A new mathematical model for radiation cell killing mechanism: Target cumulating model

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Abstract

There are numerous mathematical or statistical models have been given out for radiation cell killing mechanism. Unfortunately, none of the model could explain the mechanism perfectly. The more advanced model for it is still necessary to be researched. Following common assumption, a new theoretical model named “target cumulating” model is induced from the molecular and particle physics level. The result of theoretical calculation gives the equation of cell survival rate corresponding to delivered dose and other sensitivity parameters.

In addition to fit the cell survival curve well, the new model showed advantages with comparing to previous models. Also, the new model predicts or explains some phenomenon that had been observed in laboratory (e.g. dose rate effect and low dose hypersensitivity).

Key words: cancer, radiation, model, cell survival.

Introduction

Since the technology was developing, the research of cancer was deep into the cell level and then the molecular. There is no doubt that radiobiology has been very fruitful in generation of new ideas and in the identification of potentially exploitable mechanisms in cancer cells and molecules. Research in radiobiology deals at the fundamental level with molecular, biochemical and biophysical mature of radiation damage. Models are a necessary part and the model of predicting the DNA damage and cell killing that caused by radiation was considered as the key to specific treatment strategies. There were numerous models in past decades. Some were based on

experience and another some were combined with theoretical induction. Unfortunately few of these have so far led to demonstrable clinical gains, though some models such as linear-quadratic equation seem to be successful. Beyond this, the ability of laboratory science to guide the radiotherapist in choice of specific protocols is limited by the inadequacy of the theoretical and experimental models.

Two of the most successful models are the multi-target single-hit model and linear-quadratic model. But both of them happened to “disaster” at low or high dose region. This situation occurred many times in science history, such as the problem of “black body” irradiation. What for we necessary to do is that just like Planck had done, combining the theory and conquer the “disaster”.

The new model named “target cumulating” model was induced in this paper from the physical and biological model under reasonable assumptions. The final result gives the equation for cell survival in form as follow:

$$S(d) = \exp\left\{-\left(\alpha+\beta-\frac{r}{u}\right)\times d+\left(C-\frac{Cr}{u\beta}\right)\times\left[1-\exp\left(-\frac{\beta}{C}d\right)\right]\right\}$$

In addition to fit the cell survival curve well, the new model showed advantages with comparing to previous models. Also, the new model predicts or explains some phenomenon that had been observed in laboratory (e.g. dose rate effect and low dose hypersensitivity). All these indicate that this new model could be a good choice of theory with regard to the molecular level.

Theory and method

Previous models

The target theory is one of the simplest and basically model. The idea of how radiation might

kill cells is that there may be specific regions of the DNA that are important to maintain the reproductive ability of cells. These sensitive regions could be thought of as specific targets for radiation exposure would be related to the number of targets inactivated. To derive an equation for this survival curve, Poisson statistics can be applied. The formula for multi-target single-hit inactivation cell survival is: $P(survival)=1-[1-exp(-D/D_0)]^n$ where the n was considered to be the number of the sensitive targets. While n=1, it becomes the single-target single hit model. The key difficulty with this concept is that so far the specific radiation targets have not been identified for mammalian cells, despite considerable effort to search for them. And an obvious shortcoming of the multi-target model is that, it predicts a response that is flat for very low doses. This is not supported by experimental data: there is good evidence for significant cell killing at low dose and for cell survival curves that have a finite initial slope.[1]

The Linear-quadratic model (Chadwick and Leenhouts, 1973) [2] is now in widespread use in both experimental and clinical radiobiology and generally works well in describing responses to radiation in vitro and also in vivo. The formula for cell survival is: $P(survival)=exp(-\alpha D -\beta D^2)$. The simple is that the linear component [$exp(-\alpha D)$] might be due to single-track events while the quadratic component [$exp(-\beta D^2)$] might arise from two-track events. Besides the continually downward bending of the cell survival curve is not fit the clinical results at the high dose region, the nature of the interactions between separate tracks is still a matter of considerable debate.

