = \alpha R + pR \varepsilon B.$$  \hfill (3)

The solution for $C(t)$ is obtained by integrating equation (3), using equation (2) as the expression for the quantity $B(t)$. Following the notation of Dale (1985), the $\alpha$-type damage is defined as damage occurring directly from $A$ to $C$, and the $\beta$-type damage as originating from the $B$ box and going into the $C$ box. The equations for these quantities are:

$$\alpha - \text{type} = \alpha R \int_0^T dt = \alpha RT = \alpha D,$$

$$\beta - \text{type} = pR \varepsilon \int_0^T B(t) \, dt$$

$$= pR \varepsilon \int_0^T \frac{2pR}{\mu} \left[1 - \exp \left(-\mu t \right)\right] \, dt$$

$$= \frac{2\varepsilon p^2 R^2}{\mu} \left[T - \frac{1}{\mu} \left[1 - \exp \left(-\mu T \right)\right]\right].$$  \hfill (4)

The linear–quadratic expression is obtained by replacing $\varepsilon p^2$ with $\beta$ in equation (4); factoring out $T$ from the square brackets, multiplying the entire expression by $T/T$, and finally substituting $D = RT$. This yields

$$\beta - \text{type} = \frac{2}{\mu T} \left[1 - \frac{1}{\mu T} \left[1 - \exp \left(-\mu T \right)\right]\right] \beta D^2 = G(\mu T) \beta D^2.$$
The total damage is the $\alpha$-type summed with the $\beta$-type. Cell survival is given using the Poisson approximation to estimate the probability that no lesions remain after irradiation, and so cell survival is given by:

$$S = \exp \left( -\alpha D - G(\mu T)\beta D^2 \right).$$

This is the LQ expression including dose rate dependence. Using a similar method, it can easily be shown that figure 1 can also be used to derive the expression for the RE of permanent implants as originally derived by Dale (1985).

Apart from the assumptions about the formation rate of sublethal and lethal damage, figure 1 shows two assumptions needed to derive the LQ model: that sublethal lesion repair is the dominant process in depleting the pool of sublethal lesions (as compared to a lethal exchange) and that lethal exchanges are a linear process. The first assumption about the LQ formalism is well known (Sachs et al 1997). Removing this assumption produces a compartmental model that is shown in figure 2. The differential equations that govern figure 2 are:

$$\frac{dB}{dt} = 2pR - \mu B - pR\varepsilon B, \quad (5)$$

$$\frac{dC}{dt} = \alpha R + pR\varepsilon B. \quad (3)$$

The differential equation for $C(t)$ is unchanged; however, the quantity $B(t)$ that should be used in equation (3) is obtained by solving equation (5), which is similar to equation (1) except that there is an additional term $pR\varepsilon B$. Using the variable $\mu' = \mu + pR\varepsilon$, the solution for $C(T)$ is:

$$C(T) = \alpha RT + \frac{2p^2\varepsilon R^2}{\mu'} \left( T - \frac{1}{\mu'} \left[ 1 - \exp \left( -\mu' T \right) \right] \right).$$

Using the Poisson assumption, survival is given by

$$S = \exp \left[ -\alpha RT - \frac{2p^2\varepsilon R^2}{\mu'} \left( T - \frac{1}{\mu'} \left[ 1 - \exp \left( -\mu' T \right) \right] \right) \right]. \quad (6)$$
Equation (6) is identical to the modified LQ model proposed by Guerrero and Li. This is seen by factoring out $T$ from the brackets in equation (6),

$$S = \exp \left[ -\alpha D - \frac{2p^2 \varepsilon R^2 T^2}{\mu T} \left\{ 1 - \frac{1}{\mu' T} \left[ 1 - \exp(-\mu' T) \right] \right\} \right],$$

and substituting $RT$ with the dose $D$ and $p^2 \varepsilon$ with $\beta$:

$$S = \exp \left[ -\alpha D - \beta D^2 G (\mu T) \right].$$

Replacing $p \varepsilon$ with $\delta$:

$$S = \exp \left[ -\alpha D - \beta D^2 G (\mu T + \delta D) \right].$$

Equation (7) is the modified LQ model of Guerrero and Li. Figure 2 thus shows the mechanistic basis for the modified LQ model. $\delta$ of the modified LQ model represents the formation rate of sublethal lesions multiplied by the probability of interaction. In terms of Guerrero and Li’s model the ratio of $\beta/\delta$, which yields $p$, gives the production rate of sublethal lesions, and the quantity $\delta^2/\beta$ gives the probability of interaction of sublethal lesions, $\varepsilon$.

By differentiation of equation (6), it can be shown that the modified linear–quadratic model of Guerrero and Li has a constant final slope. For cell survival plotted on a semi-log plot, with $p^2 \varepsilon$ replaced by $\beta$:

$$-\ln(S) = \alpha R T + \frac{2\beta R^2}{\mu} \left[ T - \frac{1}{\mu} \left[ 1 - \exp(-\mu' T) \right] \right],$$

$$-\frac{d}{dD} \ln(S) = \frac{d}{dt} \frac{d}{dD} \ln(S) = \frac{d}{dt} \frac{1}{R} \ln(S),$$

$$-\frac{d}{dD} \ln(S) = \alpha + \frac{2\beta R}{\mu'} \left[ 1 - \exp(-\mu' t) \right].$$

The final slope is the slope after a long time, $t \gg \ln(2)/\mu'$

$$-\left[ \frac{d}{dD} \ln(S) \right]_{t \gg \ln(2)/\mu'} = \alpha + \frac{2\beta R}{\mu'}. $$

This quantity is independent of dose, which indicates a linear region of the survival curve at large doses. This result addresses a long standing problem with the linear–quadratic formalism: the poor description of the high dose section of survival curves is due to the assumption that repair is the dominant method of sublethal lesion removal. By retaining the assumption that sublethal lesion interaction is a linear process, the linear–quadratic features of the model are thus preserved at low dose. For these reasons, we feel that the modification of Guerrero and Li to the LQ model is important and significant. Since this model exhibits linear–quadratic–linear features, we suggest the name ‘linear–quadratic–linear’ as we feel this name provides a more physical meaning for the model.

