A note on modeling of tumor regression for estimation of radiobiological parameters

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Purpose: Accurate calculation of radiobiological parameters is crucial to predicting radiation treatment response. Modeling differences may have a significant impact on derived parameters. In this study, the authors have integrated two existing models with kinetic differential equations to formulate a new tumor regression model for estimation of radiobiological parameters for individual patients.

Methods: A system of differential equations that characterizes the birth-and-death process of tumor cells in radiation treatment was analytically solved. The solution of this system was used to construct an iterative model (Z-model). The model consists of three parameters: tumor doubling time T_d , half-life of dead cells T_r , and cell survival fraction SF_D under dose D . The Jacobian determinant of this model was proposed as a constraint to optimize the three parameters for six head and neck cancer patients. The derived parameters were compared with those generated from the two existing models: Chvetsov's model (C-model) and Lim's model (L-model). The C-model and L-model were optimized with the parameter T_d fixed.

Results: With the Jacobian-constrained Z-model, the mean of the optimized cell survival fractions is 0.43 ± 0.08 , and the half-life of dead cells averaged over the six patients is 17.5 ± 3.2 days. The parameters T_r and SF_D optimized with the Z-model differ by 1.2% and 20.3% from those optimized with the T_d -fixed C-model, and by 32.1% and 112.3% from those optimized with the T_d -fixed L-model, respectively.

Conclusions: The Z-model was analytically constructed from the differential equations of cell populations that describe changes in the number of different tumor cells during the course of radiation treatment. The Jacobian constraints were proposed to optimize the three radiobiological parameters. The generated model and its optimization method may help develop high-quality treatment regimens for individual patients. © 2014 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4884019>]

Key words: tumor regression, kinetic model, radiobiological parameters, tumor control probability

1. INTRODUCTION

Tumor control probability (TCP) has played an important role in evaluation and optimization of radiation treatment plans.^{1,2} TCP calculation depends on several parameters that include tumor radiosensitivity and cell proliferation ability.³ Due to the heterogeneous population of cells in tumor,⁴ these parameters could be patient dependent. Without accurately calibrating these parameters, the TCP calculated cannot represent treatment outcomes correctly for individual patients.¹ The correlation between radiobiological parameters and radiation-induced changes in tumor volume had been modeled decades ago.^{5,6} In the recent years, with a variety of 3D images used in daily clinic, kinetic models were recalled and further developed to accommodate different clinical treatment regimens. In this regard, Lim *et al.*⁷ generated a two-compartment model (L-model) for evaluation of radiation treatment of cervical cancer patients, based on a series of MR images acquired during their treatment courses; Chvetsov⁸ presented a compact iterative model (C-model) to evaluate tumor responses for head and neck cancer patients. With these models, patient-specific radiobiological parameters can be evaluated from a series of

CT or MR images,^{9,10} and the derived parameters in turn can be used to calculate TCP for individual patients.

While derived from Fischer's modeling theory,^{5,8} the discrete models mentioned above were represented differently. The modeling difference may result in large variations in optimized parameters. In addition, the tumor doubling time was assumed to be a constant in previous studies to make it possible to optimize the cell survival fraction and half-life of dead cells.^{7,8,10} This assumption, however, may compromise the accuracy of the optimization results because the tumor doubling time actually may vary among different patients.

To address these issues, we will formulate an iterative tumor regression model directly from the analytical solution of a two-compartment differential equation that characterizes the cell birth, death, and resolving process. We will also analyze the convergence of the iterative model, and put a natural constraint on the model's Jacobian determinant to optimize all the three parameters. Finally, we will use different numbers of sample datasets to evaluate the stability of the optimized results. The similarity and difference between the new iterative model and two existing models will be analyzed and demonstrated with a set of head and neck cancer patients.