Curits(1986) [3] proposed the lethal, potentially lethal damage (LPL) model as a ‘unified repair model’ of cell killing. Ionizing radiation is considered to produce two different types of lesion: repairable lesions and non-repairable lesion. The non-repairable lesions produce single-hit lethal effects and therefore give rise to a linear component of cell killing [$=exp(-\alpha D)$]. The eventual

effect of the repairable lesions depends on competing process of repair and binary misrepair. It is this latter process that leads to a quadratic component in cell killing. The model have two sensitivity parameters (η_L determines the number of non-repairable lesions produced per unit dose, and η_{PL} the number of repairable lesions) There are also two constants (ε_{PL} determines the rate of repair of repairable lesions, andε_{2PL} the rate at which they undergo interaction and thus misrepair). This model produces almost identical cell survival curves to LQ equation, down to a survival level of perhaps 10^{-2}. It can therefore be taken to provide one possible mechanistic interpretation of the LQ equation.

Model designation and consideration

Though we believe that DNA damage is critical event in radiation cell killing and mutation, the number of lesions induced by radiation in DNA is far greater than those that eventually lead to cell killing. In a variety of experimental situations it has been found that the incidence of cell killing fails to correlate with the number of single strand break (SSB) induced, but relates better to the incidence of double strand break (DSB).[4] On this basis it is generally believed that DSB are the critical lesions for radiation cell killing in most cell types. Reference from the previous theories, the new model of radiation cell killing is built on simple physics and biology as follow.

There are two basic assumptions for the theory：

1. Cells are lethally damaged by radiation through breaks in the DNA molecule that lead to cell death at mitosis although in some cases cell death may occur before this (apoptosis). It is also the main assumption of most of the previous model (e.g. L-Q model et al).
2. Some of these lethal breaks are produced by a single photon track that causes an unrepairable double-strand break (DSB) – “one track action”. Other lethal lesions are caused by incorrectly repaired near pairs of DSB’s resulting from the passage of pairs of photons within the

timescale that it takes to repair DNA damage. In these cases, the individual DSB's may not have been lethal on their own but when another lesion nearby occurring within the repair time scale, the unrepaired DSB is lethal.

The occurring of one track action of DSBs could be simply described as a statistic probability for every delivered dose. The most challenge is how to describe the sublethal deposits, although the LPL model presented this problem by parameters η_{PL}, ε_{PL} and ε_{2PL}. To solve the problem, we set a model as follow: The realization that radiation produces 'hot spots' in which clusters of ionizations may occur within a diameter of a few nanometers has led to the notion that such an event may produce a particularly severe lesion if it impinges on the DNA molecule, such as DSB. Assuming the DSB creates a sublethal, thus another lesion nearby occurring within the repair time scale will make the unrepaired DSB lethal. In other word, this DSB creates a target region for next DSB to hit (Fig.1). However, every sublethal DSB falls on the sensitivity of DNA may create target for hit (Fig.2). While these targets are hit before repaired, the lesion could be lethal (Fig.3). It is suitable to term this model as "target cumulating" (TC) model .

On this hypothesis, the dynamics of radiation cell killing could be explained as follow.

Calculation

$$\Delta N = \frac{C - N(d)}{C} \times \beta \times \Delta d \qquad (1)$$

Where, ΔN is the number of increased target regions, C is the maximum number of the sensitive regions that could be contained in the DNA, N(d) is the number of existed target in the DNA after radiation of dose d was delivered, β (dimensioned times/Gy) is the frequency of the sublethal DSB occurring during the dose Δd was delivered.

