A SIMPLIFIED MATHEMATICAL MODEL OF SOLID TUMOR REGROWTH WITH THERAPIES

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Abstract. A simplified mathematical model of solid tumor regrowth is analyzed. When the model system is disturbed by radiation and chemotherapy, which are given by discontinuous functions, the system loses its smoothness. For the purpose of comparison and verification of therapy efficacy, a weak solution is constructed. Some suggestions about effective combination of treatments are also given.

1. **Introduction.** Glioblastoma is the most malignant solid brain tumor; it is usually fatal. The current standard of care for newly diagnosed glioblastoma is surgical resection followed by radiotherapy and chemotherapy. In a recent paper [1], Tian et al introduced a mathematical model to study the efficacy of resection, with the combination of radiation and chemotherapy on glioblastoma. Their model is a free boundary problem. To get a sound understanding with detailed analysis, we simplify their partial differential equations (PDEs) system to an ordinary differential equation (ODE) system. In the ODE system, we are still able to address the tumor growth in terms of radius of the tumor although we ignore the spatial distribution of cell densities. By comparing numerical studies of the PDE system and the ODE systems, there does not seem to be much difference for understanding the growth pattern.

In the present paper, we study the ODE version of a tumor regrowth model. Particularly, when the therapy is given by discontinuous functions, we can get explicit continuous solutions, weak solutions, without using distribution theory. In section 2, we will briefly describe the model and simplify it. In section 3, we first give a kind of quasi-stead state analysis for the system without treatments. An explicit solution is also given for comparison. We then construct a weak solution to the system with therapies. By concrete computation, we verify the efficacy of treatments. In section 4, we discuss several points about treatment protocols from the analysis in section 3.

2. **Model description and simplification.** It is assumed that the tumor is spherical, and the tumor radius $R(t)$ evolves with time. When taking surgical resection, the radius is $R(0) = R_0$. In the partial resection, a smaller ball of radius R_* is removed, while residual tumor cells remain in the region between the two concentric balls. After surgery, the ball of radius R_* fills with cerebro-spinal fluid, and the residual tumor begins to regrow outward.

The mathematical model describes the tumor regrowing after surgical resection. The tumor contains tumor cells (x) and necrotic cells (y). The quantity x represents the number density of tumor cells; the quantity y represents the number density of necrotic cells. It is assumed that the number density of cells in the tumor is a constant [2], that is, $x + y$ = number of cells in one mm^3, which is 10^6 [3]. New tumor cells are produced through proliferation, and they transit to necrotic cells by lysis. Tumor cells that are near to the expanding surface of the solid tumor receive more nutrients and proliferate faster than tumor cells that are near the core of the tumor. For simplicity it is assumed that the proliferation rate, λ, is constant. Also the rate of cells becoming necrotic, δ, is constant. The necrotic cells are removed at a constant rate μ.

The proliferation and removal of cells cause a movement of cells within the tumor, and the velocity field is represented by $u(r,t)$, where r is the distance from a point to the origin. By mass conservation law,

$$\frac{\partial x(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)x(r,t)) = \lambda x(r,t) - \delta x(r,t), \tag{1}$$

$$\frac{\partial y(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)y(r,t)) = \delta x(r,t) - \mu y(r,t). \tag{2}$$

By adding equations (1) and (2) together, we get an equation for the radial velocity:

$$\frac{\theta}{r^2}\frac{\partial}{\partial r}(r^2 u) = (\lambda + \mu)x(r,t) - \mu\theta. \tag{3}$$

The tumor radius evolves according to

$$\frac{dR}{dt} = u(R(t),t). \tag{4}$$

After resection, radiotherapy combined with chemotherapy is administered. The basic strategy is described by the following two discontinuous functions.