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Reply to ‘The modified linear–quadratic model of Guerrero and Li can be derived from a mechanistic basis and exhibits linear–quadratic–linear behaviour’

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The Editor,
Sir,

We would like to thank Dr Carlone and his collaborators for their interest in our article. We appreciate their comments that the modification to the linear–quadratic (LQ) model introduced by us (Guerrero and Li 2004) to obtain what they call the linear–quadratic–linear model (LQL) (a notation that we shall follow), is welcome and useful. They point out, however, that our proposed modification was introduced in a way that could appear arbitrary. Dr Carlone and his collaborators also propose a possible mechanistic justification for the new term in the dose-protraction factor based in a compartmental model.

We concede that our modification to the LQ model is an ad-hoc formula. However, it is not completely arbitrary since it was designed to match the behaviour of the lethal-potentially lethal (LPL) model (Curtis 1986) at large doses and dose-rates. Nevertheless, we welcome the contribution by Dr Carlone et al, since they demonstrated that our ad-hoc formula could be derived from a kinetic model. The compartmental model proposed by Carlone et al denotes the number of sites in a cell with sublethal damage as $B$ and the number of sites with irreparable damage as $C$. Carlone et al assume that lethal exchanges are a linear process proportional to the number of pre-existing lesions $B$ and the new lesion production rate (equation (3) above).

On the other hand, the LQL matches the behaviour of the LPL model over a wide range of doses and survival fractions, implying that the compartmental model from Carlone et al is equivalent to the LPL model in terms of cell survival fractions. This is particularly interesting, since the LPL model is a kinetic model where the lethal exchange is quadratic in the number of pre-existing lesions, as opposed to linear as in Carlone et al’s model. This equivalence in cell survival predictions of different kinetic models poses a difficulty in the search for underlying mechanisms, since distinctions are almost non-existent in cell-survival experiments.
There is, however, an important difference between the LPL and the compartmental model from Carlone et al. In the LPL there is another parameter that comes into play: the time elapsed after irradiation and plating of the cells \( (t_r) \) (Curtis 1986). Usually, a sufficiently long time is allowed for repair to take place after irradiation. According to the LPL model, the cell survival fractions vary for a short \( t_r \) and saturate when \( t_r \) becomes much larger than the repair time (Curtis 1986). In the Carlone et al model, the lesions repaired after irradiation do not come into play, since the production rate of irreparable lesions \( C \) is proportional to the dose-rate (equation (3) above).

Based on what we have proposed (Guerrero and Li 2004) on the correlation of the LQL and the LPL models and the correspondence (Carlone et al) \( p = \beta / \delta \) (\( p \) is the yield per unit of dose of sublethal lesions (Dale 1985)) and \( \epsilon = \delta^2 / \beta \) (\( \epsilon \) is the probability of interaction between lesions), we have extended table 1 and table 2 from Guerrero and Li (2004) to include the parameters \( p \) and \( \epsilon \). Note that in terms of the LPL parameters (Curtis 1986) \( p = \eta_{PL}/3 \) and \( \epsilon = 9\delta_{PL}/2\lambda \). According to these values, most cell lines have \( p \) between 0.1 and 1 Gy\(^{-1}\). The values of \( \epsilon \) vary from very small (0.03 for HX156) to very large (2151 for oat cell carcinomas). The interpretation of \( \epsilon \) as a probability of lesion interaction breaks down for \( \epsilon \) larger than 1.0. This problem can be circumvented by assuming that of all irreparable lesions only a fraction become lethal and the rest become non-lethal mutations (Sachs et al 1997, Stewart 2001). If we introduce a parameter \( a \) in equation (4) of Carlone et al so that

\[
\beta - \text{type} = apR\epsilon \int_0^T B(t)dt,
\]
we shall have $\beta = p^2 \varepsilon a$ while $\delta = p \varepsilon$ as before. Therefore, $\delta^2/\beta = \varepsilon/a$ and $\beta/\delta = pa$. In principle, lymphoma cell lines and oat cell carcinomas could be interpreted as having a small value of $a$.

The difference in the high dose behaviour between the LQ and the LQL models is perhaps better understood by considering the high dose-rate (HDR) limit. In the LQ model, for the HDR limit, $\mu T = \mu D/R \to 0$, $G(\mu T) \to 1$ and $-\ln(S) \to \alpha D + \beta D^2$ which has a constantly bending slope as a function of $D$. In the LQL model, for HDR, $\mu' T = \mu D/R + \delta D \to \delta D$, so $G(\mu' T) \to G(\delta D)$, and if $\delta D >> 1$ then $-\ln(S) \to \alpha D + 2\beta D/\delta = (\alpha + 2\beta/\delta)D$ which has a constant slope as a function of $D$.

We thank Dr Carlone and his collaborators again for their interesting comments and look forward to exchanging further stimulating discussions in the future.

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