While take Δd as a fractional dose ∂d, thus ΔN becomes $\partial N(d)$. It gives

$$\frac{\partial N(d)}{C - N(d)} = \frac{\beta}{C}\partial d \qquad (2)$$

Solve the equation (2), the result gives $N(d) = C - e^{-\frac{\beta d}{C} + K_1}$. Where K_1 is the constant determined by condition. When d=0, N (d) should be zero as the virgin cell. Then, K_1=lnC.

Assume the rate of DNA repairing for specific cell is invariableness that corresponds to cell variety and phase. Considering the repairing, the equation (1) should be

$$\Delta N = \frac{C - N(d)}{C} \times \beta \times \Delta d - r\Delta t \qquad (3)$$

Where r is the DNA repairing rate, and Δt is the time duration of Δd deliver. When the radiation out put rate set to u, Δd =u Δt . For fractional radiation, it has

$$\partial N(d) = \frac{C - N(d)}{C} \times \beta \times \partial d - \frac{r}{u}\partial d \qquad (4)$$

It gives

$$N(d) = C - \frac{Cr}{\beta u} - e^{-\frac{\beta}{C}d + K_2} \qquad (5)$$

Substitute d=0 and N(d)=0, we got $K_2 = \ln\left(C - \frac{Cr}{\beta u}\right)$, thus

$$N(d) = C\left(1 - \frac{r}{\beta u}\right)\left(1 - e^{-\frac{\beta}{C}d}\right). \qquad (6)$$

One hypothesis is: the probability of immediate lethal DSB occurring is a constant value that determined by the character of the specific DNA. Thus, the probability of killing cell by single DSB could be presented as $p(DSB_{kill}) = \frac{\alpha \times \Delta d}{n}$, where the α (dimensioned times/Gy) is the frequency of lethal DSB occurring during the delivered dose Δd, and n is the number of cell correspond to the one photon's energy transfer. In most of cases, single photon track could only cause damage to one cell, thus n=1. It's no matter whether the lethal DSB hit the target region created by sublethal DSB or not.

Since we assumed one sublethal DSB hit on the target region could also lead to cell death. The probability of such cell killing could be deduced as follow: $p(SUB_{kill}) = \left[\frac{N(d)}{C} \times \beta \times \Delta d\right] \Big/ n$. The difference of survival fraction after

delivered dose Δd could be presented as follow:

$$S(d+\Delta d)-S(d)=-S(d)\times[p(DSB_{kill})+p(SUB_{kill})] \quad (7)$$

Where S(d) is the survival fraction after total dose d has been delivered. Transfer $S(d+\Delta d)-S(d)$ to $\Delta S(d)$, and take the fractional form similar as we done to equation (1) and (3). Then substitute N(d), p(DSB_{kill}) and p(SUB_{kill}) to equation (7), consider n=1, it becomes

$$\partial S(d)=-S(d)\times\left[\alpha\times\partial d+\left(1-\frac{r}{\beta u}\right)\left(1-e^{-\frac{\beta}{C}d}\right)\times\beta\times\partial d\right] \quad (8)$$

Solve the equation, we get

$$S(d)=\exp\left[-\left(\alpha+\beta-\frac{r}{u}\right)\times d-\left(C-\frac{Cr}{u\beta}\right)\times\exp\left(-\frac{\beta}{C}d\right)+K_3\right] \quad (9)$$

Substitute d=0, S(d)=1, it gives $K_3=C-\frac{Cr}{u\beta}$, thus we get

$$S(d)=\exp\left\{-\left(\alpha+\beta-\frac{r}{u}\right)\times d+\left(C-\frac{Cr}{u\beta}\right)\times\left[1-\exp\left(-\frac{\beta}{C}d\right)\right]\right\} \quad (10)$$

Result and discussion

Evaluation parameter D

Seeing equation (10), the single lethal DSB contribute the part -αd and the sublethal DSB contribute the part $-\left(\beta-\frac{r}{u}\right)\times d+\left(C-\frac{Cr}{u\beta}\right)\times\left[1-\exp\left(-\frac{\beta}{C}d\right)\right]$. Referring to the parameter D=α/β in LQ, similar D value in the TC model could be given as the solution of the Transcendental equation $\left(\beta-\frac{r}{u}-\alpha\right)\times d=\left(C-\frac{Cr}{u\beta}\right)\times\left[1-\exp\left(-\frac{\beta}{C}d\right)\right]$.