The radiation activity function is

$$\rho(t) = \begin{cases} 1 & \text{if } 6 \leq t \leq 12, \\ 0 & \text{otherwise.} \end{cases}$$

The chemotherapy drug dosing function is

$$\tau(t) = \begin{cases} 1 & \text{if } 6 \leq t \leq 12, \\ 2 & \text{if } 12 \leq t \leq 20, \\ \frac{8}{3} & \text{if } 20 \leq t \leq 40, \\ 0 & \text{otherwise.} \end{cases}$$

The radiation kills tumor cells at a rate A, so that the death rate by radiotherapy is $A\rho(t)$. The drug kills tumor cells at a rate B, thus the killing rate by chemotherapy treatment is $B\tau(t)$. After including those therapies, the equations 1 and 2 are replaced by

$$\frac{\partial x(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)x(r,t)) = \lambda x(r,t) - \delta x(r,t) - A\rho(t)x(r,t) - B\tau(t)x(r,t), \tag{5}$$

and

$$\frac{\partial y(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)y(r,t)) = \delta x(r,t) + A\rho(t)x(r,t) + B\tau(t)x(r,t) - \mu y(r,t). \quad (6)$$

For a complete description of this model, please refer [1]. Now, let's simplify it, starting with the case without the therapies.

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t)x(r,t)) = \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u(r,t))x(r,t) + u(r,t)\frac{\partial x}{\partial r},$$

then,

$$\frac{\partial x}{\partial t} + u\frac{\partial x}{\partial r} = \lambda x - \delta x - (\frac{\lambda + \mu}{\theta}x - \mu)x.$$

¿From velocity equation, we have

$$\frac{\partial}{\partial r}(r^2 u) = (\frac{\lambda + \mu}{\theta}x - \mu)r^2,$$

and

$$r^2 u = \int_{R_*}^{r} (\frac{\lambda + \mu}{\theta}x(r,t) - \mu)r^2 dr.$$

For the boundary,

$$R^2 u(R,t) = \int_{R_*}^{R} (\frac{\lambda + \mu}{\theta}x - \mu)r^2 dr.$$

Set

$$x(r,t) = x(t), \qquad y(r,t) = y(t)$$

then

$$\frac{dx}{dt} = (\lambda + \mu - \delta)x - \frac{\lambda + \mu}{\theta}x^2,$$

and

$$u(R,t) = \frac{1}{R^2}\int_{R_*}^{R} (\frac{\lambda + \mu}{\theta}x(t) - \mu)r^2 dr = \frac{R^3 - R_*^3}{3R^2}(\frac{\lambda + \mu}{\theta}x - \mu).$$

The tumor radius is

$$\frac{dR}{dt} = u(R,t) = \frac{R^3 - R_*^3}{3R^2}(\frac{\lambda + \mu}{\theta}x - \mu).$$

Therefore, we have

$$\frac{dx}{dt} = (\lambda + \mu - \delta)x - \frac{\lambda + \mu}{\theta}x^2, \quad (7)$$

$$\frac{dy}{dt} = \delta x - \frac{\lambda + \mu}{\theta}xy, \quad (8)$$

$$\frac{dR}{dt} = \frac{R^3 - R_*^3}{3R^2}(\frac{\lambda + \mu}{\theta}x - \mu), \quad (9)$$

and initial conditions, $x(0) \geq 0$, $y(0) \geq 0$, and $R(0) = R_0$.

Similarly, we have an ODE system with therapies.

$$\frac{dx}{dt} = (\lambda + \mu - \delta - A\rho(t) - B\tau(t))x - \frac{\lambda + \mu}{\theta}x^2, \quad (10)$$

$$\frac{dy}{dt} = (\delta + A\rho(t) + B\tau(t))x - \frac{\lambda + \mu}{\theta}xy, \quad (11)$$

$$\frac{dR}{dt} = \frac{R^3 - R_*^3}{3R^2}(\frac{\lambda + \mu}{\theta}x - \mu). \quad (12)$$

3. Model analysis.

3.1. **Nondimensionalization.** Since $x(t) + y(t) = \theta$, a constant, we only need to consider one of them, say $x(t)$. Set $\overline{x} = \frac{x}{\theta}$, $\overline{y} = \frac{y}{\theta}$, and $\overline{t} = \delta t$, we have

$$\frac{d\overline{x}}{d\overline{t}} = (\frac{\lambda + \mu}{\delta} - 1 - \frac{A}{\delta}\rho(\overline{t}) - \frac{B}{\delta}\tau(\overline{t}))\overline{x} - \frac{\lambda + \mu}{\delta}\overline{x}^2,$$

$$\frac{dR}{d\overline{t}} = \frac{R^3 - R_*^3}{3R^2}(\frac{\lambda + \mu}{\delta}\overline{x} - \frac{\mu}{\delta}).$$