2. MATERIALS AND METHODS

2.A. Formulation of a two-compartment iterative model

Ionizing radiation may induce cell death either in the form of reproductive cell death, which is termed “mitotic death,”^{11,12} or by interphase cell death.¹³ Interphase death or “apoptosis” as coined by Kerr *et al.*¹⁴ is defined as an impairment of cellular metabolism and death of the cells before their first post-mitotic division.¹³ Apoptotic cells could be observed as early as one hour after irradiation, and most such cells appeared within 24 h.¹¹ On the other hand, mitotic death is the dominant mechanism of cell death induced by irradiation,¹⁵ and is defined by the ability of the cell to divide before dying.¹³ Cells exposed to high level radiation doses may still produce metabolically viable daughter cells, which may ultimately disintegrate by mitotic catastrophe. Based on this consideration, Fischer⁵ ignored the possibility of a transient increase in the number of dead cells, and assumed the mitotic death of tumor cells at their first attempted division. Due to asynchronous cell populations in patients, the average time of cell death caused by either apoptosis or mitotic catastrophe, consequently, could be assumed within 24 h after radiation delivery.¹⁶

Radiation-induced cell death and cell repopulation may change the number of the total surviving cancer cells during the course of radiation treatment. Let $S(t)$ and $K(t)$ represent the numbers of the surviving and dead cancer cells at time t . Assume the changes caused by the cell proliferation and radiation-induced cell death are proportional to the number of the total surviving cells with coefficients a_1 and a_2 , respectively. Then the change of $S(t)$ in the time interval of Δt can be written as $\Delta S = a_1 S(t) \Delta t - a_2 S(t) \Delta t$. As Δt tends to zero, the differential form of $S(t)$ can be derived with the result shown in Eq. (1). Similarly, suppose the change caused by clearance of the dead cells is proportional to the total number of the dead cells with the linear coefficient c . Then the differential forms of $S(t)$ and $K(t)$ can be represented by

$$\begin{aligned} \frac{dS(t)}{dt} &= (a_1 - a_2)S(t), \\ \frac{dK(t)}{dt} &= cK(t) + a_2 S(t). \end{aligned} \quad (1)$$

Assume that the surviving cells are counted one day (24 h) after radiation treatment. Then the survival fraction of the cells under dose D satisfies $SF_D = \exp(-a_2)$, i.e., $-a_2 = \ln(SF_D)$. If T_d and T_r denote the tumor doubling time and the half-life of dead cells, respectively, then the cell proliferation rate a_1 can be represented by $a_1 = \ln 2/T_d$, and the coefficient c represented by $c = -\ln 2/T_r$. Consequently, Eq. (1) can be written as

$$\frac{dS(t)}{dt} = (\ln 2/T_d + \ln(SF_D))S(t), \quad (2)$$

$$\frac{dK(t)}{dt} = -(\ln 2/T_r)K(t) - \ln(SF_D)S(t). \quad (3)$$

The system of Eqs. (2) and (3) can be analytically solved with its general solution represented by

$$S(t) = A_1 e^{(\ln 2/T_d + \ln(SF_D))t}, \quad (4)$$

$$K(t) = B_1 e^{(-\ln 2/T_r)t} + B_2 e^{(\ln 2/T_d + \ln(SF_D))t}, \quad (5)$$

where A_1 and B_i , $i = 1, 2$, are constants. Let $t = 0$, then from Eqs. (4) and (5), it can be found that $A_1 = S(0)$ and $B_1 = K(0) - B_2$. By substituting Eq. (5) into Eq. (3), we get $B_2 = \frac{-\ln(SF_D)}{\ln 2/T_d + \ln(SF_D) + \ln 2/T_r} S(0)$.

For the i th treatment fraction, the system of differential equations (2) and (3) can be solved in the same manner as the formulation of the solution (4) and (5). The analytic solution of this system at fraction i can be represented by

$$\begin{aligned} S_i &= F_1(S_{i-1}, K_{i-1}) = S_{i-1} e^{\ln 2/T_d + \ln(SF_D)}, \\ K_i &= F_2(S_{i-1}, K_{i-1}) \\ &= \left(K_{i-1} + \frac{\ln(SF_D)}{\ln 2/T_d + \ln(SF_D) + \ln 2/T_r} \right. \\ &\quad \left. \times (1 - e^{\ln 2/T_d + \ln 2/T_r SF_D}) S_{i-1} \right) e^{-\ln 2/T_r}, \end{aligned} \quad (6)$$

where the second term in K_i is related to the number of the cells killed by the i th fraction. It should be mentioned that mitotic death occurs only at the time of cell division which could be hours later after treatment,^{12,16} and apoptotic cells, on the other hand, may also take several hours to appear.¹¹ The hours extended for the cell death at each fraction are related to the cell doubling time T_d . The delayed hours in turn will affect the number of the dead cells cleared each day. Consequently, both the parameters T_d and T_r are included in the function K_i .