Slope k and comparing

It is common to scale the cell survival curve in log(or ln) with the survival rate, transfer equation (10) as

$$\ln S(d)=-\left(\alpha+\beta-\frac{r}{u}\right)\times d+\left(C-\frac{Cr}{u\beta}\right)\times\left[1-\exp\left(-\frac{\beta}{C}d\right)\right] \quad (11)$$

The slope k of $\ln S(d)$ could be calculated as $\partial[\ln S(d)]/\partial d$, it gives $k = -(\alpha + \beta - \frac{r}{u}) + (\beta - \frac{r}{u}) \times \exp\left(-\frac{\beta d}{C}\right)$. While d is very low, k=-α ; and while d is high enough, $k = -(\alpha + \beta - \frac{r}{u})$. It indicates: at low dose region, single lethal DSB dominate the cell killing; at high dose region, both the lethal and sublethal DSB contribute to cell killing. This case could be explained as: after the delivered high dose, the cell is "weak" enough and full of sensitivity "target", thus all the sublethal DSB occurring could be lethal.

Comparing to LQ model, multi-target single-hit model and LPL model

Contrast to the LQ model, the TC model also presents radio-sensitivity increasing while the delivered dose increasing. But the TC model predicts a killing rate limit, which dose not exist in the LQ model for the continue bending tail. (Fig.4)

Contrast to the Multi-target single-hit model, the TC model don't have the problem with the low dose flat, and also the key difficulty with the concept of "target" was well explained in molecular mechanics.

Contrast to the LPL model, the TC model extends the simple parameters to α, β, C and r/u with reasonable physics and biology explanations.

And comparing to the other model (LQ, multi-target single-hit and LPL), the TC model directly gives the dose rate as a sensitivity parameter in the equation. It indicate the increasing dose rate provide inverse effect to repairing ability in normal situation (C>0). This result also accords to some early studies [5,6,7]. But the reported inverse dose rate effect [8,9] still can't be explained by this equation unless the C<0.

Low dose hypersensitivity

There has been considerable interest in studies indicating that some cell lines respond to low

radiation doses with an increased cell kill per Gy, termed “low dose hypersensitivity” (HRS). This phenomenon has been demonstrated in vitro and in vivo[10 – 14]. The “Induced-Repair”(IR) model based on LQ model explained this phenomenon by assuming the α value in LQ model was not a constant at the sub-gray level [15,16]. In the TC model, if we consider the idea of “Induced-Repair” for the parameter r. It is reasonable to assume the r with the form like $r = r_m\left[1-\exp(-\lambda d)\right]$, where r_m is the threshold of molecular repairing ability, λ is the sensitivity parameter of DNA repairing response after delivered dose d. Then, equation (10) become

$$S(d)=\exp\left\{-\left(\alpha+\beta-\frac{r_m\left[1-\exp(-\lambda d)\right]}{u}\right)\times d+\left(C-\frac{Cr_m\left[1-\exp(-\lambda d)\right]}{u\beta}\right)\times\left[1-\exp\left(-\frac{\beta}{C}d\right)\right]\right\} \quad (12)$$

The evaluation of equation (12) plot showed in Fig.5 fit well with the observed data including sub-dose hypersensitivity region.

Conclusion

The TC model showed advantages to the previous three models (LQ, multi-target single-hit and LPL model).

1. It solves the problem that happened to LQ model at high dose region for its continuous bending tail.
2. It doesn’t have the unreasonable flat at low dose region of multi-target single-hit model.
3. It gives the quantitative parameters in form of equation for evaluating the survival rate.
4. It was directly Inferential reasoning from the physical and biological model under reasonable assumptions.
5. It directly gives the effect of dose rate in the equation.

