Pesquisa e Ensino em Ciências Exatas e da Natureza
7: e1987 (2023)
Research and Teaching in Exact and Natural Sciences

ARTIGO

ISSN 2526-8236 (edição online)
Pesquisa e Ensino em Ciências Exatas e da Natureza

Some comments on radiobiological models and the consistent Taylor series model

Dedicatory: To the Memory of Professor Diomar Cesar Lobão.

Gustavo Benitez Alvarez[1,2] & Diomar Cesar Lobão[1,2]

(1) Master's Programme in Computational Modeling in Science and Technology, Federal Fluminense University, Av. dos Trabalhadores, 420, Vila Santa Cecília, CEP 27255-125, Volta Redonda, RJ, Brazil. E-mail: benitez.gustavo@gmail.com
(2) Department of Exact Sciences, Federal Fluminense University, Brazil. E-mail: lobaodiomarcesar@yahoo.ca

Gustavo Benitez Alvarez & Diomar Cesar Lobão (2023). Some comments on radiobiological models and the consistent Taylor series model. *Pesquisa e Ensino em Ciências Exatas e da Natureza*, 7: e1987. http://dx.doi.org/10.56814/pecen.v7i1.1987

Editor acadêmico: Fernando Antônio Portela da Cunha. **Recebido:** 31 de janeiro de 2023. **Aceito**: 18 de maio de 2023. **Publicado:** 30 de maio de 2023.

Alguns comentários sobre modelos radiobiológicos e o modelo consistente da série de Taylor

Resumo: Aqui é demonstrado matematicamente que polinômios de ordem superior são necessários para ter uma única fórmula que descreva a sobrevivência de todas as linhagens celulares em todas as faixas de dose, que o modelo Linear Quadrático é insuficiente, e que o parâmetro β deste modelo depende da faixa de dose usada para o ajuste da curva. Com base na série de Taylor e em duas hipóteses matemáticas, é possível mostrar que os parâmetros livres são dependentes entre si, e uma nova abordagem é proposta. Dados experimentais de sobrevivência celular indicam que existem pelo menos três comportamentos diferentes. A análise teórica é testada para esses três comportamentos, incluindo também cinco modelos conhecidos não baseados em séries de Taylor. Com base nos dados experimentais de sobrevivência celular é possível gerar gráficos da dose total isoefetiva no fracionamento. É realizado um estudo comparativo entre os dados experimentais e os modelos em diferentes esquemas de fracionamento. Dados experimentais mostram que o fracionamento nas faixas de dose baixa e média pode apresentar um comportamento não monotônico diferente do comportamento da maioria dos modelos. Por fim, mostra-se que para algumas linhagens celulares o hiperfracionamento apresenta um ganho terapêutico considerável, pois há casos em que a dose total isoefetiva é muito menor que a dose total no fracionamento convencional.

Palavras-chave: Radioterapia, Modelos radiobiológicos, Fracionamento de dose, Série de Taylor, Modelo LQ

Abstract: Here it is mathematically shown that higher-order polynomials are needed to have a single formula that describes the survival of all cell lines at all dose ranges, that the Linear Quadratic model is insufficient, and that the β parameter of this model is dependent on the dose range used for curve fitting. Based on the Taylor series and two mathematical hypotheses, it is possible to show that the free parameters are dependent on each other, and a new approach is proposed. Experimental cell survival data indicate that there are at least three different behaviors. The theoretical analysis is tested for these three behaviors, including also five known models not based on Taylor series. Based on experimental cell survival data it is possible to generate charts on the isoeffective total dose in fractionation. A comparative study is carried out between experimental data and models in different fractionation schemes. Experimental data show that the fractionation in the low and medium dose ranges can present a non-monotonic behavior different from the behavior of most models. Finally, it is shown that for some cell lines, hyperfractionation presents a considerable therapeutic gain, since there are cases in which the isoeffective total dose is much lower than the total dose in conventional fractionation.
Key words: Radiotherapy, Radiobiological models, Dose fractionation, Taylor series, LQ model

Introduction

This paper deals with radiobiological models that describe the survival curves of cells subjected to photon irradiation. In radiation oncology, radiobiological models are important in the search for an increasingly better radiotherapy. All existing models need to determine a certain amount of free parameters by curve fitting with experimental data. Therefore, they can be seen in some ways as phenomenological models, although some use mechanistic-radiobiologic arguments to explain the shape of the survival curve S. To date, there is no model based solely on "First Principles" that describes well the experimental data in all dose ranges: low, medium and high (Andisheh et al., 2013; Joiner & van der Kogel, 2018). Thus, all models attempt to approximately describe the mathematical relationship between S and the dose D. Furthermore, in a way all the proposed models implicitly assume that the mathematical expression for $S(D)$ must be the same for all cell lines. However, experimental data indicate that there are at least three different types of cell response to radiation that will be described in the next section.

In mathematical terms, a model with a greater number of free parameters should better fit the experimental data. The existing models can be divided into two groups: those based on Taylor series expansion (TSE) and those that deviate from it. However, models that deviate from TSE seek to hit a part of the unknown function $S(D)$, and therefore should have fewer free parameters than those based solely on TSE. If, for these models to approximate this function with accuracy similar to TSE, it is necessary that they have the same number of free parameters as TSE, then the choice of TSE is mathematically preferable, since it has a consistent and robust mathematical foundation, which makes it possible to take advantage of the relationship between the free parameters as new expansion terms are added according to the need imposed by the precision of the experimental data.

The Linear Quadratic (LQ) model is based on TSE (McMahon, 2019; Garcia et al., 2006), and has been the most used in decades. All the models proposed so far are important for several reasons. Perhaps the most important reason is that they highlight two limitations of the LQ model. First, the approximation

$$S(D) = e^{-[\alpha D+\beta D^2]} \tag{1}$$

with α and β as free parameters is insufficient to properly describe $S(D)$ $\forall D \in [0, D_{max}]$, where D_{max} is the highest dose that can be applied in a cell survival experiment at a particular cell line (McMahon, 2019; Bender & Gooch, 1962; Hug & Kellerer, 1963; Scholz & Kraft, 1994; Lind et al., 2003; Guerrero & Li, 2004; Park et al., 2008; Kavanagh & Newman, 2008; McKenna & Ahmad, 2009; Ekstrand, 2010; Wang et al., 2010; Belkić & Belkić, 2011; Andisheh et al., 2013; Shuryak & Cornforth, 2021). Second, the LQ model is also insufficient to describe $S(D)$ for all cell lines, although it presents adequate accuracy when restricted only to certain dose ranges contained in $[0, D_{max}]$, as verified by several researchers.

In many existing models it is common to assume that this relation is of type $S(D) = e^{-f(D)}$, in addition to requiring that $S(D)$ and its derivatives up to order m, denoted by $S^{(m)}(D) = \frac{d^m S}{dD^m}$, be continuous over the entire dose interval $[0, D_{max}]$. Therefore, these will be the only two mathematical hypotheses assumed in this work. With the experimental data available so far, it is not possible to perceive that there is any physico-chemical-biological phenomenon or process that indicates the discontinuity of derivatives up to order m, nor that there is any dose threshold for survival (Joiner & van der Kogel, 2018). Therefore, all models that use transition dose to mathematically break the function into dose intervals imply discontinuity of the derivatives from some value m, even if S is continuous. But this does not mean that these models do not have theoretical and practical relevance.

It seems to be consensual that radiation oncology is an interdisciplinary field, where several areas of knowledge (physics, medicine, biology, chemistry, mathematics, computing, engineering, etc.) contribute to the construction of a more complete approach with a multidisciplinary profile. Here we present an approach from a physical, mathematical and computational point of view that seeks a precise formula for $f(D)$ with the fewest possible terms in the TSE. In honor of all the importance that the LQ model had until today, and the efforts of many researchers to improve this model, we suggest calling our development the Consistent Taylor Series Model (CTS). In addition to the mathematical advantages of using the TSE mentioned above, the CTS model also has practical advantages. The first is that it would be easy to manipulate for clinical use, since it only uses polynomials. The second is that all the knowledge accumulated about the free parameters α and β of the LQ model can be used.

Other important advantages of the CTS model are the following. Instead of fitting free generic α, β and γ parameters as is done for existing models, the CTS model fits the values of the derivatives of $S(D)$ at the point D_0, where D_0 is the center of the neighborhood with radius R containing all D values for which the Taylor series converges. As the TSE can accurately represent $f(D)$, as new terms are added to the series, the values of the derivatives of $S(D)$ at the point D_0 must be better determined. This makes it possible to create an increasingly accurate and reliable database of these derivatives for each type of tissue. In contrast, the free parameters of non-TSE based models require building a new database for each model, as the α and β of the LQ model is different from the α and β from the Padé Linear Quadratic (PLQ) model for example (Belkić & Belkić, 2011; Andisheh et al., 2013). The derivatives of $S(D)$ at D_0 have a well-known mathematical interpretation, which in the future may be placed in correspondence with an interpretation in the context of the kinetics and/or dynamics of the cellular response to radiotherapy. Differently, for the free parameters of the other models it will be more laborious to make this interpretation, since each model proposes a different mathematical formula for $S(D)$. Finally, since the exact $f(D)$ is unknown it will be very difficult to guess its correct mathematical expression. In contrast, the CTS model allows one to approximate $f(D)$ with increasing precision as new terms are added to the series. For this, it is crucial that the experimental data from cell survival assays are increasingly accurate, and this is possible to be achieved with the advancement of experimental techniques and technology.

The consistent Taylor series model

To develop the CTS model it is necessary to make two mathematical hypotheses. The first (H1) consists of assuming that the dose–survival relationship is of the type

$$S(D) = e^{-f(D)} \quad \text{or} \quad f(D) = -log_e(S(D)) \quad \forall D \in [0, D_{max}]. \tag{2}$$

This hypothesis is plausible, since several existing models have this form, although this form for $S(D)$ can be derived by applying Poisson statistics (Joiner & van der Kogel, 2018). The second hypothesis (H2) is to assume that $S(D)$ and all its derivatives up to order m are continuous functions of dose. There are intense debates about the need for continuity of $S(D)$ and its derivatives, which has motivated even the emergence of new radiobiological models (Scholz & Kraft, 1994; Guerrero & Li, 2004; Park et al., 2008; Kavanagh & Newman, 2008; McKenna & Ahmad, 2009). The second hypothesis is justified because to date there is no experimental evidence to deny this continuity. Consequently, $f(D)$ and all its derivatives up to order m are also continuous functions. In other words, the derivatives $f^{(1)}(D) = -\frac{S^{(1)}(D)}{S(D)}$, $f^{(2)}(D) = -\frac{S^{(2)}(D)S(D)-S^{(1)}(D)S^{(1)}(D)}{[S(D)]^2}$, $f^{(3)}(D) = -\frac{S^{(3)}(D)[S(D)]^2-3S^{(2)}(D)S^{(1)}(D)S(D)+2[S^{(1)}(D)]^3}{[S(D)]^3}$ and so on are continuous functions $\forall D \in [0, D_{max}]$.

As $f(D)$ is unknown (Joiner & van der Kogel, 2018), and since $f(D)$ is continuously differentiable, then it can be approximated by the Taylor series around the point $D_0 \in [0, D_{max}]$ as

$$f(D) = \sum_{k=0}^{\infty} \frac{f^{(k)}(D_0)}{k!}(D - D_0)^k \quad \forall D \in [0, D_{max}]. \tag{3}$$

This TSE had already been proposed by other authors (McMahon, 2019). In this version, the exact function $f(D)$ requires determining an infinite number of coefficients that are related to the derivatives $f^{(k)}(D_0)$ (Belkić & Belkić, 2011). These coefficients are the free parameters to be determined by curve fitting with the experimental data. The greater the number of free parameters, the better the fit with the experimental data. On the other hand, the Taylor series can be represented exactly with a finite number m of terms as

$$f(D) = \sum_{k=0}^{m-1} \frac{f^{(k)}(D_0)}{k!}(D - D_0)^k + \frac{f^{(m)}(D_x)}{m!}(D - D_0)^m \quad \forall D \in [0, D_{max}], \tag{4}$$

where $D_x \in [D_0, D]$ and depends on the value of D (Burden et al., 2016). Note that in this version of the Taylor series the set of infinite free parameters $f^{(k)}(D_0)$ with $k \geq m$ is replaced by a single unknown $f^{(m)}(D_x)$. This unknown requires knowledge of the derivative $f^{(m)}(D)$ evaluated at the unknown point D_x, that is, it is necessary to know the exact mathematical expression for $f^{(m)}(D)$ and the exact value of D_x. Otherwise, we will always have an approximation of $f(D)$ whose accuracy will depend on the degree of regularity of this function and the number of free parameters. Equation (4) allows us to obtain a mathematically accurate formula for $f(D)$ with few terms of the Taylor series and consequently few free parameters, in addition to enabling our mathematical analysis of radiobiological models.