Let $\alpha = \frac{\lambda + \mu}{\delta}$, $\beta = \frac{\mu}{\delta}$, $a = \frac{A}{\delta}$ and $b = \frac{B}{\delta}$, and drop the bar over variables, we get

$$\frac{dx}{dt} = (\alpha - 1 - a\rho(t) - b\tau(t))x - \alpha x^2, \tag{13}$$

$$\frac{dR}{dt} = \frac{R^3 - R_*^3}{3R^2}(\alpha x - \beta). \tag{14}$$

Similarly, we get a nondimensionalized version of the system without treatments,

$$\frac{dx}{dt} = (\alpha - 1)x - \alpha x^2, \tag{15}$$

$$\frac{dR}{dt} = \frac{R^3 - R_*^3}{3R^2}(\alpha x - \beta). \tag{16}$$

3.2. **Equilibria, bifurcation, and solutions of the system without therapy.** The non-dimensionalized system without therapy is given by (15) and (16). Since $x(t)$ and $y(t)$ are number densities of different tumor cell populations, and the total number density of tumor cells is constant, the tumor volume increasing or decreasing is because the total number of tumor cells is changing with time. When $x(t)$ and $y(t)$ reach their equilibrium states, the sign of $\frac{dR}{dt}$ will not change with $x(t)$ anymore. If $\frac{dR}{dt} > 0$, the radius $R(t)$ will monotonically increase; if $\frac{dR}{dt} < 0$, the radius $R(t)$ will monotonically decrease; if $\frac{dR}{dt} = 0$ the radius $R(t)$ also reaches a stationary state. Therefore, the equilibrium states of cell populations will give us information about tumor growth pattern. This type of steady states we refer to as quasi-stead state. A similar method is used in [4]. It is easy to compute equilibria, bifurcation value for parameter α. We write those results as a theorem. Also see the bifurcation diagram Figure 1.

Theorem 3.1. *The equilibria are $x = 0$ and $x = \frac{\alpha - 1}{\alpha}$. The bifurcation values is $\alpha = \frac{\lambda + \mu}{\delta} = 1$. When $\alpha < 1$, $x = 0$ is stable and $x = \frac{\alpha - 1}{\alpha}$ is unstable. When $\alpha > 1$, $x = 0$ is unstable and $x = \frac{\alpha - 1}{\alpha}$ is stable. The bifurcation diagram consists of up-moved hyperbolic curve and α axis which intersect at $(\alpha, 0)$ on $\alpha - x$ plane. The bifurcation point is transcritical bifurcation point.*

The origin of the $\alpha - x$ plane is not a bifurcation point since $x = 0$ is always stable whenever $|\alpha| < 1$. So, we can regard the ∞ as an intersection of the hyperbolic curve and α axis.

When $0 < \alpha < 1$, the equilibrium $x = \frac{\alpha - 1}{\alpha}$ has no biological meaning. But, the $x = 0$ is a stable equilibrium point, and the radius is $R^3 = R_*^3 + (R_0^3 - R_*^3)e^{-\beta t}$ when $x = 0$. We see the tumor will shrink to R_*^3 as we expect.