6. It could also explain the low dose hypersensitivity well by combining with the IR model.

Thus, we conclude the TC model the new advanced model of radiation cell killing and fit the cell survival curve well.

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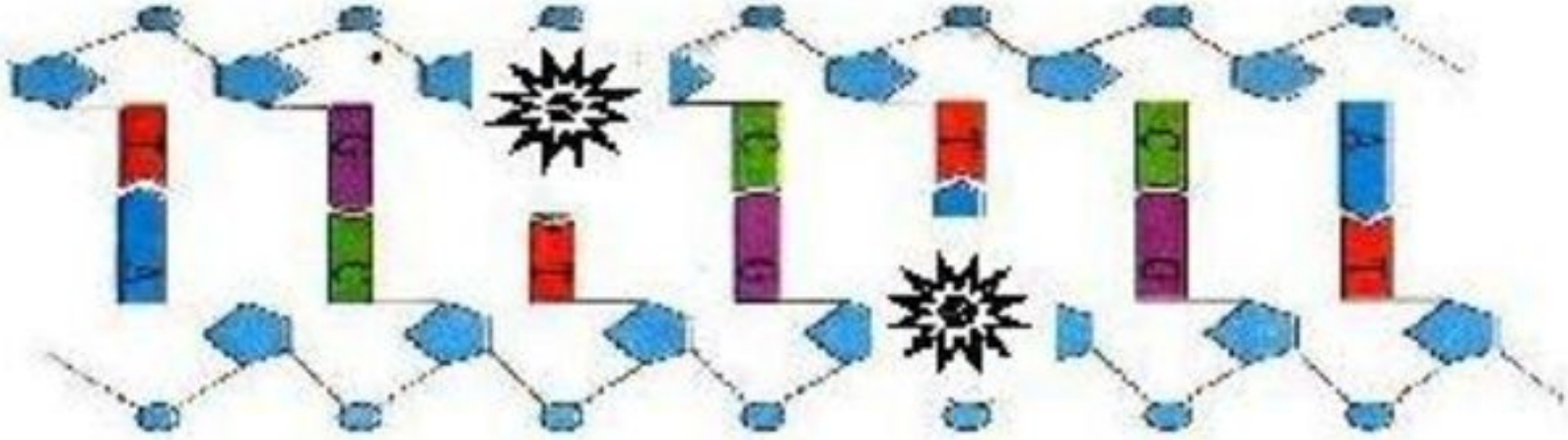

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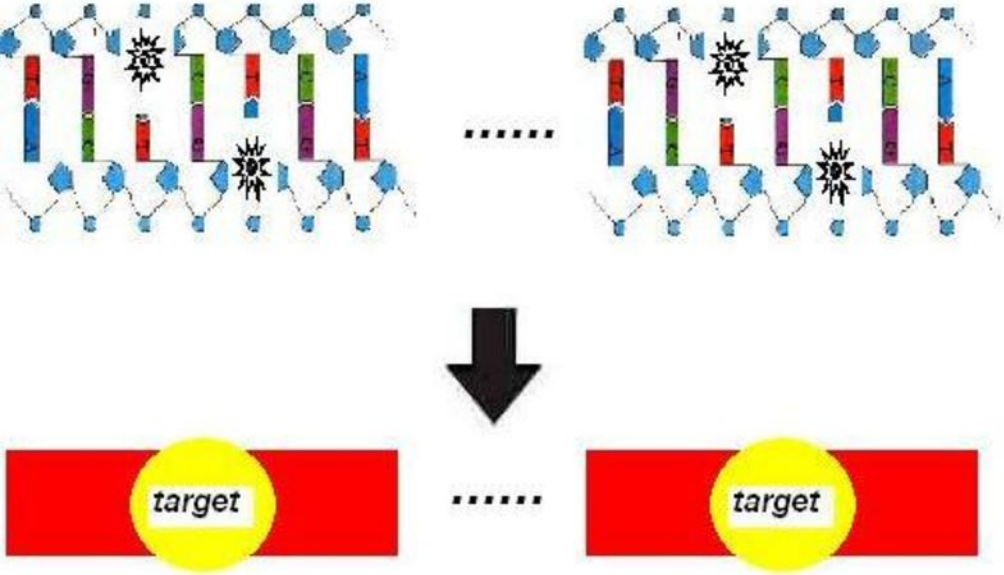