It is important to highlight that the Taylor series convergence is guaranteed by mathematical theorems (Apostol, 1967). Therefore, it is not necessary to carry out any statistical test to verify the convergence of the Taylor series, just verify the hypotheses of the theorems. However, those models whose convergence is not mathematically demonstrated need some kind of convergence guarantee, such as statistical tests. This research work uses the Taylor series to adequately

approximate $S(D)$, and the terms of the series that have been implemented so far show the need for polynomials of degree greater than six.

When $D_0 = 0$ Gy and a second order polynomial are chosen, then $f(D)$ is

$$f(D) = -S^{(1)}(0)D - \frac{[S^{(2)}(D_x)S(D_x) - S^{(1)}(D_x)S^{(1)}(D_x)]}{2[S(D_x)]^2}D^2 \tag{5}$$

because $S(D=0) = 1$, since no dose threshold for cell survival has yet been observed (Joiner & van der Kogel, 2018). Consequently, $f(0) = f^{(0)}(0) = 0$ and $f^{(1)}(0) = -S^{(1)}(0)$. Equation (5) is an exact formula if the values of $S^{(1)}(0)$, $S(D_x)$, $S^{(1)}(D_x)$ and $S^{(2)}(D_x)$ are known exactly. It should be noted that $S^{(1)}(0)$ is a constant value, and unlike the values $S(D_x)$, $S^{(1)}(D_x)$ and $S^{(2)}(D_x)$ are non-constants that depend on the value of D. Since the exact mathematical expression for $S(D)$ is unknown, these values will be approximated by curve fitting with the experimental data. Consequently, the equation (5) becomes an approximation. This approximation is mathematically equivalent to the LQ model (1), where $\alpha = f^{(1)}(0) = -S^{(1)}(0)$ e $2\beta = f^{(2)}(D_x)$. Thus, the mathematical interpretation of the parameter α is the derivative of the survival curve evaluated at $D = 0$ Gy with a negative sign. The sign of α depends on the sign of $S^{(1)}(0)$.

The experimental evidence available to date indicates that the $S(D)$ function exhibits at least three different behaviors depending on the type of cancer cell line. Long known and occurring in most cell types, in the first behavior $S(D)$ is a monotone decreasing function over the entire dose range. Several human lung cancer cell lines can be mentioned as examples of this behavior (Carmichael et al., 1989), in addition to the 12 human tumour cell lines studied in Steel et al. (1987), and some others reanalyzed in Guerrero & Li (2004) and Andisheh et al. (2013). In the second behavior initially at low doses $S(D)$ increases until reaching its absolute maximum at the point D_c, later for $D > D_c$ it becomes monotonous decreasing. Human prostate cancer cells such as CP3 cell lines (Garcia et al., 2006) are an example of this behavior. This means that for these cells low doses contribute to increase the survival of cancer cells. Third, at low doses initially $S(D)$ decreases until reaching a relative minimum at D_{c1}, from dose D_{c1} there is an increase until reaching a relative maximum at point D_{c2}, and later the function becomes monotone decreasing. This type of behavior is known as low-dose hyper-radiosensitivity (HRS) and increased radioresistance (IRR) (Krueger et al., 2007; Fernandez-Palomo et al., 2016). Among the cell lines with this behavior are: hamster fibroblast cells as CHOAA8 cell line (Garcia et al., 2006), human glioma cells as U373MG cell line (Garcia et al., 2006), human prostate cancer cells as DU145 cell lines (Garcia et al., 2006) and human glioma cell line as T98G (Fernandez-Palomo et al., 2016). Theoretically, the first and second behavior of the $S(D)$ function could be adequately described by approximating $f(D)$ by a second-order polynomial (LQ model). However, the third behavior requires at least third-order polynomials. Moreover, in the first behavior there is no experimental evidence of the existence of relative extremes, so $S^{(1)}(D) \neq 0$ $\forall D \in [0, D_{max}]$. For cells that exhibit the second behavior, the experimental data indicate the existence of a relative/absolute maximum at the point D_c, so $S^{(1)}(D_c) = 0$ and $S^{(2)}(D_c) < 0$. For cells that exhibit the third behavior, the experimental data indicate the existence of a relative minimum at the point D_{c1} ($S^{(1)}(D_{c1}) = 0$ and $S^{(2)}(D_{c1}) > 0$) and a relative maximum at point D_{c2}. These relative extreme points should be understood as transition points in the radiobiological context, where the $S(D)$ can change its behavior. In other words, they are dose values at which cells for some reason change their response to radiation.

It should be noted that our approach shows that in the LQ model, unlike α, the parameter β depends on the unknown point D_x. This means that β is not a constant and its value will depend on the dose range that corresponds to the experimental data being analyzed. In Garcia

et al. (2006) an equivalent conclusion is reached by performing curve fitting experiments at different dose intervals for various cell lines. Often, in clinical practice for each tissue type it is common to assume β as being constant, and even more $\frac{\alpha}{\beta}$ a fixed value that is related to the early or late response of the cells tissue to radiation regardless of the dose range under analysis (Joiner & van der Kogel, 2018; Garcia et al., 2006, 2007). Our mathematical analysis shows that these radiobiological claims are not completely verified by the LQ model, since $\frac{\alpha}{\beta} = \frac{2S^{(1)}(0)[S(D_x)]^2}{[S^{(2)}(D_x)S(D_x) - S^{(1)}(D_x)S^{(1)}(D_x)]}$ depends on D_x. In Steel et al. (1987), using the LQ model, the expression for split-dose recovery ratio $e^{(2\beta d^2)}$ for 12 human tumour cell lines is studied. In three cell lines this expression greatly underestimates the observed recovery, and in another cell line this expression considerably overestimates. As an explanation the authors say that "*the scatter in these results may be due to the fact that recovery ratio in the equation given above depends steeply on the value of* β *(which is often poorly defined by cell survival data)*". In addition, one of the conclusions obtained in Garcia et al. (2007) is that the α and β parameters depend on the dose range used to perform the curve fitting, and that this strongly impacts the $\frac{\alpha}{\beta}$ ratio. Subsequently, our analysis will show that the β parameter, in addition to being dose dependent (D_x) in the LQ model, also depends on the α parameter.

To have a parameter β independent of the dose D_x it is necessary to choose a third order polynomial. In this way, if $D_0 = 0$ Gy is obtained

$$f(D) = f^{(1)}(0)D + \frac{1}{2}f^{(2)}(0)D^2 + \frac{1}{6}f^{(3)}(D_x)D^3, \tag{6}$$

where $f^{(1)}(0)$, $f^{(2)}(0)$ and $f^{(3)}(D_x)$ must be determined by fitting the experimental data. Note that now $f^{(1)}(0) = \alpha$, $f^{(2)}(0) = 2\beta$ and $f^{(3)}(D_x) = 6\gamma$. The α parameter remains the same, but the β parameter is different from the LQ model as it is not dose dependent D_x. That is, $\beta = -\frac{[S^{(2)}(0) - S^{(1)}(0)S^{(1)}(0)]}{2}$. Only the γ parameter depends on the unknown point D_x. Always the parameter corresponding to the highest power of the polynomial will be dependent on the dose range used in the experiment so that $f(D)$ is exact, since it depends on finding $f^{(m)}(D_x)$. Determining a good bound for $f^{(m)}(D_x)$ on a given interval is considered a difficult problem in numerical analysis (Burden et al., 2016). This analysis shows that the free parameters obtained via curve fitting in a certain dose range should not be used to estimate $S(D)$ in doses that extrapolate this dose range, since the last free parameter explicitly depends on the range used in the curve fitting.

To fit the $S(D)$ curve, taking advantage of the implications of hypotheses H1 and H2, it is convenient to define $\hat{\beta} = -S^{(2)}(0)$ and $\check{\gamma} = f^{(3)}(D_x)$. In this way $\beta = \frac{1}{2}(\hat{\beta} + \alpha^2)$, $\gamma = \frac{\check{\gamma}}{6}$ and

$$S(D) = e^{-[\alpha D + \frac{1}{2}(\hat{\beta}+\alpha^2)D^2 + \frac{1}{6}\check{\gamma}D^3]}, \tag{7}$$

where α, $\hat{\beta}$ and $\check{\gamma}$ are the free parameters to be determined by fitting the experimental data. It should be noted that α influences the value of β, but not of $\hat{\beta}$. Also, now $\frac{\alpha}{\beta} = \frac{2S^{(1)}(0)}{[S^{(2)}(0) - S^{(1)}(0)S^{(1)}(0)]} = \frac{2\alpha}{[\hat{\beta}+\alpha^2]} = \frac{2\frac{\alpha}{\beta}}{[1+\alpha\frac{\alpha}{\beta}]}$ is a fixed value that does not depend on the dose range being analyzed (D_x), and this must be its mathematical interpretation because it remains the same when $f(D)$ is approximated by a higher order polynomial than three. It is interesting to note that $\frac{\alpha}{\hat{\beta}} = \frac{S^{(1)}(0)}{S^{(2)}(0)}$, that is, the ratio of the first two derivatives of the survival curve in $D_0 = 0$ Gy.

Furthermore, as a consequence of hypothesis H1 it is possible to show mathematically that the curvature of $S(D)$ is related to $\hat{\beta}$ and not to β. Considering a two-dimensional space, the

curvature of $S(D)$ is defined for each dose value D as $\kappa = \frac{\left|S^{(2)}(D)\right|}{[1+[S^{(1)}(D)]^2]^{3/2}}$, and its corresponding radius of curvature at this point is $\rho = \frac{1}{\kappa}$ (Apostol, 1967). The sign of $S^{(2)}(D)$ determines the type of concavity of the graph. If $S^{(2)}(D) > 0$ the graph has an upward concavity. If $S^{(2)}(D) < 0$ the graph has a downward concavity. If $S^{(2)}(D) = 0$, then there exists for this value D an inflection point of the curve or a relative extreme. Our development indicates that at the point $D = 0$ Gy the curvature of $S(D)$ is $\kappa = \frac{|\hat{\beta}|}{[1+\alpha^2]^{3/2}}$, and the concavity of the graph is determined by the sign of $\hat{\beta}$. In other words, the slope of $S(D)$ at the point $D = 0$ Gy and its curvature are determined by the free parameters α and $\hat{\beta}$. If only a second order polynomial is used, then the second free parameter β becomes dependent on the dose range used for the curve fitting. This justifies the need for a higher order polynomial. In the future, with this mathematical basis, it will be possible to assign to the free parameters a radiobiological interpretation in context of the kinetics and/or dynamics of the cellular response to radiotherapy.

If the free parameters are not redefined as above to take advantage of hypotheses H1 and H2, then the standard TSE model for third order polynomial would be

$$S(D) = e^{-[\alpha D+\beta D^2+\gamma D^3]}. \tag{8}$$

This model is similar to the Linear-Quadratic-Cubic model (Joiner & van der Kogel, 2018), but with the difference that our approach does not impose any restrictions on the sign of the third-order coefficient. Often in the literature constraints are imposed on the signs of the free parameters to avoid 'misestimated' $\frac{\alpha}{\beta}$ ratios (Guerrero & Li, 2004). The signs of the free parameters must naturally arise from the curve fitting, and they are related to the sign of the different derivatives of $S(D)$ at the point D_0.

Similarly, the procedure can be repeated for $D_0 = 0$ Gy and a fourth order polynomial. Thus $\alpha = -S^{(1)}(0)$, $\hat{\beta} = -S^{(2)}(0)$, $\beta = \frac{1}{2}(\hat{\beta}+\alpha^2)$, $\hat{\gamma} = -S^{(3)}(0)$, $\gamma = \frac{1}{6}(\hat{\gamma}+3\alpha\hat{\beta}+2\alpha^3)$, $\check{\lambda} = f^{(4)}(D_x)$, $\lambda = \frac{1}{24}\check{\lambda}$ and

$$S(D) = e^{-[\alpha D+\frac{1}{2}(\hat{\beta}+\alpha^2)D^2+\frac{1}{6}(\hat{\gamma}+3\alpha\hat{\beta}+2\alpha^3)D^3+\frac{1}{24}\check{\lambda}D^4]}, \tag{9}$$

where α, $\hat{\beta}$, $\hat{\gamma}$ and $\check{\lambda}$ are the free parameters to be determined by fitting the experimental data. Now γ depends on α and $\hat{\beta}$, but not $\hat{\gamma}$. This interdependence between the model parameters implies that their values determined by the fit with the experimental data will have small changes as the higher order terms of the series are added. However, these small modifications tend to have a limit, since the Taylor series is convergent. Therefore, starting from some specific value of k it is to be expected that $\left|f^{(k)}(0)\right| > \left|f^{(k+1)}(0)\right| > \left|f^{(k+2)}(0)\right| >> \left|f^{(m)}(D_x)\right|$, indicating that higher order terms contribute less and less. In other words, the more terms in the series, the more accurate these parameters will be, and this will be shown in Tables 1, 2 and 3. The ratio $\frac{\alpha}{\beta}$ remains the same, and new ratios arise that do not depend on D_x like $\frac{\beta}{\gamma}$ and $\frac{\alpha^2}{\gamma}$. All of these ratios are dose specific values that may have radiobiological significance. In this case the standard TSE model would be

$$S(D) = e^{-[\alpha D+\beta D^2+\gamma D^3+\lambda D^4]}. \tag{10}$$

In this way, the standard CTS and TSE models for polynomials of degree five and six are obtained.