When $\alpha > 1$, the radii are given by $R^3 = R_*^3 + (R_0^3 - R_*^3)e^{-\beta t}$ and $R^3 = R_*^3 + (R_0^3 - R_*^3)e^{(\alpha - 1 - \beta)t}$ corresponding to $x = 0$ and $x = \frac{\alpha - 1}{\alpha}$ respectively. The condition $\alpha - 1 - \beta < 0$ means that $\lambda < \delta$. When $\alpha - 1 - \beta < 0$, the tumor radius will shrink to R_*^3. This is biologically reasonable, since tumor cell proliferation rate
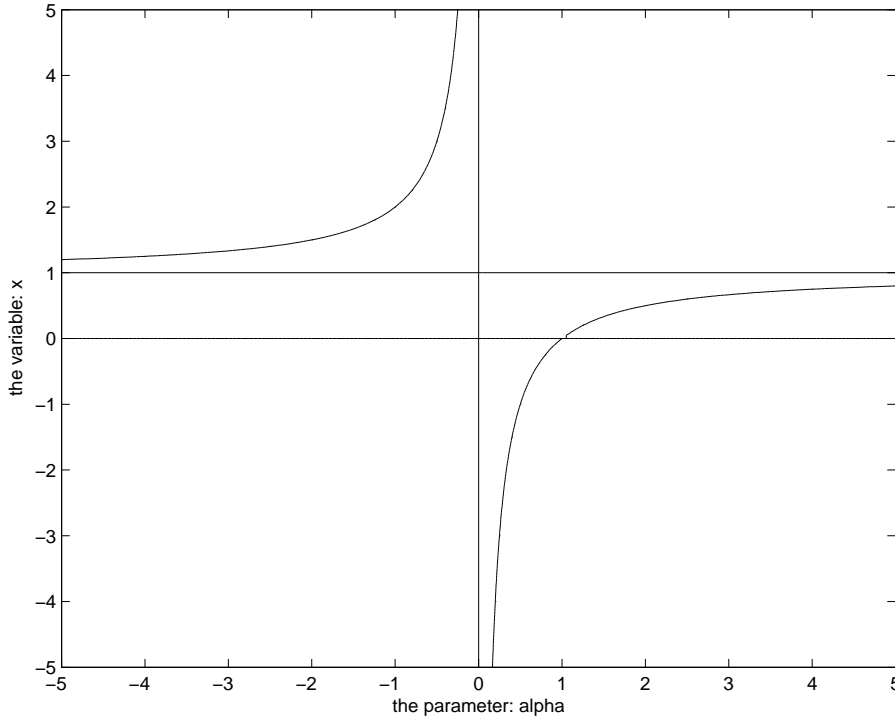
FIGURE 1. The bifurcation diagram in $\alpha - x$ plane, consisting of the up-moved hyperbolic curve and α axis.

is smaller than tumor cell transition rate. If $\alpha - 1 - \beta > 0$, that is $\lambda > \delta$, the tumor will grow exponentially. If $\alpha - 1 - \beta = 0$, $\lambda = \delta$ the tumor will reach a stationary radius R_0^3, and this is stable.

Since the system is partially decoupled, it can be solved explicitly. The solutions are in the following. They are smooth, we use subscript s to denote that in comparing with weak solutions in next section.

Theorem 3.2. *Given initial conditions $x(0)$ and $R(0)$, the solution to the system of (15) and (16) is given by*

$$x_s(t) = \frac{\alpha - 1}{\alpha} \frac{ke^{(\alpha-1)t}}{1 + ke^{(\alpha-1)t}}, \quad R_s^3(t) = R_*^3 + \frac{c}{1+k}e^{-\beta t} + \frac{ck}{1+k}e^{(\alpha-1-\beta)t},$$

where $k = \frac{\alpha x(0)}{\alpha - 1 - \alpha x(0)}$, $c = R^3(0) - R_*^3$.

For any initial conditions $0 \leq x(0) \leq 1$ and $R(0) \geq R_*$, the solution satisfies $0 \leq x_s(t) \leq 1$ and $R_s(t) \geq R_*$.

We know the parameter α is positive, so that $\frac{\alpha-1}{\alpha} < 1$. From the bifurcation diagram, when $0 \leq \frac{\alpha-1}{\alpha} \leq x(0) \leq 1$, $x_s(t)$ will decrease to $\frac{\alpha-1}{\alpha}$. When $\frac{\alpha-1}{\alpha} < 0$ and $0 \leq x(0) \leq 1$, $x_s(t)$ will decrease to 0. When $0 \leq x(0) \leq \frac{\alpha-1}{\alpha}$, $x_s(t)$ will increase to $\frac{\alpha-1}{\alpha} < 1$.

From $R_s^3(t) = R_*^3 + (R^3(0) - R_*^3)e^{\int_0^t (\alpha x - \beta)dt}$, it is easy to see $R_s(t) \geq R_*$ if $R(0) \geq R_*$.

We also can get the same exact information about the tumor regrowth pattern by analysis these solutions.

3.3. **The weak solution to the system with therapies.** Most drug treatments are administered within a finite period of time. Their effects may change the whole dynamics of the disease system, or may just delay the development of the disease. Although the asymptotical behavior of the systems with therapies is important for gaining insight, the behavior with finite time is more important for medical practice. In [5], they study long-term behavior of drug disturbed systems. For our model here, we can specifically find weak solutions for the purpose of analysis.