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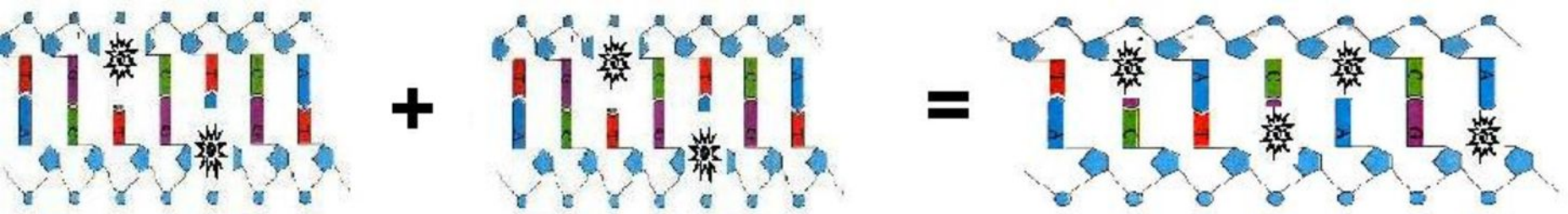

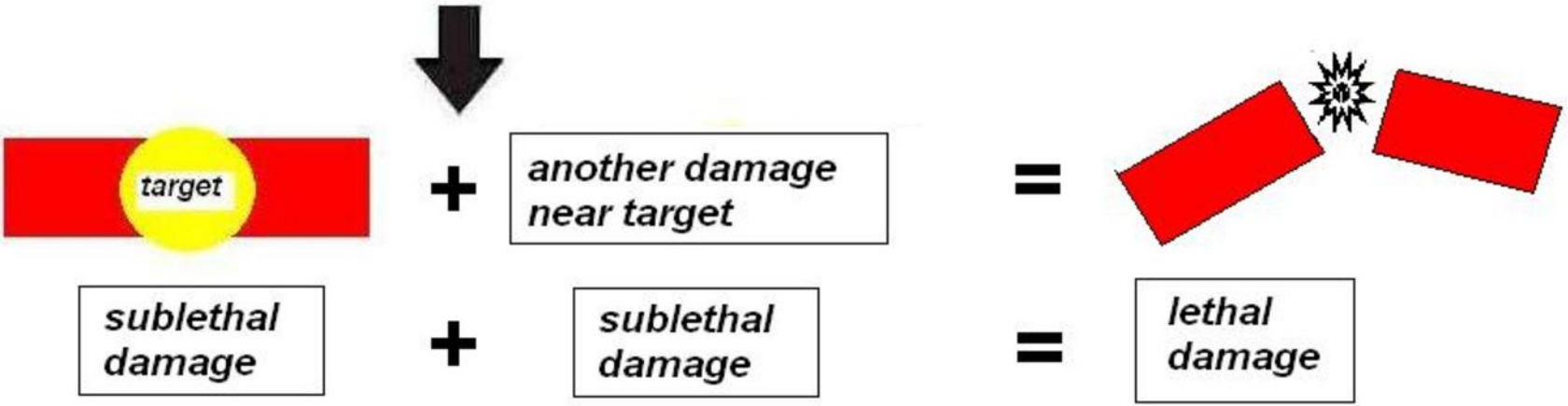