$$S(D) = e^{-[\alpha D+\frac{1}{2}(\hat{\beta}+\alpha^2)D^2+\frac{1}{6}(\hat{\gamma}+3\alpha\hat{\beta}+2\alpha^3)D^3+\frac{1}{24}(\hat{\lambda}+4\hat{\gamma}\alpha+3\hat{\beta}^2+12\alpha^2\hat{\beta}+6\alpha^4)D^4+\frac{1}{120}\check{\mu}D^5]}, \tag{11}$$

where $\hat{\lambda} = -S^{(4)}(0)$, $f^{(4)}(0) = \hat{\lambda} + 4\alpha\hat{\gamma} + 3\hat{\beta}^2 + 12\alpha^2\hat{\beta} + 6\alpha^4$, $\breve{\mu} = f^{(5)}(D_x)$ and $\mu = \frac{1}{120}\breve{\mu}$.

$$S(D) = e^{-[\alpha D + \beta D^2 + \gamma D^3 + \lambda D^4 + \mu D^5]}. \tag{12}$$

$$S(D) = e^{-[\alpha D + \frac{1}{2}(\hat{\beta}+\alpha^2)D^2 + \frac{1}{6}(\hat{\gamma}+3\alpha\hat{\beta}+2\alpha^3)D^3 + \frac{1}{24}(\hat{\lambda}+4\hat{\gamma}\alpha+3\hat{\beta}^2+12\alpha^2\hat{\beta}+6\alpha^4)D^4 + \frac{1}{120}\breve{\mu}D^5 + \frac{1}{720}\breve{\eta}D^6]}, \tag{13}$$

where $\hat{\mu} = -S^{(5)}(0)$, $f^{(5)}(0) = \breve{\mu} = \hat{\mu} + 5\alpha\hat{\lambda} + 10\hat{\beta}\hat{\gamma} + 20\alpha^2\hat{\gamma} + 30\alpha\hat{\beta}^2 + 60\alpha^3\hat{\beta} + 24\alpha^5$, $\breve{\eta} = f^{(6)}(D_x)$ and $\eta = \frac{1}{720}\breve{\eta}$.

$$S(D) = e^{-[\alpha D + \beta D^2 + \gamma D^3 + \lambda D^4 + \mu D^5 + \eta D^6]}. \tag{14}$$

Finally, the standard TSE model for a polynomial of degree seven is given by equation (15)

$$S(D) = e^{-[\alpha D + \beta D^2 + \gamma D^3 + \lambda D^4 + \mu D^5 + \eta D^6 + \nu D^7]}. \tag{15}$$

Thus, what is being estimated by the least squares fit when using CTS models are the derivatives of $S(D)$ evaluated at the point $D = 0$ Gy. However, when the standard TSE model is used, we are estimating mathematical relationships between the derivatives of $S(D)$ evaluated at the point $D = 0$ Gy. In other words, the parameters α, $\hat{\beta}$, $\hat{\gamma}$, ... are independent of each other, while the parameters α, β, γ, ... are dependent on each other. In Garcia et al. (2007), it was shown through numerical experiments of curve fitting for different dose ranges that in the region of low doses the parameters α and β present large uncertainties, and that they are highly negatively correlated. Finally, it must be said that the more accurate the experimental data is, it will be necessary to increase the degree of the polynomial. However, this analysis predicts that if exact $f(D)$ is a polynomial of finite order m, then $f^{(m+1)}(D_x) = 0$, otherwise higher order terms must be entered from the series.

Dose fractionation, isoeffect and entire survival curve

The isoeffect E of a fractionation with n equal doses d such that the isoeffective total dose $D = nd$ is $E = -n\log_e(S(d)) = nf(d)$, where $S(d)$ is the entire survival curve $\forall d \in [0, D_{max}]$ (Joiner & van der Kogel, 2018). If $f(d)$ is known exactly, then for two fractionation schemes $D_1 = n_1 d_1$ and $D_2 = n_2 d_2$ the same isoeffect is $E = n_1 f(d_1) = n_2 f(d_2)$. Thus,

$$\frac{D_1}{D_2} = \frac{\alpha + \sum_{k=2}^{m-1}\left[\frac{f^{(k)}(0)}{k!}d_2^{(k-1)}\right] + \frac{f^{(m)}(d_{x2})}{m!}d_2^{(m-1)}}{\alpha + \sum_{k=2}^{m-1}\left[\frac{f^{(k)}(0)}{k!}d_1^{(k-1)}\right] + \frac{f^{(m)}(d_{x1})}{m!}d_1^{(m-1)}}, \tag{16}$$

where the unknown values $d_{x1} \in [0, d_1]$ and $d_{x2} \in [0, d_2]$. Here, it is assumed that all free parameters $f^{(k)}(0)$ were obtained with the same curve fit performed in the dose range $[0, D_{max}]$. For this reason, the same values can be considered for the $f^{(k)}(0)$ appearing in the numerator and denominator of (16). However, this is not valid for the last free parameter obtained in the curve fitting, since this parameter depends on unknown value of dose. That is, the last free parameter obtained from curve fitting is $f^{(m)}(D_x)$, and in general $f^{(m)}(D_x) \neq f^{(m)}(d_{x1}) \neq f^{(m)}(d_{x2})$.

In practice, when $f(d)$ is approximated by a polynomial of degree m $\forall d \in [0, D_{max}]$, then $E_1 = n_1 f(d_1) \approx n_2 f(d_2) = E_2$. In this case, the same isoeffect is guaranteed if the fractions d_1 and d_2 belong to the same dose range used to determine the free parameters in the curve fitting. So, equation (16) which is exact will be approximated by

$$\frac{D_1}{D_2} \cong \frac{\alpha + \sum_{k=2}^{m-1}\left[\frac{f^{(k)}(0)}{k!}d_2^{(k-1)}\right] + \frac{f^{(m)}(D_x)}{m!}d_2^{(m-1)}}{\alpha + \sum_{k=2}^{m-1}\left[\frac{f^{(k)}(0)}{k!}d_1^{(k-1)}\right] + \frac{f^{(m)}(D_x)}{m!}d_1^{(m-1)}}. \tag{17}$$

The error to assume $f^{(m)}(d_{x1}) = f^{(m)}(d_{x2}) = f^{(m)}(D_x)$ should not be very large, since when there is convergence the higher order terms tend to contribute less to the series. Therefore, when making comparisons between two different fractionation schemes, it is necessary that the two fractions d_1 and d_2 belong to the same dose range in which the data fit was performed. This is because the determination of free parameters depends on the dose range in which the fit is being made (Joiner & van der Kogel, 2018). This is one of the reasons for the need to have an $S(D)$ that describes survival over the entire dose range $[0, D_{max}]$ to which a given cell line can be subjected. In other words, if d_1 corresponds to low doses and d_2 to high doses, and if the experimental data for the fit of $f(D)$ do not contain values in these two dose ranges, then great care must be taken because the free parameters obtained for each range may be different. Similar recommendations are made in Joiner & van der Kogel (2018) when it is said that $\frac{\alpha}{\beta}$ is dose dependent.

In addition, the Biological Effective Dose (BED) defined as $BED = \frac{E}{\alpha}$ will be

$$BED(d_x) = D\Big[1 + \sum_{k=2}^{m-1} \frac{f^{(k)}(0)}{\alpha k!} d^{(k-1)} + \frac{f^{(m)}(d_x)}{\alpha m!} d^{(m-1)}\Big], \tag{18}$$

where $d_x \in [0, d]$. In the particular case that $m = 2$, the well-known formula for the BED of the LQ model is obtained. For $m = 3$ and $m = 4$ the CTS and TSE models generate the equations (19) and (20)

$$BED(d_x) = D\Big[1 + \frac{1}{2}\Big(\frac{\hat{\beta}}{\alpha} + \alpha\Big)d + \frac{\check{\gamma}(d_x)}{6\alpha} d^2\Big] = D\Big[1 + \frac{\beta}{\alpha} d + \frac{\gamma(d_x)}{\alpha} d^2\Big]. \tag{19}$$

$$\begin{aligned} BED(d_x) &= D\Big[1 + \frac{1}{2}\Big(\frac{\hat{\beta}}{\alpha} + \alpha\Big)d + \frac{1}{6}\Big(\frac{\hat{\gamma}}{\alpha} + 3\hat{\beta} + 2\alpha^2\Big)d^2 + \frac{\check{\lambda}(d_x)}{24\alpha} d^3\Big] \\ &= D\Big[1 + \frac{\beta}{\alpha} d + \frac{\gamma}{\alpha} d^2 + \frac{\lambda(d_x)}{\alpha} d^3\Big]. \end{aligned} \tag{20}$$

In a similar way formulas for Equivalent Dose in 2 Gy Fractions (EQD2) and Total Effect (TE) can be obtained. Note that BED, EQD2 and TE depend on the fraction d and the value d_x. Therefore, they depend on the dose range used to determine the free parameters. Furthermore, $BED = \frac{E}{\alpha}$ and $TE = \frac{E}{\beta}$ explicitly use free parameters α and β in their definition, so this implies possible extra errors when compared to another definition that does not explicitly use any free parameters like the equation (16).

Analysis of experimental data

Our approach is applied to the three cell survival behaviors mentioned above. As an example for each behavior were chosen: H460 non-small cell lung cancer cell line (Andisheh et al., 2013), CP3 human prostate cancer cells line (Garcia et al., 2006), and CHOAA8 hamster fibroblast cells line (Garcia et al., 2006). The CTS model using polynomials of order 3, 4, 5 and 6 are analyzed. In addition, the standard TSE model using polynomials of order 2, 3, 4, 5, 6 and 7 are analyzed. Also, by way of comparison, the results of curve fittings are presented for four other known models whose functions $S(D)$ and their derivatives are continuous up to order m. The first is the PLQ model (Belkić & Belkić, 2011; Andisheh et al., 2013) described by (21). The other two are the McKenna and Ahmad (MA) (McKenna & Ahmad, 2009) and Hug and Kellerer (HK) (Hug & Kellerer, 1963; Ekstrand, 2010) models described by (22) and (23). The

last model are two versions proposed by Kavanagh and Newman (Kavanagh & Newman, 2008). Equation (24) is the initial model with two free parameters, and (25) introduces two other free parameters to account for the repair effects that occur in the low-dose hypersensitivity region.

$$S(D) = e^{-\frac{(\alpha D+\beta D^2)}{(1+\gamma D)}} \text{ PLQ model.} \tag{21}$$

$$S(D) = e^{-[\alpha D+\frac{\beta D^2}{(1+\beta D/\gamma)}]} \text{ MA model.} \tag{22}$$

$$S(D) = e^{[-\alpha D+\beta(1-e^{-\gamma D})]} \text{ HK model.} \tag{23}$$

$$S(D) = e^{[-\alpha D(1-e^{-\beta D})]} \text{ KN-1 model.} \tag{24}$$

$$S(D) = e^{[-\alpha D(1-e^{-\beta D})-\gamma D e^{-\lambda D}]} \text{ KN-2 model.} \tag{25}$$

It must be said that there are significant mathematical differences to determine the free parameters of the models by the method of least squares. For TSE models the problem can be transformed into finding the solution of a linear system of algebraic equations, while for CTS models it is necessary to solve a nonlinear system of algebraic equations. The dimension of the linear and nonlinear system increases when the order of the Taylor polynomial increases. The linear system will have a unique solution if the matrix is non-singular. However, the nonlinear system can have more than one unique solution. Furthermore, solving the nonlinear system can be more complicated than solving the linear system, since numerical challenges can arise that affect the convergence of the solution of the nonlinear system. In future works, a more in-depth study on this should be carried out.

On the other hand, the CTS model becomes the TSE model if the free parameters are determined as follows. First the free parameters of the TSE model are determined by the least squares method, and later the parameters of the CTS model are determined by solving the equations that establish the relationship between the derivatives of $S(D)$. That is, $\alpha_{TSE} = \alpha_{CTS}$, $\beta_{TSE} = \frac{1}{2}(\beta_{CTS} + \alpha_{TSE}^2)$, $\gamma_{TSE} = \frac{1}{6}(\gamma_{CTS} + 3\alpha_{TSE}\beta_{CTS} + 2\alpha_{TSE}^3)$ and so on. However, here the free parameters of the CTS model are determined directly by the least squares method. Two computational codes were developed using the MATLAB® software. Similar results for curve fitting were obtained using the MATLAB® functions 'fminsearch' and 'lsqnonlin'. In Tables 1, 2 and 3 are presented the results obtained with the 'lsqnonlin' function that solves a nonlinear least-squares problem. Default options of the 'lsqnonlin' function were used and the data was not weighted, that is, curve fittings were performed assuming that all data have the same weight equal to 1. As can be seen in Tables 1, 2 and 3, the solutions of the CTS and TSE models shown here are different. The computational codes were executed on a PC 64-bit Operating System Windows 7 Ultimate with an Intel(R) Core(TM) i7 CPU 860 @ 2.80 GHz and 8 GB of RAM. It can be stated that the computational effort (memory + time) demanded by the code is low. Memory usage is less than 30% of available resources on used PC. The time needed to run all the calculations of all the models and build the figures is less than 10 seconds.