Recall that SF_D is the survival fraction of cells under dose D . If there is no treatment on two weekend days, then the dose D is zero, and SF_D equals to one. Consequently, Eq. (6) will generate that $S_i = S_{i-1} e^{\ln 2/T_d} = S_{i-2} e^{2 \ln 2/T_d}$. The kinetic model (6), named as Z-model, is the analytical solution of the governing Eq. (1). The semantics of the model can be tracked down to the general assumptions made for Eq. (1).

2.B. Optimization of radiobiological parameters

It can be assumed that tumor volume is proportional to the number of its clonogens.¹⁷ The parameters T_d , T_r , and SF_D consequently can be optimized from measured tumor volumes with an objective function defined by

$$Q = \sum_{i=0, \dots, n} |\tilde{R}_i(SF_D, T_r, T_d) - \tilde{M}_i|^2, \quad (7)$$

where $\tilde{M}_i = M_i/M_0$, $\tilde{R}_i(SF_D, T_r, T_d) = (S_{t_i} + K_{t_i})/R_0$, M_i is the tumor volume measured on day t_i , R_0 is the total number of the tumor cells before treatment, S_{t_i} and K_{t_i} are the numbers of the surviving and dead cells on day t_i , predicted by the kinetic model (6), respectively. The model was iterated t_i times to calculate each S_{t_i} and K_{t_i} in $\tilde{R}_i$. To ensure that the iterative model converges, its Jacobian determinant needs to

be less than or equal to μ , where μ is a constant smaller than one.

Note that for the kinetic model (6), its Jacobian determinant can be calculated by

$$|J_F(S, K)| = \begin{vmatrix} \frac{\partial F_1}{\partial S} & \frac{\partial F_1}{\partial K} \\ \frac{\partial F_2}{\partial S} & \frac{\partial F_2}{\partial K} \end{vmatrix} = SF_D \exp(\ln 2/T_d - \ln 2/T_r). \quad (8)$$

The Jacobian determinant that contains all the three parameters SF_D , T_d , and T_r characterizes the rate of tumor regression during the course of radiation treatment. For large T_d and T_r , it can be found that $|J_F(S, K)| \approx (1 + O(1/T_d))(1 - O(1/T_r)SF_D)$, so the Jacobian function is largely determined by the component SF_D .

In previous studies, T_d was fixed to reduce the sensitivity of the parameter optimization to uncertainties in tumor volume measurements. For example, T_d was assumed to be the potential doubling time T_{pot} which was 5.5 for head and neck patients,⁸ and for cervical cancer patients, T_{pot} was assumed to be 5 by Lim *et al.*,⁷ and 4.5 by Huang *et al.*¹⁰ In this study, we use a constraint naturally assumed on the Jacobian determinant, instead of fixing T_d . Note that the Jacobian of the iterative model is related to daily tumor regression, and dominated by the factor SF_D . Following the general limits given by Lim *et al.*⁷ for SF_2 , it is assumed that $0.1 < |J_F(S, K)| < 0.9$, and the constraint of $T_d = 5.5$ is then alleviated to the general assumption of $T_d < 33$ which is six times greater than the fixed constraint. With these conditions, a simulated annealing algorithm was implemented using C++ on a linux computer. This program allows all the three parameters to be optimized simultaneously.

2.C. Comparison of tumor regression models and their convergences

To simulate tumor regression during the course of radiation treatment, Chvetsov⁸ presented the following two-

compartment cell population model (C-model):

$$\begin{aligned} S_i &= G_1(S_{i-1}, K_{i-1}) = S_{i-1}(SF_D)e^{\ln 2/T_{pot}}, \\ K_i &= G_2(S_{i-1}, K_{i-1}) = [K_{i-1} + (1 - SF_D)S_{i-1}]e^{-\ln 2/T_r}, \end{aligned} \quad (9)$$

where K_{i-1} is the number of the dead cells on day $(i-1)$, and $(1 - SF_D)S_{i-1}$ is the number of the dead cells newly contributed from S_{i-1} on day i . Because the terms K_{i-1} and $(1 - SF_D)S_{i-1}$ were counted on different days, their sum is not the number of the total dead cells on day $i-1$. Consequently, the sum multiplied by $e^{-\ln 2/T_r}$ is not exactly the number of the dead cells K_i on day i , but is a good approximation. Furthermore, C-model has the Jacobian determinant $|J_G(S, K)| = SF_D \exp(\ln 2/T_{pot} - \ln 2/T_r)$, which is equivalent to that of Z-model shown in Eq. (8).