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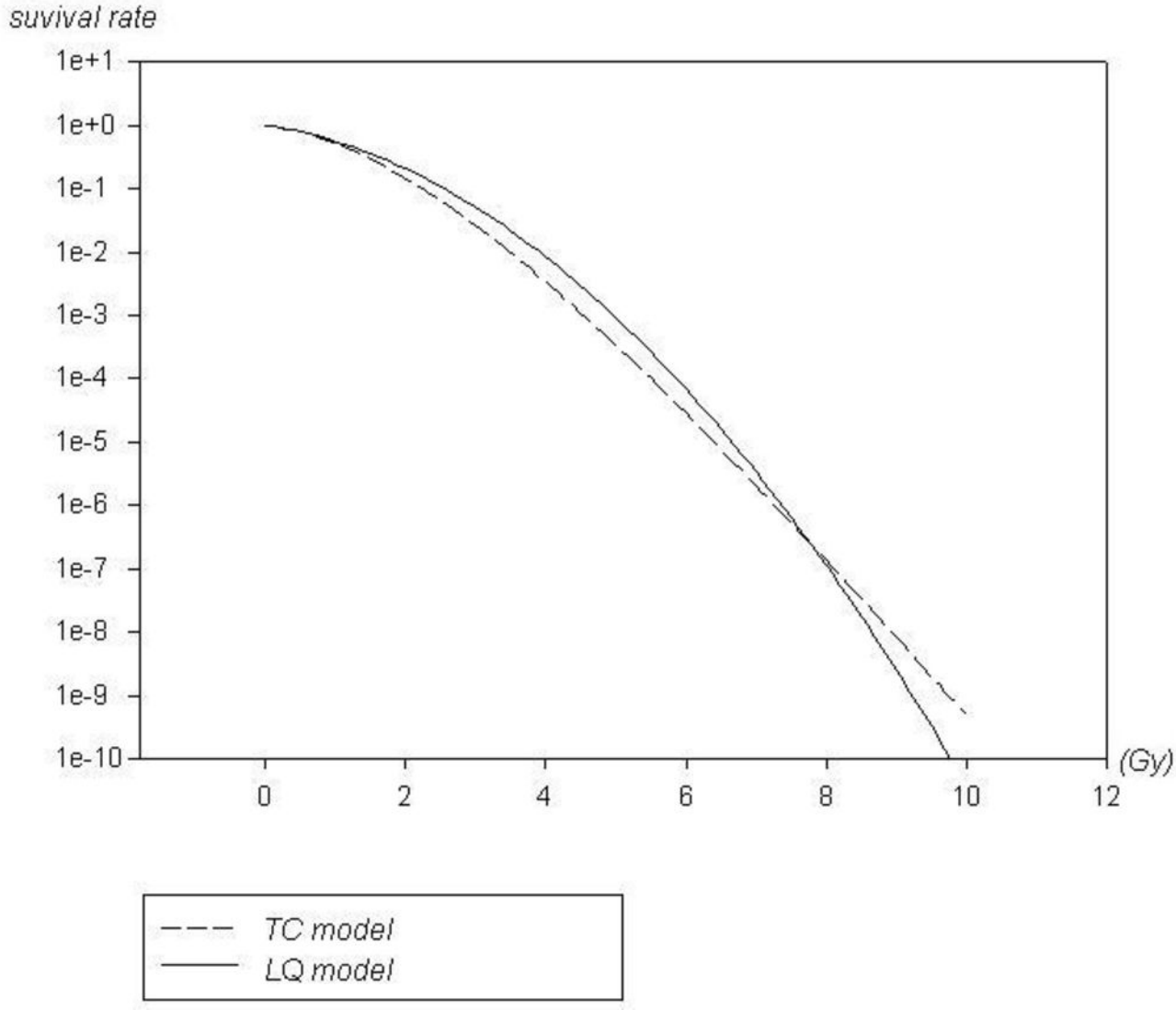
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