It should be remembered that the derivative of $S(D)$ vanishes at critical points D_c ($S^{(1)}(D_c) = 0$), which are called transition points in the radiobiological context. The TSE and CTS models have a similar condition for the existence of critical points determined by

$$\alpha + 2\beta D_c + 3\gamma D_c^2 + 4\lambda D_c^3 + 5\mu D_c^4 + 6\eta D_c^5 + 7\nu D_c^6 = 0. \tag{26}$$

The other models present the following constraints for the critical points.

$$\beta\gamma D_c^2 + 2\beta D_c + \alpha = 0 \text{ for PLQ model.} \tag{27}$$

$$\frac{\beta^2}{\gamma}(1+\frac{\alpha}{\gamma})D_c^2+2\beta(1+\frac{\alpha}{\gamma})D_c+\alpha=0 \text{ for MA model.} \tag{28}$$

$$\beta\gamma e^{-\gamma D_c}=\alpha \text{ for HK model.} \tag{29}$$

$$(1-\beta D_c)=e^{\beta D_c} \text{ for KN-1 model.} \tag{30}$$

$$\alpha[-1+(1-\beta D_c)e^{-\beta D_c}]=\gamma[1-\lambda D_c]e^{-\lambda D_c} \text{ for KN-2 model.} \tag{31}$$

Thus, the PLQ and MA models can describe up to the two critical points. However, if new critical points arise with the advance in the precision of the experimental data, these models could not consider these new critical points. The HK and KN-1 models only present one critical point. The KN-2 model apparently can describe up to two critical points, but it is difficult to estimate how many points there are since the equation (31) is transcendental with four free parameters. For example, the NK-2 model has no critical point for H460 and CHOAA8 cells, and has a single critical point for CP3 cells. It should be noted that only for the KN-1 model does the critical point depend on a single free parameter. For all other models the critical points always depend on all free parameters of the model.

Tables 1, 2 and 3 present the values of the free parameters for all models, whose intention is not to show which is the best model, although it can be noticed that as the number of free parameters increases (degree of the polynomial) the sum of residuals squared (SRS) decreases as a trend. For this reason, no statistical test was used to compare the models, and experimental errors were not considered. Only the results of a mathematical problem of curve fitting using the least squares method are shown, where the fitting parameters are related to the Taylor series coefficients.

Behavior 1. In the case of H460 cell line, the function $S(D)$ does not show evidence of the existence of relative extreme points. Thus, the critical points that exist must be inflection points of the curve or the relative extremes correspond to negative values of D_c. Table 1 shows the free parameters for all models. In Tables 1, 2 and 3 the last column always represents the SRS. In columns with different versions of the parameter, it must be understood that the value corresponds to the parameter defined in the model equation. For reasons of space, the physical units of the free parameters are not included in the tables, but it should be understood that the units of each parameter is a power of $(1/\text{Gy})^k$ because the dose is measured in Gy.

Table 1: Least squares fit for the H460 cell line.

Model	α	β, $\hat{\beta}$	γ, $\hat{\gamma}$, $\check{\gamma}$	λ, $\hat{\lambda}$, $\check{\lambda}$	μ, $\hat{\mu}$, $\check{\mu}$	η, $\check{\eta}$	ν	SRS
LQ (1)	0.222	0.0489	—	—	—	—	—	2.073
TSE (8)	-0.0712	0.112	-0.00298	—	—	—	—	0.576
TSE (10)	0.105	0.0393	0.00523	-0.000272	—	—	—	0.405
TSE (12)	0.431	-0.170	0.0463	-0.00341	0.0000818	—	—	0.166
TSE (14)	0.146	0.0982	-0.0352	0.00726	-0.000545	0.0000135	—	0.087
TSE (15)	-0.192	0.538	-0.224	0.0442	-0.00417	0.000187	-0.00000323	0.042
CTS (7)	-0.0712	0.220	-0.0179	—	—	—	—	0.576
CTS (9)	0.105	0.0675	0.00758	-0.00654	—	—	—	0.405
CTS (11)	0.192	-0.103	0.174	-0.167	0.192	—	—	0.253
CTS (13)	0.160	0.147	-0.272	0.225	0.154	0.00947	—	0.087
PLQ (21)	-0.115	0.144	0.0771	—	—	—	—	0.853
MA (22)	-0.115	0.153	1.984	—	—	—	—	0.853
HK (23)	1.548	9.769	0.169	—	—	—	—	0.787
KN-1 (24)	1.362	0.0794	—	—	—	—	—	0.836
KN-2 (25)	1.369	0.0787	0.264	1.227	—	—	—	0.818

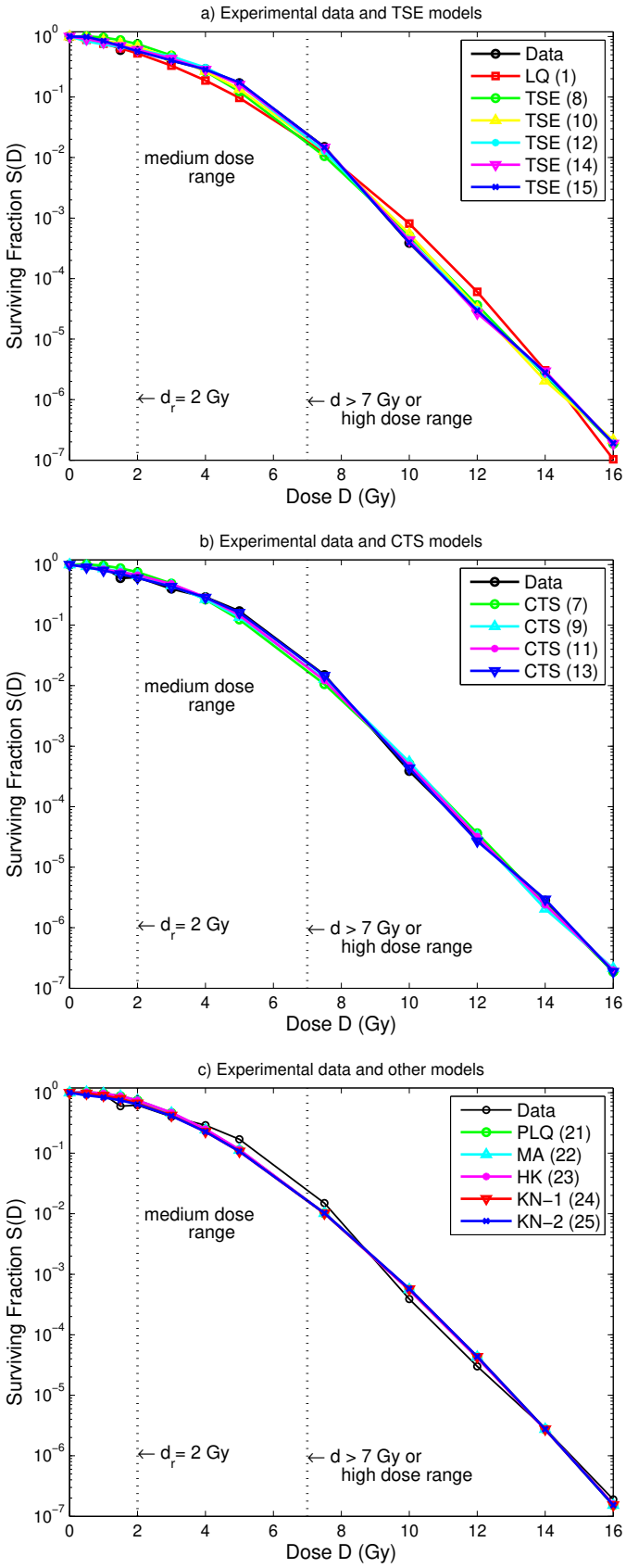

Figure 1: Surviving fraction $S(D)$ for the H460 cell line.

For TSE models the SRS decreases as the degree of the polynomial increases. The $|\alpha|$ and $|\beta|$ parameters undergo large variations and do not seem to approach a stable value yet. Stable value means that when the degree of the polynomial increases, the free parameter must vary less and less, asymptotically approaching the value for which the Taylor series converges. In CTS models also the SRS decreases as the degree of the polynomial increases. The $|\alpha|$ parameter does not show large variations when compared to the TSE model and seems to approach a stable value. Note that the first digit after the decimal point tends to set (0.1). The $\left|\hat{\beta}\right|$ parameter presents variations, but smaller than the $|\beta|$ of the TSE model and tends to a stable value. It must be said that more accurate and stable results will depend on more accurate experimental data. The experimental data used here were taken from the figures of the aforementioned articles, and they have two sources of error. The first is the error due to carrying out the experiment itself. The second is due to the approximation made when collecting the values of the figures, since a table with the experimental values was not found. In this way, it can be stated that the data used here are reliable up to the first significant digit.

Models based on Taylor series (TSE and CTS) have lower SRS when compared to other models with three and four free parameters. This is an argument in favor of these models and shows a mathematical advantage of using polynomials. The HK model (23) has three free parameters with SRS greater than TSE model (8) and CTS model (7). The KN-2 model (25) has four free parameters with SRS greater than TSE model (10) and CTS model (9). This supports our statement in the Introduction "*If, for these models to approximate this function with accuracy similar to TSE, it is necessary that they have the same number of free parameters as TSE, then the choice of TSE is mathematically preferable*".

For the TSE models it is verified that $|\gamma| > |\lambda| > |\mu| > |\eta| > |\nu|$, which is important because it indicates that higher order terms contribute less and less, and this is related to the convergence of the Taylor series. Two remarks must be made to clarify the preceding sentence. First, although the free parameters have different physical units, in the above comparison only numerical values were considered. This is possible because $f(D)$ is a function without physical units, and it is possible to adimensionalize the dose by introducing the variable $\bar{D} = D/D^*$. Consequently the dimensionless free parameters will be $\bar{\alpha} = \alpha D^*$, $\bar{\beta} = \beta(D^*)^2$ and so on. Choosing $D^* = 1$ Gy, then the dimensionless free parameters match the numerical value of the parameters with physical units. The second remark is that the convergence of the Taylor series refers only to the range of doses used for the curve fitting $[0, D_{max}]$, since the Taylor series approximates the function in the neighborhood of the point D_0 and has a radius of convergence R. Therefore, Taylor series approximation should not be used to extrapolate results beyond D_{max}, and even less if D_{max} is greater than the radius of convergence of the power series. For CTS models this behavior seems to start from the order 6 polynomial ($|\hat{\mu}| > |\check{\eta}|$), which may be an indication that for this cell line polynomials of order greater than 6 or more accurate experimental data are needed. Figure 1 shows the cell survival curves for all models and the experimental data, where some differences are noticeable. However, these differences between the models and the experimental data will be more evident in the study on dose fractionation, where the need to use higher order polynomials will be more clearly verified.

Behavior 2. In the case of CP3 cell line, the function $S(D)$ shows evidence of the existence of a relative maximum in the low dose region at the point $D_c \approx 1$ Gy. Table 2 shows the free parameters for all models. For these parameters, the models that predict this relative maximum are: LQ (1) at $D_c \approx -2.11$ Gy, TSE (8) at $D_c \approx -0.013$ Gy, TSE (10) at $D_c \approx 0.21$ Gy, TSE (12) at $D_c \approx 0.45$ Gy, TSE (14) at $D_c \approx 0.62$ Gy, TSE (15) at $D_c \approx 0.61$ Gy, CTS (7) at $D_c \approx -0.013$ Gy, CTS (9) at $D_c \approx 0.20$ Gy, CTS (11) at $D_c \approx 0.032$ Gy, CTS (13) at $D_c \approx 0.23$ Gy, PLQ at $D_c \approx 0.33$ Gy, MA at $D_c \approx 0.33$ Gy, HK at $D_c \approx 0.25$ Gy, KN-1 at $D_c \approx 0$ Gy and KN-2

at $D_c \approx 0.44$ Gy. It is known that negative doses are not physically realistic, and this is one more argument against models that present these negative values. For TSE and CTS models, polynomials of degree greater than or equal to four are needed to describe positive values of D_c. TSE models estimate this critical point closer to the experimental value as the degree of the polynomial increases. In the CTS models, there is a reversal of this trend for the degree five polynomial (CTS (11)), but the trend is again verified for the degree six polynomial CTS (13).

Table 2: Least squares fit for the CP3 cell line.