On the other hand, Lim *et al.*⁷ derived a formula (L-model) to calculate the total number of tumor cells for evaluation of radiation treatment. The L-model is similar to the iterative model (9) except that the term $(1 - SF_D)S_{i-1}$ in the function G_2 is represented by $(1 - SF_D)e^{\ln 2/T_{pot}}S_{i-1}$. The formulation of the L-model is based on the assumption that the number of cells that are irreparably damaged by the k th of n fractions is the difference between the number surviving after fraction $(k-1)$ and the number surviving after fraction k .⁷ This assumption, however, is not accurate. Actually, the number of the cells damaged by fraction k is the number of the surviving cells counted in the case of no radiation delivery subtracted by the number counted after the delivery of fraction k . This is not the difference between the number counted after fractions k and that counted after fraction $(k-1)$.

While the L-model and C-model have the same Jacobian and are equivalent for a sufficiently large T_{pot} , different assumptions made in these models may result in different parameters. As demonstrated by Fig. 1, tumor volumes measured from two head and neck patients reported in Chvetsov's study⁸ can be fitted well with either the L-model or C-model, but the parameters derived from the two models are different. Actually, the C-model deviated largely from the measured data if its parameters were taken from the optimized L-model.

FIG. 1. (a) and (b) show tumor volume regressions simulated with C-model and L-model for two head and neck cancer patients.

FIG. 2. (a)–(f) Tumor regression was simulated with C-model and Z-model at $T_d = 5.5$ days for six head and neck cancer patients.

These examples suggested that the modeling difference may significantly impact the optimized parameters.

3. RESULTS

3.A. Optimization of tumor regression models with T_d fixed

The Z-model and C-model were compared on six patient datasets reported by Chvetsov.⁸ For each of these patients, tumor volumes were manually extracted from Fig. 1 in Ref. 8 at their first 15 measurement points. The measured tumor volumes were used to optimize the two models, where SF_D and T_r were calculated with T_d fixed at 5.5 days. The optimized models were used to calculate the regression of tumor volumes for the six patients. The computed results in Fig. 2 show

that the measured data can be fitted almost equally well by the two models.

While the two models can generate similar tumor volumes for each patient, the parameters used to generate these volumes are different. Unlike the L-model shown in Fig. 1, the Z-model only has small differences from the C-model in their computed tumor volumes. The parameters optimized for the six patients are shown in Fig. 3, and the mean difference between the two models is 3.1% for T_r , and 30.3% for SF_D .

3.B. Different optimization constraints

The three models were optimized with different strategies: C-model and L-model were optimized with T_d fixed at 5.5 days, and Z-model was optimized with its Jacobian constraints. The optimized parameters are shown in Fig. 4. The

FIG. 3. Parameters optimized with C-model and Z-model at $T_d = 5.5$ days: (a) the half-life of dead cells T_r , and (b) cell survival fraction SF_D .

mean difference between the Z-model and C-model for the six patients is $1.2 \pm 1.3\%$ for T_r and $20.3 \pm 17.5\%$ for SF_D , and between the Z-model and L-model is $32.1 \pm 37.3\%$ for T_r and $112.3 \pm 190.1\%$ for SF_D .

For each patient, the first n samples of the 15 measured tumor volumes aforementioned were substituted into the objective function (7) to optimize the Z-model. Let $n = 1, \dots, 15$, respectively, and then we get 15 sets of the optimized parameters. From Fig. 5, it can be found that the optimized parameters tend to converge as n increases, and the variations of these parameters decrease substantially after the first few samples.

For the parameters shown in Fig. 5, their mean and standard deviation were calculated over the range of n from 4 to 15 for each patient. The resultant means and standard deviations were averaged over the six patients with the results shown in the last column of Table I. It can be found that when more than four measured datasets were used in optimization, the standard deviations of the resultant parameters became small.