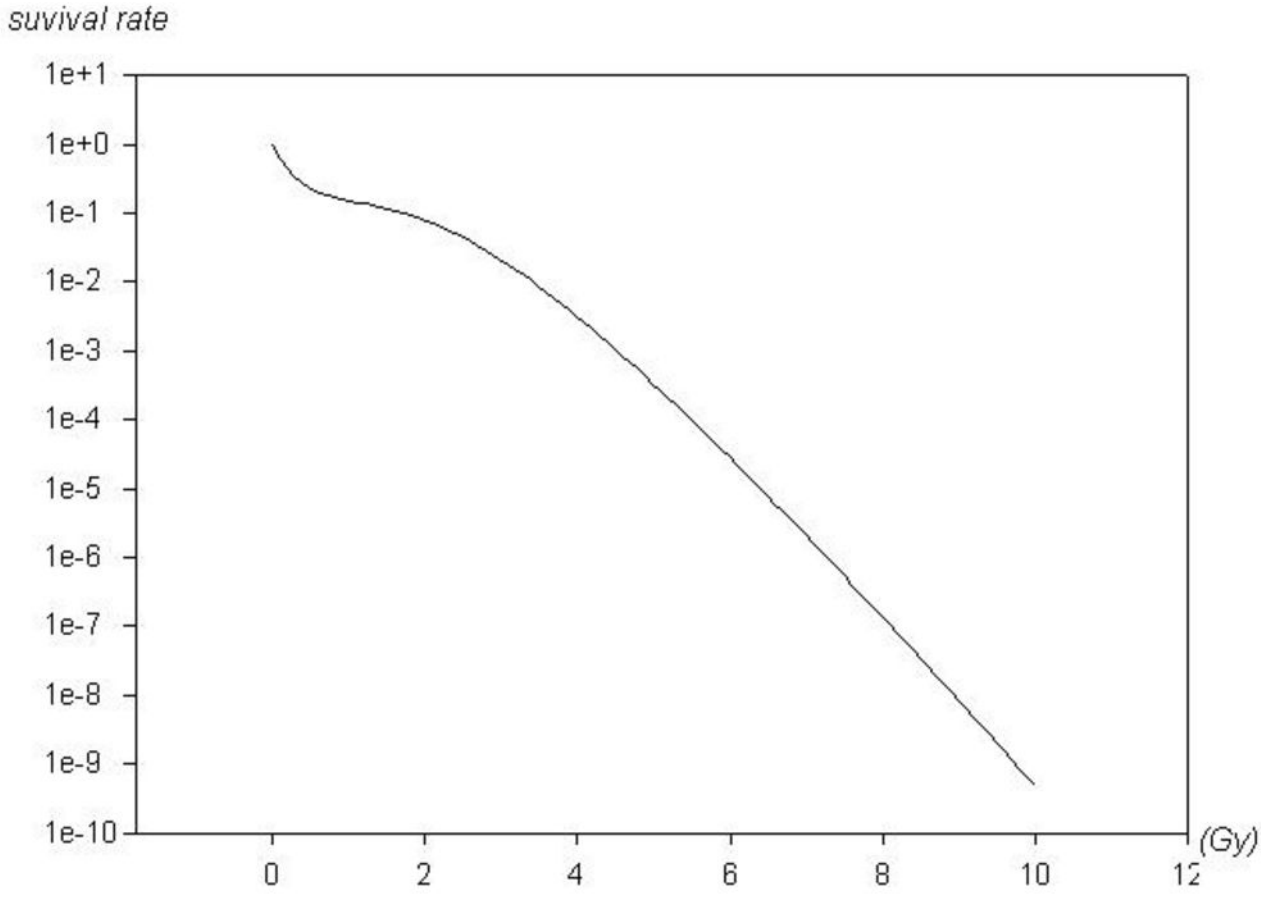
(Gy)
TC model
LQ model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