Model	α	β, $\hat{\beta}$	γ, $\hat{\gamma}$, $\check{\gamma}$	λ, $\hat{\lambda}$, $\check{\lambda}$	μ, $\hat{\mu}$, $\check{\mu}$	η, $\check{\eta}$	ν	SRS
LQ (1)	0.175	0.0416	—	—	—	—	—	1.610
TSE (8)	0.00228	0.0822	-0.00213	—	—	—	—	0.922
TSE (10)	-0.0410	0.1005	-0.00438	0.0000843	—	—	—	0.910
TSE (12)	-0.135	0.162	-0.0174	0.00119	-0.0000324	—	—	0.889
TSE (14)	-0.469	0.476	-0.116	0.0152	-0.000936	0.0000218	—	0.779
TSE (15)	-0.552	0.580	-0.162	0.0247	-0.00194	0.0000744	-0.00000108	0.776
CTS (7)	0.00228	0.164	-0.0128	—	—	—	—	0.922
CTS (9)	-0.0410	0.199	-0.00162	0.00202	—	—	—	0.910
CTS (11)	-0.00540	0.164	-0.00522	-0.0844	0.0113	—	—	0.919
CTS (13)	-0.0535	0.229	-0.0207	-0.151	0.0902	0.000640	—	0.897
PLQ (21)	-0.0813	0.118	0.0819	—	—	—	—	0.901
MA (22)	-0.0813	0.125	1.532	—	—	—	—	0.901
HK (23)	1.226	7.558	0.169	—	—	—	—	0.906
KN-1 (24)	1.065	0.0845	—	—	—	—	—	0.926
KN-2 (25)	1.059	0.0853	-1.551	1.998	—	—	—	0.783

For TSE models the SRS decreases as the degree of the polynomial increases. The $|\alpha|$ and $|\beta|$ parameters show large variations and do not seem to approach a stable value yet. However, the α parameter must be negative and the LQ model is unable to predict this behavior. The TSE and CTS models predict negative α for polynomials from the fourth order. In CTS models the SRS decreases as the degree of the polynomial increases. The $|\alpha|$ and $\left|\hat{\beta}\right|$ parameters show smaller variations when compared to the $|\alpha|$ and $|\beta|$ of the TSE model.

For the TSE models it is verified that $|\gamma| > |\lambda| > |\mu| > |\eta| > |\nu|$ indicating that higher order terms contribute less and less. For the CTS models this property seems to start from the order six polynomial ($|\hat{\mu}| > |\check{\eta}|$), which again may be an indication that for this cell line polynomials of order greater than 6 are needed. The HK model (23) needed a high value for the second parameter, which differs from the range of values of the other models. Figure 2 shows the cell survival curves for all models and the experimental data, where some differences are perceptible that will become more evident in the study on dose fractionation.

Behavior 3. In the CHOAA8 cell line case, for low dose region the function $S(D)$ shows evidence of the existence of a relative minimum at point $D_{c1} \approx 1$ Gy and a relative maximum at point $D_{c2} \approx 1.5$ Gy. Table 3 shows the free parameters for all models.

For TSE models the SRS decreases as the degree of the polynomial increases. The $|\alpha|$ and $|\beta|$ parameters show large variations and do not seem to approach a stable value yet. It is observed that $|\gamma| > |\lambda| > |\mu| > |\eta| > |\nu|$ indicating that higher order terms contribute less and less. However, it appears that polynomials of order greater than 6 are required for this cell line.

In CTS models the SRS decreases as the degree of the polynomial increases. The $|\alpha|$ parameter does not show large variations when compared to the TSE model and seems to approach a stable value. Note that the first digit after the decimal point tends to set (0.1). The $\left|\hat{\beta}\right|$ parameter presents variations, but smaller than the $|\beta|$ of the TSE model and tends to a stable value. For CTS (13) model the $|\alpha|$, $\left|\hat{\beta}\right|$ and $|\hat{\gamma}|$ values are similar or $\left|S^{(1)}(0)\right| \approx \left|S^{(2)}(0)\right| \approx \left|S^{(3)}(0)\right|$, which

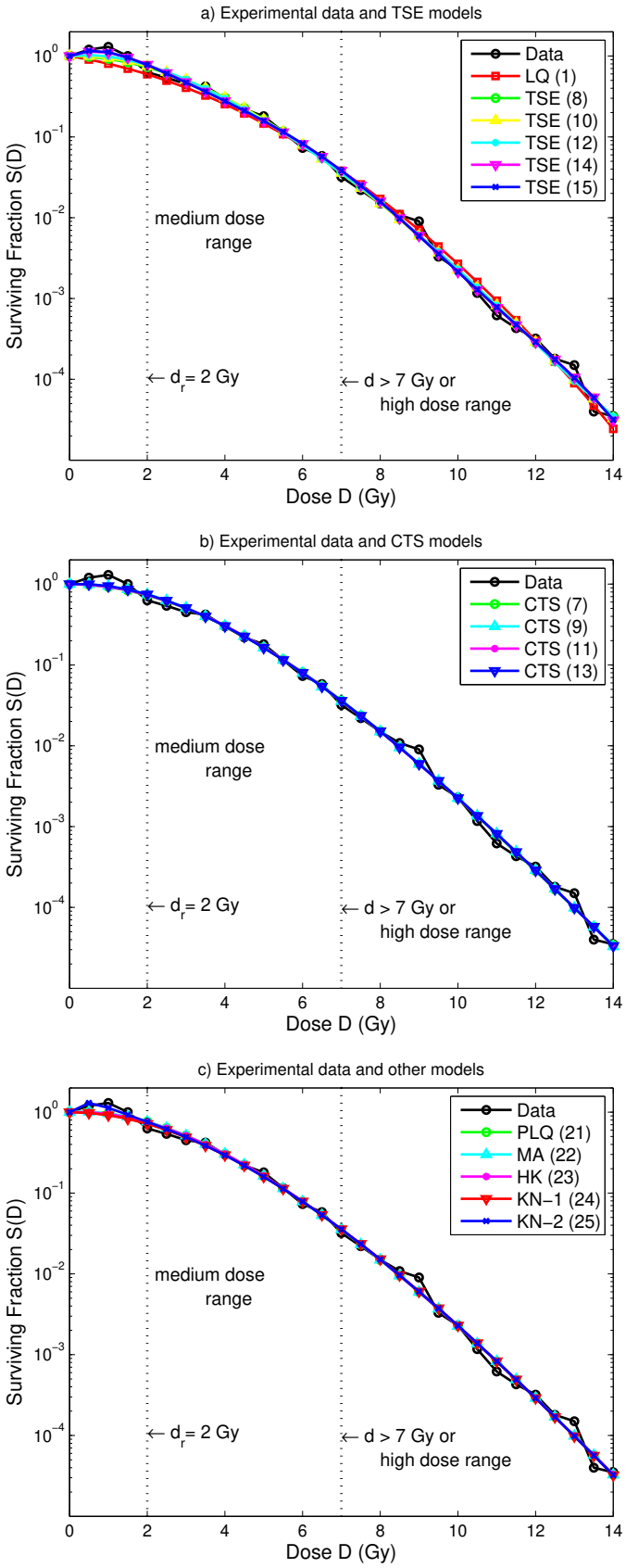

Figure 2: Surviving fraction $S(D)$ for the CP3 cell line.

Table 3: Least squares fit for the CHOAA8 cell line.

Model	α	β, $\hat{\beta}$	γ, $\hat{\gamma}$, $\check{\gamma}$	λ, $\hat{\lambda}$, $\check{\lambda}$	μ, $\hat{\mu}$, $\check{\mu}$	η, $\check{\eta}$	ν	SRS
LQ (1)	0.140	0.0230	—	—	—	—	—	1.699
TSE (8)	0.278	-0.00519	0.00130	—	—	—	—	1.058
TSE (10)	0.176	0.0326	-0.00277	0.000133	—	—	—	0.959
TSE (12)	0.554	-0.184	0.0374	-0.00284	0.0000764	—	—	0.468
TSE (14)	0.526	-0.164	0.0320	-0.00219	0.0000409	0.00000073	—	0.469
TSE (15)	0.733	-0.396	0.122	-0.0186	0.00156	-0.0000695	0.00000126	0.426
CTS (7)	0.278	-0.0878	0.00781	—	—	—	—	1.058
CTS (9)	0.176	0.0341	-0.0456	0.00321	—	—	—	0.959
CTS (11)	0.105	0.0826	-0.0419	-0.0160	0.0257	—	—	0.950
CTS (13)	0.108	0.108	-0.104	0.0330	0.0593	0.00226	—	0.770
PLQ (21)	0.252	-0.00419	-0.0410	—	—	—	—	0.903
MA (22)	0.140	0.0230	200409.04	—	—	—	—	1.699
HK (23)	2.274	85.0207	0.0253	—	—	—	—	1.900
KN-1 (24)	0.759	0.0680	—	—	—	—	—	3.006
KN-2 (25)	5.290	0.00635	0.358	0.234	—	—	—	1.204

is not the case with the TSE models. In this cell line, to achieve the behavior that higher-order terms contribute less and less to the Taylor series, it seems to require polynomials of order greater than 6 ($|\hat{\mu}| > |\check{\eta}|$).

The PLQ model (21) has the lowest SRS for three free parameters, but higher order polynomials achieve better performance. The MA model (22) needed a very high value for the third parameter. The HK model (23) needed a high value for the second parameter. These high values may deviate from an acceptable radiobiological interpretation, and are out of line with the range of values used by other models.

As this cell line apparently has two critical points, it is necessary that $f(D)$ is at least a degree 3 polynomial to predict these transition points. However, considering the curve fitting it is possible that higher order polynomials are needed to accommodate these points. This is a mathematical argument that shows the inability of the LQ model to describe this behavior. The HK and KN-1 models only present one critical point, and it is insufficient to describe the third behavior (HRS and IRR).

Finally, two curious or interesting observations for the CTS model. First, the α parameter seems to tend towards similar values (0.1) in the case of H460 and CHOAA8 cell lines. Second, the $\hat{\beta}$ parameter also seems to tend towards similar values (0.1) in the case of these two cell lines. In addition, the Taylor polynomial performs a local approximation around a point D_0. The construction of the TSE and CTS models is carried out around the point $D_0 = 0$ Gy, but this value is not a restriction for these models. This value was chosen to make comparisons with existing models. However, this does not mean that this is the most appropriate value for expanding the Taylor series. In future works we intend to carry out a study on what would be the most appropriate D_0 value.

Analysis of experimental and theoretical fractionations

Consider a conventional fractionation schedule with isoeffective total dose $D_r = 60$ Gy. This dose will be delivered in $n_r = 30$ fractions of $d_r = 2$ Gy, and it will be used as a reference dose per fraction for comparison with other fractionation schemes. Considering the experimental cell survival data, it is possible to construct a graph of the experimental fractionation for each cell line. Since the isoeffect is guaranteed if $n_i \log_e(S^{exp}(d_i)) = n_r \log_e(S^{exp}(d_r))$, then the experimental isoeffective total dose D_i^{exp} corresponding to fractionation with dose per fraction d_i

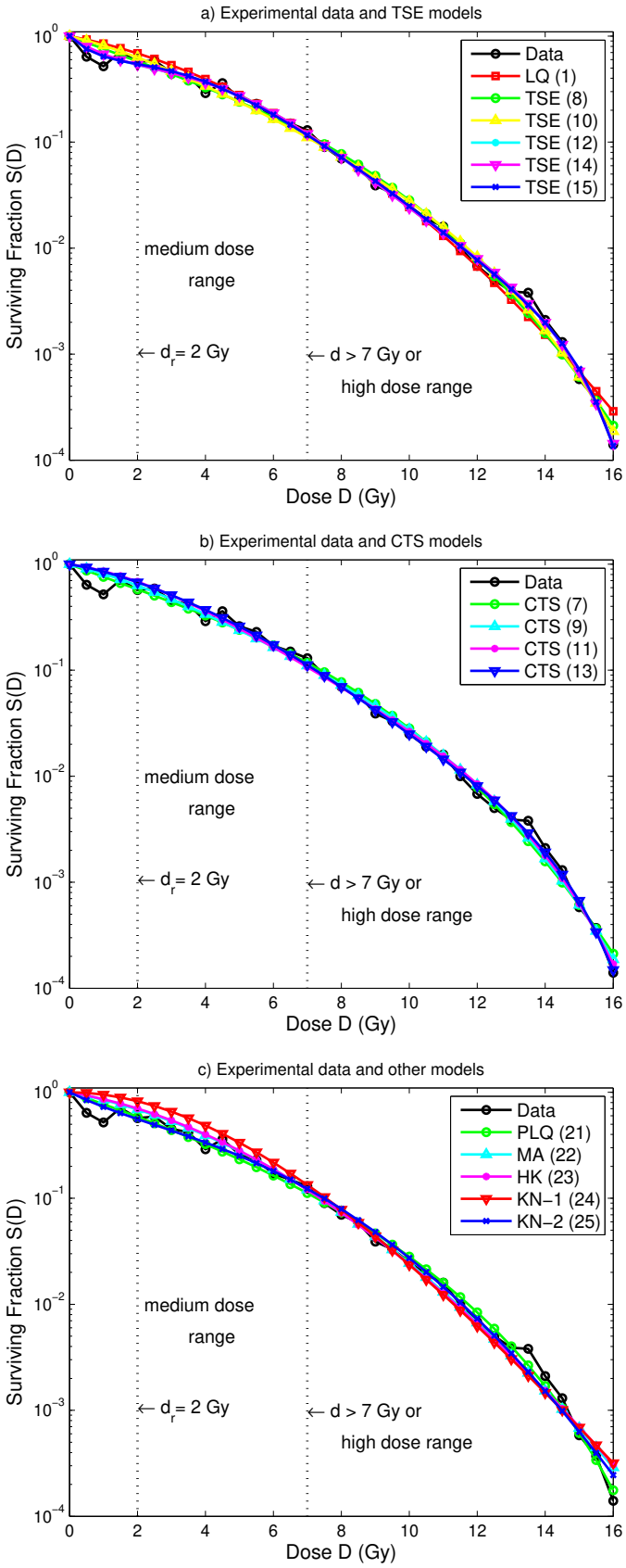

Figure 3: Surviving fraction $S(D)$ for the CHOAA8 cell line.