4. DISCUSSION

Patient-specific radiobiological parameters can be used to calculate tumor control probability that may help design optimal treatment regimens for individual patients. In the past years, many efforts had been made to quantify these parameters.^{6,18–20} The pioneering work was presented by Fischer⁵ who demonstrated that radiobiological parameters can be calculated from changes in tumor volume during the course of radiation treatment. From these studies, several discrete models were investigated to estimate radiobiological parameters for individual patients, based on their treatment regimens and corresponding CT or MR images.^{7,9,21}

Different from the previous models, the Z-model presented in this study was constructed directly from the solution of the governing differential equations (2) and (3). It can be found that for large T_r and T_d , $e^{\ln 2/T_d + \ln 2/T_r} \rightarrow 1$ and $\frac{\ln(SF_D)}{\ln 2/T_d + \ln(SF_D) + \ln 2/T_r} \rightarrow 1$. In this case, both the C-model and the L-model are equivalent to the Z-model. Also the three models have a similar Jacobian determinant, and after

FIG. 4. Parameters optimized using C-model and L-model at $T_d = 5.5$ days, and Z-model with its Jacobian constrained: (a) the half-life of dead cells T_r , and (b) cell survival fraction SF_D .

FIG. 5. The Jacobian-constrained Z-model fitted with different numbers of sample datasets for evaluation of the parameters: (a) T_r , (b) T_d , and (c) SF_D .

optimization they can fit the sequences of the measured tumor volumes well for the six head and neck cancer patients.

To optimize these models, the parameter T_d was fixed as a constant in the previous studies.^{7,9,21} For example, T_d was assumed to be the “potential doubling time” T_{pot} which was 5.5 days for head and neck patients.⁸ While T_{pot} can be estimated with cell mitotic labeling techniques, cell loss in patients may take away a large portion (77%) of tumor proliferation.¹⁵ Furthermore, tumor doubling time could vary from patient to patient.²² The constant T_{pot} assumed for T_d may induce biases into optimized parameters. In contrast, the Jacobian determinant of the iterative Z-model is a characteristic function to determine the model’s convergence, and is related to daily changes in tumor volume. An appropriate range assumed for the Jacobian term may help optimize the three parameters. It

has been shown that the optimized parameters tend to converge as the number of sample datasets increases.

It should be mentioned that cell death is a complicated and heterogeneous process.²³ As the dominant mechanism of cell death,¹⁵ mitotic death is defined at the time of cell division.¹¹ The time of cell division is randomly distributed due to the property of asynchronous cell populations in patients. Consequently, the rate of cell death in tumor can be considered as a continuous function within 24 h after radiation treatment.^{11,16} In this study, this function was assumed a constant to simplify the solution of the system of equations. This simplification may introduce uncertainties in the computed results. In the future, nonlinear coefficients will be included to help improve the accuracy of this model. Also the six sample datasets used in this study were manually extracted from a figure in

TABLE I. The parameters T_r , SF_D , and T_d of the Z-model were optimized using the first n measured tumor volumes, $n = 4, \dots, 15$, respectively, resulting in 12 sets of (T_r , SF_D , T_d). The means and standard deviations of the 12 parameter sets were calculated for each patient.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Average
T_r	4.8 ± 1.3	25.4 ± 2.6	17.3 ± 7.1	21.2 ± 2.2	19.9 ± 1.2	16.3 ± 4.6	17.5 ± 3.2
SF_D	0.62 ± 0.09	0.35 ± 0.09	0.40 ± 0.13	0.13 ± 0.05	0.45 ± 0.06	0.68 ± 0.06	0.43 ± 0.08
T_d	8.6 ± 1.0	29.8 ± 3.9	18.5 ± 4.6	27.5 ± 5.3	20.9 ± 2.6	19.5 ± 1.8	20.8 ± 3.2

the published paper.⁸ This may introduce some uncertainties in the tumor volumes, in addition to their measurement errors. Nonetheless, these datasets provide a platform to compare the three models so that their differences can be clearly illustrated. As shown in Figs. 3 and 4, the parameters optimized from these models are different. If the same parameters were used in different models, tumor volumes generated would be different as demonstrated in Figs. 1 and 2.

Different from the Z-model, both the C-model and L-model cannot satisfy the differential Eqs. (2) and (3), while the C-model is closer to the analytical solution of these equations than the L-model. In general, the dying, resolving, and repopulation of tumor cells are three continuous and concurrent processes. Without solving their dynamic differential equations, biases could be induced when counting the numbers of cells in different compartments.

5. CONCLUSIONS

A discrete tumor regression model has been constructed from the solution of the two-compartment cell population equations and used to optimize radiobiological parameters. The generated model and its optimization method may help improve the accuracy of the parameter calculation, and consequently help develop high-quality treatment regimens for individual patients.

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