is determined by equation (32)

$$D_i^{exp} = D_r \frac{d_i}{d_r} \frac{\log_e(S^{exp}(d_r))}{\log_e(S^{exp}(d_i))}, \tag{32}$$

where $S^{exp}(d_r)$ and $S^{exp}(d_i)$ denote the experimental cell survival data. As far as the authors know, this is the first time that equation (32) has been presented, and allows investigating dose fractionation without the need to use a radiobiological model. This eliminates the approximation error introduced by every radiological model. Analogously, equation (33) determines the isoeffective total dose D^{fit} estimated by radiobiological models.

$$D^{fit}(d) = D_r \frac{d}{d_r} \frac{\log_e(S^{fit}(d_r))}{\log_e(S^{fit}(d))} = D_r \frac{d}{d_r} \frac{f^{fit}(d_r)}{f^{fit}(d)}. \tag{33}$$

For radiobiological models based on the Taylor series, equation (33) becomes

$$D^{fit}(d) = D_r \frac{\alpha + \sum_{k=2}^{m-1} \left[\frac{f^{(k)}(0)}{k!} d_r^{(k-1)} \right] + \frac{f^{(m)}(D_x)}{m!} d_r^{(m-1)}}{\alpha + \sum_{k=2}^{m-1} \left[\frac{f^{(k)}(0)}{k!} d^{(k-1)} \right] + \frac{f^{(m)}(D_x)}{m!} d^{(m-1)}}, \tag{34}$$

where the parameters $f^{(k)}(0)$ and $f^{(m)}(D_x)$ are determined by the curve fits for each model. Equation (34) is equivalent to equation (17). Thus, it is possible to estimate the error considering the 'experimental fractionation' and that predicted by the curve fit as $error_i = \left| D_i^{fit} - D_i^{exp} \right|$. It is possible to define the relative error $RED^{fit} = \frac{\|error\|_{\max,j}}{\left|D_j^{exp}\right|}$ using the vector norm $\|error\|_{\max,j} = \max_{1 \le i \le np} \{error_i\}$, where np is the total number of experimental points, and j denotes the point where the maximum value is reached. Analogously, the relative error for $S^{fit} = S^{fit}(d)$ is defined as RES^{fit}. Table 4 presents these relative errors for all radiobiological models in ordered pair form. That is, the ordered pair (d, RES^{fit}) or (d, RED^{fit}) determines the maximum relative error point.

Table 4: Relative errors RES^{fit} and RED^{fit} for radiobiological models.

Model	H460 cell	CP3 cell	CHOAA8 cell
	(d, RES^{fit}), (d, RED^{fit})	(d, RES^{fit}), (d, RED^{fit})	(d, RES^{fit}), (d, RED^{fit})
LQ (1)	(1.0, 0.1889), (1.0, 0.6944)	(1.0, 0.3810), (1.0, 2.3531)	(1.0, 0.6321), (0.5, 2.8946)
TSE (8)	(1.5, 0.4536), (0.5, 4.9056)	(1.0, 0.2915), (0.5, 6.8249)	(1.0, 0.4614), (0.5, 2.1423)
TSE (10)	(1.5, 0.2802), (1.0, 0.6495)	(1.0, 0.2720), (0.5, 28.876)	(1.0, 0.5648), (0.5, 2.8309)
TSE (12)	(1.0, 0.2150), (1.0, 0.7869)	(1.0, 0.2389), (1.0, 14.661)	(0.5, 0.2348), (0.5, 1.1094)
TSE (14)	(1.0, 0.1430), (1.0, 0.6985)	(1.0, 0.1533), (3.5, 0.5426)	(0.5, 0.2462), (0.5, 1.1729)
TSE (15)	(1.5, 0.1625), (0.5, 3.5797)	(1.0, 0.1400), (3.5, 0.5310)	(1.5, 0.1772), (1.5, 0.3119)
CTS (7)	(1.5, 0.4536), (0.5, 4.9056)	(1.0, 0.2915), (0.5, 6.8249)	(1.0, 0.4614), (0.5, 2.1423)
CTS (9)	(1.5, 0.2802), (1.0, 0.6495)	(1.0, 0.2720), (0.5, 28.876)	(1.0, 0.5648), (0.5, 2.8309)
CTS (11)	(1.5, 0.2607), (1.0, 0.7113)	(1.0, 0.2866), (0.5, 7.8213)	(1.0, 0.6559), (0.5, 3.7000)
CTS (13)	(1.0, 0.1479), (1.0, 0.7048)	(1.0, 0.2711), (0.5, 98.308)	(1.0, 0.6400), (0.5, 3.5576)
PLQ (21)	(1.5, 0.4560), (0.5, 2.5267)	(1.0, 0.2570), (0.5, 9.1154)	(1.0, 0.4845), (0.5, 2.3037)
MA (22)	(1.5, 0.4561), (0.5, 2.5246)	(1.0, 0.2570), (0.5, 9.1159)	(1.0, 0.6321), (0.5, 2.8946)
HK (23)	(1.5, 0.4607), (0.5, 2.6775)	(1.0, 0.2672), (0.5, 177.68)	(1.0, 0.6549), (0.5, 3.1044)
KN-1 (24)	(1.5, 0.3247), (1.0, 0.5020)	(1.0, 0.2943), (0.5, 6.9324)	(1.0, 0.8294), (0.5, 11.079)
KN-2 (25)	(1.5, 0.2448), (1.0, 0.6826)	(1.0, 0.1296), (3.5, 0.4569)	(1.0, 0.4005), (0.5, 1.7526)

For the H460 cell line, all models have RED^{fit} in the dose range between 0.5 Gy and 1.0 Gy. For the CP3 cell line, disregarding the singularity point, most models present RED^{fit} in the

dose range between 0.5 Gy and 1.0 Gy. Only the TSE (14), TSE (15), KN-2 models present RED^{fit} at 3.5 Gy. For the CHOAA8 cell line, only the TSE model (15) presents RED^{fit} at 1.5 Gy. All other models have RED^{fit} at 0.5 Gy. Furthermore, for all cases RED^{fit} is always greater than RES^{fit}, and both errors are significantly large. For the three cell lines, no model has an error RES^{fit} of less than 12% and an error RED^{fit} of less than 31%.

Figures 4, 5 and 6 show the values estimated by equations (32) and (33) for the total dose that guarantees the same isoeffect. Theoretically, as the degree of the polynomial used to approximate $f(D)$ increases, this isoeffective total dose (34) should tend to a limit closer and closer to the experimental value (32), since higher order polynomials better approximate $f(D)$. In general, as can be seen in Table 4 and Figure 4, the analyzed radiobiological models better approximate the experimental data for cell lines such as *Behavior 1*. This is because $S(D)$ is a monotonic function for these cell lines, as it is monotonically decreasing function over the entire dose range. However, the error of the radiobiological models is greater for *Behavior 2* and 3, as can be seen in Table 4, Figures 5 and 6. The explanation for this is that $S(D)$ is not a monotonic function for these cell lines, as it has critical points that delimit regions where the function is monotonically decreasing and monotonically increasing.

For cells with the first behavior (Figure 4), in the high dose range ($d > 7$ Gy) the TSE (12) and CTS (13) models predict a dose fractionation more similar to the experimental one, while the NK-2 (25) model presents the best performance among models not based on Taylor series. Among these three models, the closest to the experimental data is the TSE (12) model, although the CTS (13) model presents a behavior very similar to the TSE (12) model. In the medium dose range (2 Gy$< d < 7$ Gy) the models that most resemble the behavior of experimental data are TSE (15) and CTS (13). The LQ (1) model is very close to the experimental data up to $d = 5$ Gy. The models not based on Taylor series present considerable difference with the experimental data in the medium dose range, with the NK-2 (25) model showing the smallest difference. For example, for $d = 5$ Gy the experimental data estimate $D_i^{exp} \approx 40.5$ Gy while $D_i^{fit} \approx 29.89$ for the KN-2 (25) model and $D_i^{fit} \approx 20.54$ for PLQ (21), MA (22) and HK (23) models. These large differences with a relative error that can be up to 50% can affect local tumour control. In the low dose range ($d < 2$ Gy) all models show the greatest difference with experimental data, and for some dose values they underestimate or overestimate total dose. This can be understood as an indicator that the TSE and CTS models need higher order polynomials to adequately describe low dose range. The experimental data show a very interesting behavior. It is often said that in hyperfractionation the total dose should always be greater than that of conventional fractionation, but at $d = 1.5$ Gy the experimental data estimate $D_i^{exp} \approx 42.11$ Gy, which is considerably lower than 60 Gy of conventional fractionation. However, at $d = 1.0$ Gy the experimental data estimate $D_i^{exp} \approx 231.7$ Gy. This indicates that in order to obtain therapeutic gain in hyperfractionation, it is necessary to have the entire equipment system well calibrated and to execute the protocol as accurately as possible. On the other hand, the LQ model differs more from the experimental data in the low and high dose range for this cell line, showing good accuracy for the medium dose range.

For cells with the second behavior (Figure 5), there is a mathematical singularity point at $d = 1.5$ Gy because $S^{exp}(1.5) = 1$. In this cell line, hyperfractionation should not be used, since doses $d \leq 1.5$ Gy increase the proliferation of cancer cells. Experimental data estimate negative total doses to ensure the same isoeffect as conventional fractionation. For this reason, the low dose range is not shown in Figure 5. The only models that present a negative total doses close to the experimental data are: TSE (14), TSE (15) and KN-2 (25). In the medium dose range (2 Gy $< d <$ 7 Gy) and high dose range ($d > 7$ Gy) the LQ model better approximates the total dose. The TSE and CTS models differ more from the experimental data as the degree of the polyno-

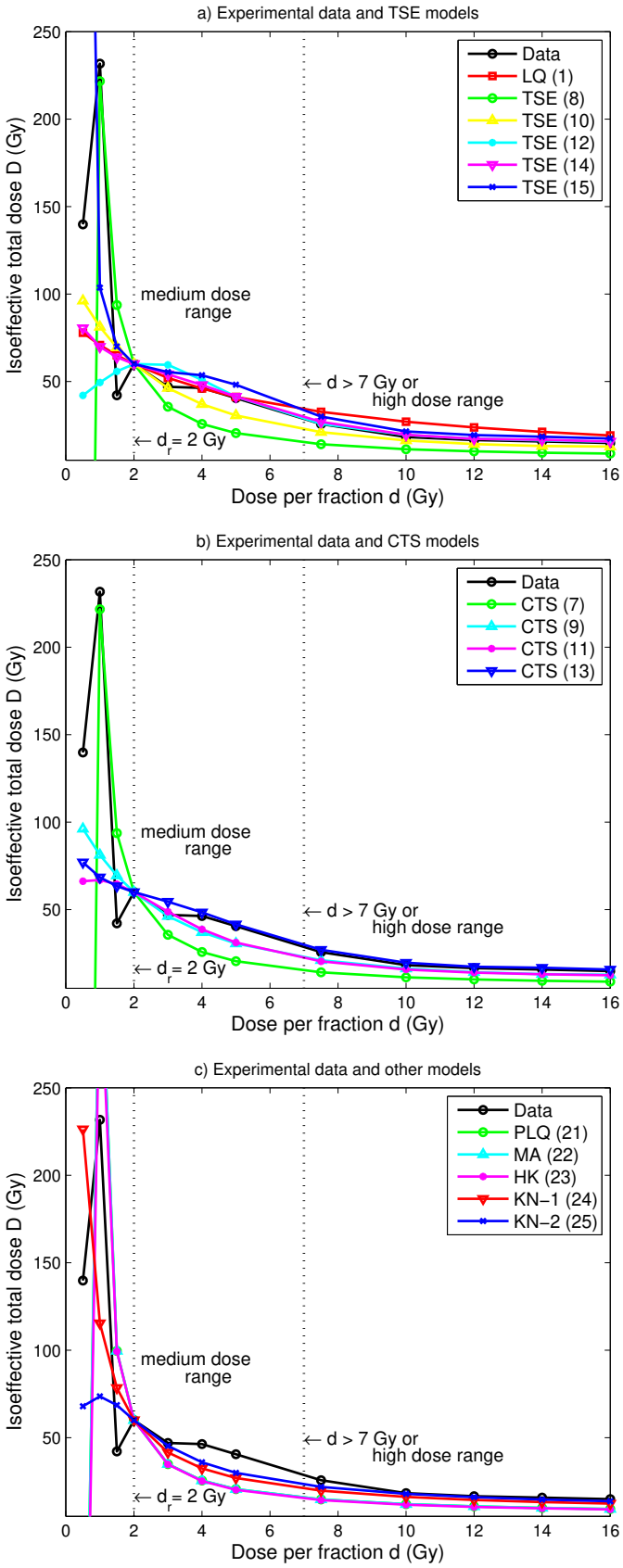

Figure 4: Experimental (32) and theoretical (33) fractionation for the H460 cell line.

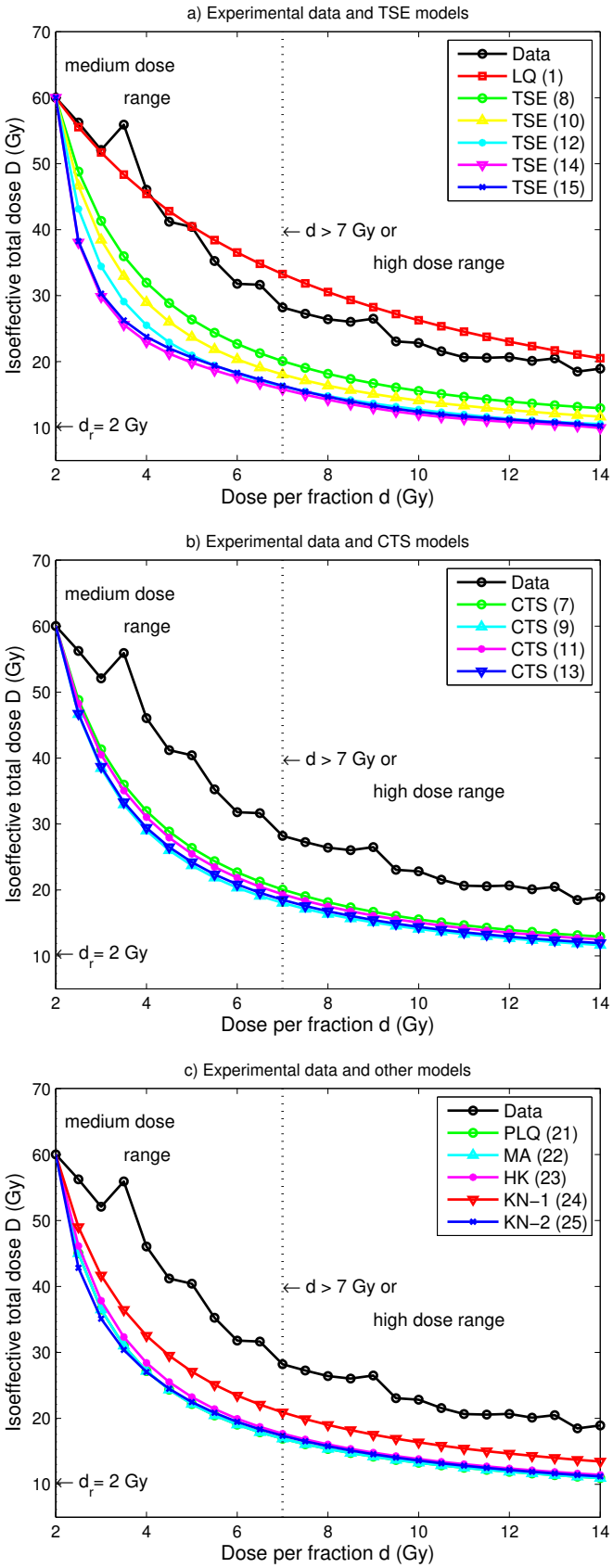

Figure 5: Experimental (32) and theoretical (33) fractionation for the CP3 cell line.

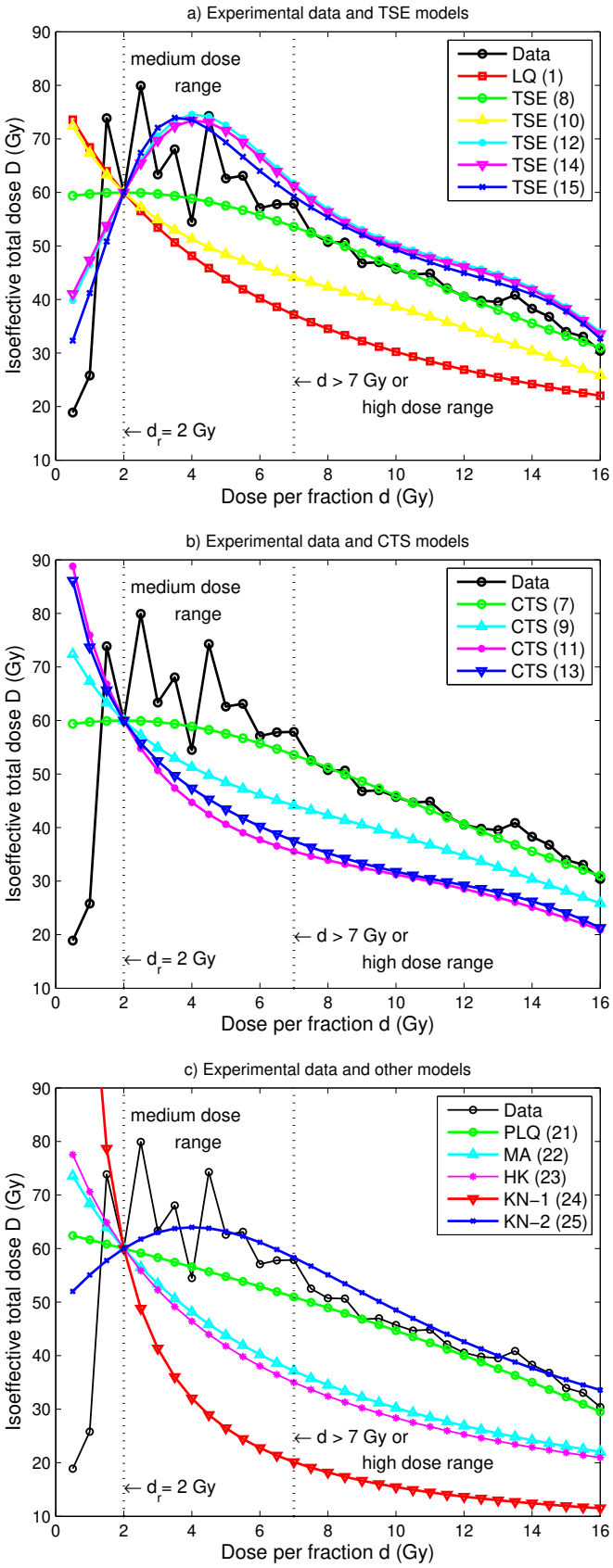

Figure 6: Experimental (32) and theoretical (33) fractionation for the CHOAA8 cell line.

mial increases. However, this trend begins to invert from a polynomial of degree seven for the TSE models (TSE (15)) and of degree six for the CTS models (CTS (13)), indicating the need for higher order polynomials. Theoretically, a polynomial with degree equal to the number of experimental points interpolates the experimental data, and consequently its fractionation curve will be equivalent to the experimental fractionation. The NK-1 (24) model presents the best performance among models not based on Taylor series. Among the TSE (15), CTS (13), PLQ (11) and KN-2 (25) models, the closest to the experimental data is the CTS (13) model, but still with considerable error when compared to the LQ model. For cells with this type of behavior, conventional fractionation or hypofractionation should be practiced. Hypofractionation should be explored with caution, as there appears to be some therapeutic gain. For example, a hypofractionation with five fractions $d = 6.5$ Gy guarantees a total dose $D = 31.64$ Gy, which produces a superior isoeffect (higher cell mortality) than the isoeffect of conventional fractionation.

For cells with the third behavior (Figure 6), in the high dose range ($d > 7$ Gy) the TSE models get closer to the experimental data as the polynomial degree increases. The LQ model is the one with the highest error among the TSE models. In contrast, CTS models differ more from the experimental data as the degree of the polynomial increases to degree five. This trend begins to invert from a polynomial of degree six (CTS (13)), indicating the need for higher order polynomials. Among the models not based on Taylor series, the PLQ (21) and KN-2 (25) models better approximate the experimental data. The KN-1 (24) model presents greater deviation with relative error that can be up to 65% for $d = 7$ Gy. The MA (22) and HK (23) models show a similar curve with considerable errors. In the medium dose range (2 Gy$< d <$ 7 Gy) the TSE models come closer to the experimental data as the degree of the polynomial increases, and the LQ model has the largest error. Again, the CTS models differ more from the experimental data as the degree of the polynomial increases to degree five, reversing this trend from the degree six polynomial. Among the models not based on Taylor series, the PLQ (21) and KN-2 (25) models better approximate the experimental data. It is important to note that in the medium dose range, the experimental data indicate that the fractionation curve is not monotone, and that the total dose may be higher than that of conventional fractionation to ensure the same isoeffect. The only models that approach this behavior are: TSE models with order polynomials starting from five and KN-2 (25). CTS models need higher order polynomials to describe this behavior. In the low dose range ($d < 2$ Gy) the TSE models are closer to the experimental data as the degree of the polynomial increases, requiring a polynomial of order greater than five to obtain similarity with the experimental data. CTS models overestimate hyperfractionation, indicating the need for higher-order polynomials. In addition, all models not based on Taylor series overestimate hyperfractionation except the KN-2 (25) model. However, the error of the KN-2 (25) model is greater than that of the TSE (12), TSE (14) and TSE (15) models. It is important to highlight that for this cell line, the experimental data show that fractionations with very small doses need a total isoeffective dose considerably lower than the 60 Gy of conventional fractionation. For example, in the fractionation scheme with doses by fraction $d_i = 0.5$ Gy the estimated value for the total dose is $D_i^{exp} \approx 18.9$ Gy. This indicates that hyperfractionation should be practiced in cells with the third radiation response behavior, as considerable therapeutic gains can be obtained.

In the fractionation analysis, isoeffective total dose $D_r = 60$ Gy and dose per fraction $d_r = 2$ Gy were chosen because they are values close to the typical values used in several treatment protocols. However, other values can be chosen to use in equations (32) and (33). To show how these values influence the fractionation analysis, results are presented for two other fractionation schemes. Figure 7 shows the fractionation results keeping $D_r = 60$ Gy fixed and varying the dose per fraction for the CHOAA8 cell line. In this case, $D_r = 60$ Gy will be delivered in 12

fractions of $d_r = 5$ Gy. Thus, it is possible to notice how equations (32) and (33) depend on the variable d_r. In Figure 8 $d_r = 5$ Gy is kept fixed and D_r is decreased for the CHOAA8 cell line. In this case, $D_r = 30$ Gy will be delivered in 6 fractions of $d_r = 5$ Gy. The variable D_r influences equations (32) and (33) only as a proportionality factor. For both fractionations, all models show the greatest differences with the experimental fractionation in the low dose region. This is the dose region corresponding to hyperfractionation, where experimental data show evidence of therapeutic gain. However, only models based on Taylor series with high order polynomials (TSE (15)) are able to indicate this therapeutic gain.

Conclusions

The Taylor series is a reliable mathematical tool for approximating the survival curve $S(D) = e^{-f(D)}$. Our mathematical analysis shows that the last Taylor series free parameter for $f(D)$ explicitly depends on the dose range used in the function fitting, and therefore this fit should not be used to estimate $S(D)$ in values of D outside this range. Based on the Taylor series and on two mathematical hypotheses, it is possible to approximate $f(D)$ in two ways: TSE and CTS models. The free parameters of the TSE model are dependent on each other, while the free parameters of the CTS model eliminate this interdependence. The free parameters of the CTS model have a very clear mathematical interpretation, which are the derivatives of $S(D)$ at the point $D = 0$ Gy.

Experimental data indicate the existence of at least three different types of cellular response to radiation. The most common is a monotone decreasing function $S(D)$ (*Behavior 1*). However, there are cell lines that exhibit a relative maximum for $S(D)$ (*Behavior 2*), and other cell lines that exhibit a relative minimum and maximum (*Behavior 3*). Our theoretical analysis confirms the need for polynomials of order greater than 2 to adequately describe all these behaviors. The analyzed experimental data show that to have the long-awaited 'entire or unified or universal' survival curve it is necessary to approximate $f(D)$ with polynomials of order greater than six. Therefore, higher-order polynomials are needed to have a single formula that describes the survival of all cell lines at all dose ranges. In a future work we intend to find the degree of the polynomial that performs this feat.

Based on the currently accepted hypotheses about fractionated radiotherapy and experimental data on cell survival, it is possible to generate charts on the isoeffective total dose in fractionation. Fractionation analysis shows that for some cell lines (*Behavior 1 and 3*) hyperfractionation can imply a therapeutic gain. Generally, in hyperfractionation the total dose is increased when compared to conventional fractionation without increasing the risk of late complications. Experimental data for CHOAA8 cells show the existence of hyperfractionation with total doses ($D_i^{exp} \approx 18.9$ Gy) much lower than the total dose of conventional fractionation (60 Gy). This confirms the radiobiological expectation that hyperfractionation can increase local tumour control without increasing the risk of late normal tissue damage. Furthermore, in the medium dose range (2 Gy$< d <$ 7 Gy) this cell line presents a behavior for fractionation very different from the known uniform monotone behavior, where most radiobiological models greatly underestimate the value of the total dose. The PLQ (21), MA (22), HK (23) and NK-1 (24) models do not predict this non-monotonic behavior. Only polynomials of higher order and NK-2 (25) model are able to predict this non-monotonic behavior. For the cell line with *Behavior 2* such as CP3, only hypofractionation can bring some therapeutic gain.

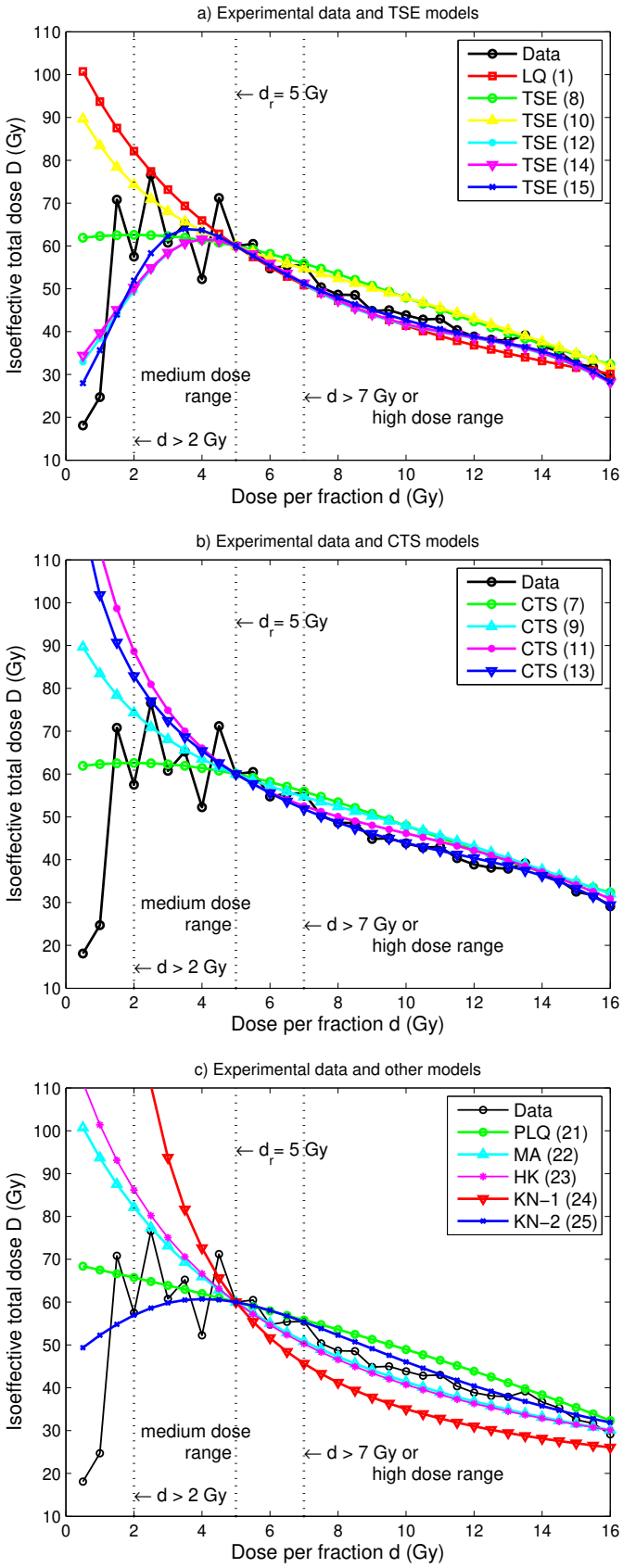

Figure 7: Experimental (32) and theoretical (33) fractionation for the CHOAA8 cell line.

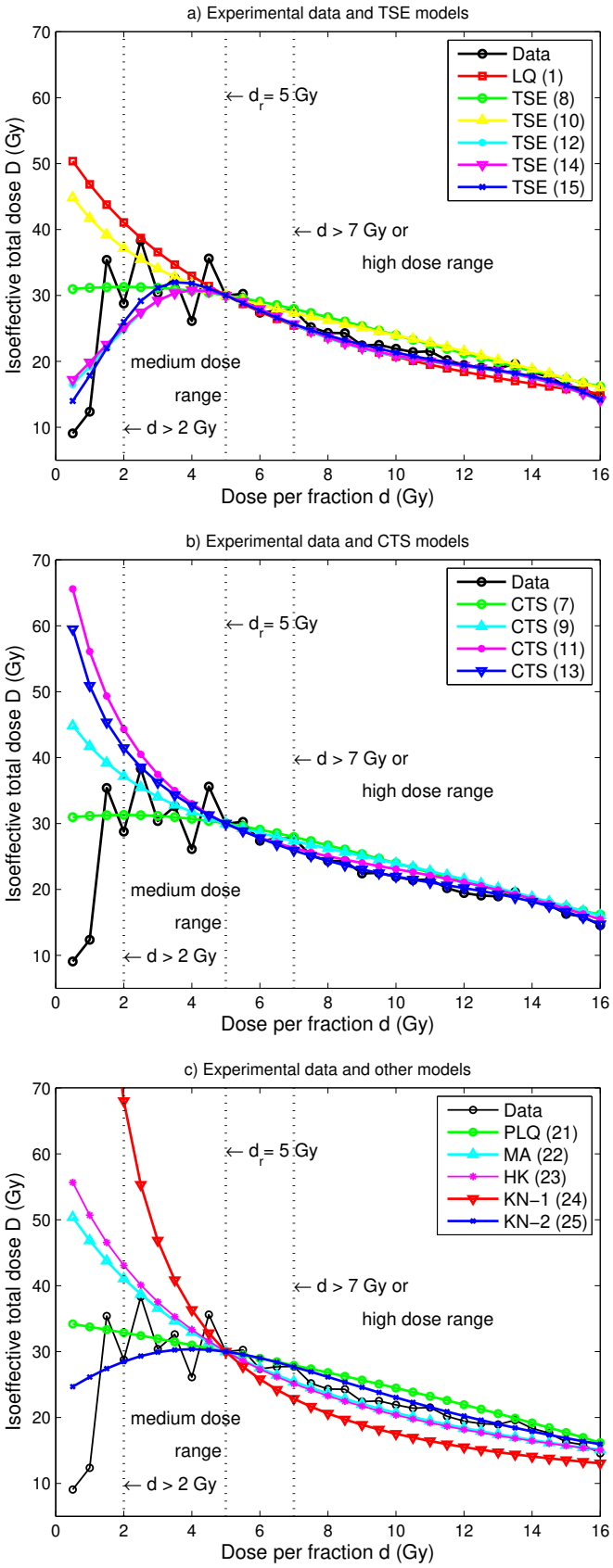

Figure 8: Experimental (32) and theoretical (33) fractionation for the CHOAA8 cell line.

Acknowledgements

This work was supported by the Universidade Federal Fluminense. The authors are grateful for the constructive comments made by the reviewers.

References

Andisheh B., Edgren M., Belkić D., Mavroidis P., Brahme A. & Lind B.K. (2013) A comparative analysis of radiobiological models for cell surviving fractions at high doses. *Technol. Cancer Res. Treat.*, 12: 183–192. doi:10.7785/tcrt.2012.500306.

Apostol T.M. (1967) Calculus, Vol. 1: One-Variable Calculus, with an Introduction to Linear Algebra. New York, NY: John WiJey & Sons.

Belkić D. & Belkić K. (2011) Padé–Froissart exact signal-noise separation in nuclear magnetic resonance spectroscopy. *J. Phys. B: At. Mol. Opt. Phys.*, 44: 125003. doi:10.1088/0953-4075/44/12/125003.

Bender M.A. & Gooch P.C. (1962) The kinetics of X-ray survival of mammalian cells in vitro. *Int. J. Radiat. Biol.*, 5: 133–145. doi:10.1080/09553006214550651.

Burden R.L., Faires J.D. & Burden A.M. (2016) Numerical Analysis. Boston, MA: Cengage Learning.

Carmichael J., Degraff W.G., Gamson J., Russo D., Gazdar A.F., Levitt M.L., Minna J.D. & Mitchell J.B. (1989) Radiation sensitivity of human lung cancer cell lines. *Eur J Cancer Clin Oncol.*, 25: 527–534. doi:10.1016/0277-5379(89)90266-6.

Ekstrand K.E. (2010) The Hug–Kellerer equation as the universal cell survival curve. *Phys. Med. Biol.*, 55: 267–273. doi:10.1088/0031-9155/55/10/n01.

Fernandez-Palomo C., Seymour C. & Mothersill C. (2016) Inter-Relationship between Low-Dose Hyper-Radiosensitivity and Radiation-Induced Bystander Effects in the Human T98G Glioma and the Epithelial HaCaT Cell Line. *Radiat Res.*, 185: 124–133. doi:10.1667/RR14208.1.

Garcia L.M., Leblanc J., Wilkins D. & Raaphorst G.P. (2006) Fitting the linear–quadratic model to detailed data sets for different dose ranges. *Phys. Med. Biol.*, 51: 2813–2823. doi:10.1088/0031-9155/51/11/009.

Garcia L.M., Wilkins D.E. & Raaphorst G.P. (2007) α/β ratio: A dose range dependence study. *Int. J. Radiat. Oncol. Biol. Phys.*, 67: 587–593. doi:10.1016/j.ijrobp.2006.10.017.

Guerrero M. & Li X.A. (2004) Extending the linear–quadratic model for large fraction doses pertinent to stereotactic radiotherapy. *Phys. Med. Biol.*, 49: 4825–4835. doi:10.1088/0031-9155/49/20/012.

Hug O. & Kellerer A.M. (1963) Zur interpretation der dosiswirkungsbeziehungen in der strahlenbiologie. *Biophysik*, 1: 20–32.

Joiner M.C. & van der Kogel A.J. (2018) Basic Clinical Radiobiology. Boca Raton, FL: CRC Press.

Kavanagh B.D. & Newman F. (2008) Toward a unified survival curve: in regard to Park et al. (Int J Radiat Oncol Biol Phys 2008;70:847–852) and Krueger et al. (Int J Radiat Oncol Biol Phys 2007;69:1262–1271). *Int. J. Radiat. Oncol. Biol. Phys.*, 71: 958–959. doi:10.1016/j.ijrobp.2008.03.016.

Krueger S.A., Collis S.J., Joiner M.C., Wilson G.D. & Marples B. (2007) Transition in survival from low-dose hyper-radiosensitivity to increased radioresistance is independent of activation of ATM Ser1981 activity. *Int. J. Radiat. Oncol. Biol. Phys.*, 69: 1262–1271. doi:10.1016/j.ijrobp.2007.08.012.

Lind B.K., Persson L.M., Edgren M.R., Hedlöf I. & Brahme A. (2003) Repairable–conditionally repairable damage model based on dual Poisson processes. *Radiat. Res.*, 160: 366–275. doi:10.1667/0033-7587(2003)160[0366:RRDMBO]2.0.CO;2.

McKenna F. & Ahmad S. (2009) Toward a unified survival curve: in regard to Kavanagh and Newman (Int J Radiat Oncol Biol Phys 2008;71:958–959) and Park et al. (Int J Radiat Oncol Biol Phys 2008;70:847–852). *Int. J. Radiat. Oncol. Biol. Phys.*, 73: 640. doi:10.1016/j.ijrobp.2008.08.063.

McMahon S.J. (2019) The linear quadratic model: usage, interpretation and challenges. *Phys. Med. Biol.*, 64: 01TR01. doi:10.1088/1361-6560/aaf26a.

Park C., Papiez L., Zhang S., Story M. & Timmerman R.D. (2008) Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.*, 70: 847–852. doi:10.1016/j.ijrobp.2007.10.059.

Scholz M. & Kraft G. (1994) Calculation of heavy ion inactivation probabilities based on track structure, X ray sensitivity and target size. *Radiat. Prot. Dosim.*, 52: 29–33. doi:10.1093/oxfordjournals.rpd.a082156.

Shuryak I. & Cornforth M.N. (2021) Accounting for overdispersion of lethal lesions in the linear quadratic model improves performance at both high and low radiation doses. *Int. J. Radiat. Biol.*, 97: 50–59. doi:10.1080/09553002.2020.1784489.

Steel G.G., Deacon J.M., Duchesne G.M., Horwich A., Kelland L.R. & Peacock J.H. (1987) The dose–rate effect in human tumour cells. *Radiother Oncol.*, 9: 299–310. doi:10.1016/s0167-8140(87)80151-2.

Wang J.Z., Huang Z., Simon S.L., Yuh W.T.C. & Mayr N.A. (2010) A generalized linear-quadratic model for radiosurgery, stereotactic body radiation therapy, and high–dose rate brachytherapy. *Sci. Transl. Med.*, 2: 39ra48. doi:10.1126/scitranslmed.3000864.