In the system of (13) and (14), the right hand side of (13) is not continuous. We will construct a weak solution which is continuous, and use it to study the efficacy of radiation and chemotherapy. We rewrite equation (13) as

$$
\frac{dx}{dt} = \begin{cases} (\alpha - 1 - a - b)x - \alpha x^2 & \text{if } 6\delta < t \leq 12\delta, \\ (\alpha - 1 - 2b)x - \alpha x^2 & \text{if } 12\delta < t \leq 20\delta, \\ (\alpha - 1 - \frac{8}{3}b)x - \alpha x^2 & \text{if } 20\delta < t \leq 40\delta, \\ (\alpha - 1)x - \alpha x^2 & \text{otherwise.} \end{cases}
$$

Given $x(0) = x_0$, we first solve (13) in the interval $[0, 6\delta]$. The solution is

$$
x_1(t) = \frac{(\alpha - 1)x_0}{\alpha x_0 + (\alpha - 1 - \alpha x_0)e^{-(\alpha-1)t}}, \quad 0 \leq t \leq 6\delta.
$$

We then solve it in the interval $[6\delta, 12\delta]$. Denote the solution by $x_2(t)$, then initial condition is $x_2(6\delta) = x_1(6\delta)$. The solution is given by

$$
x_2(t) = \frac{\alpha - 1 - a - b}{\alpha} \frac{k_2 e^{(\alpha-1-a-b)(t-6\delta)}}{1 + k_2 e^{(\alpha-1-a-b)(t-6\delta)}}, \quad 6\delta \leq t \leq 12\delta,
$$

where $k_1 = \frac{\alpha x_0}{\alpha - 1 - \alpha x_0}$ and $k_2 = \frac{(\alpha-1)k_1 e^{6(\alpha-1)\delta}}{\alpha-1-a-b-k_1(a+b)e^{6(\alpha-1)\delta}}$. Similarly, we get

$$
x_3(t) = \frac{\alpha - 1 - 2b}{\alpha} \frac{k_3 e^{(\alpha-1-2b)(t-12\delta)}}{1 + k_3 e^{(\alpha-1-2b)(t-12\delta)}}, \quad 12\delta \leq t \leq 20\delta,
$$

where $k_3 = \frac{(\alpha-1-a-b)k_2 e^{6(\alpha-1-a-b)\delta}}{\alpha-1-2b+k_2(a-b)e^{6(\alpha-1-a-b)\delta}}$;

$$
x_4(t) = \frac{\alpha - 1 - \frac{8}{3}b}{\alpha} \frac{k_4 e^{(\alpha-1-\frac{8}{3}b)(t-20\delta)}}{1 + k_4 e^{(\alpha-1-\frac{8}{3}b)(t-20\delta)}}, \quad 20\delta \leq t \leq 40\delta,
$$

here $k_4 = \frac{(\alpha-1-2b)k_3 e^{8(\alpha-1-2b)\delta}}{\alpha-1-\frac{8}{3}b-\frac{2}{3}bk_3 e^{8(\alpha-1-2b)\delta}}$; and

$$
x_5(t) = \frac{\alpha - 1}{\alpha} \frac{k_5 e^{(\alpha-1)(t-40\delta)}}{1 + k_5 e^{(\alpha-1)(t-40\delta)}}, \quad t \geq 40\delta,
$$

where $k_5 = \frac{(\alpha-1-\frac{8}{3}b)k_4 e^{20(\alpha-1-\frac{8}{3}b)\delta}}{\alpha-1+\frac{8}{3}bk_4 e^{20(\alpha-1-\frac{8}{3}b)\delta}}$. The solution made up of those five pieces can also been extended to $-\infty$. However, it is not necessary for our biological study. We denote this solution by $x_w(t)$.

Correspondingly, we derived a solution of (14) as follows.

$$
R_1^3(t) = R_*^3 + \frac{c_1}{1 + k_1}e^{-\beta t} + \frac{c_1 k_1}{1 + k_1}e^{(\alpha-1-\beta)t}, \quad 0 \leq t \leq 6\delta,
$$

where $c_1 = R^3(0) - R_*^3$. For $6\delta \le t \le 12\delta$,

$$R_2^3(t) = R_*^3 + \frac{c_2}{1+k_2}e^{-\beta(t-6\delta)} + \frac{c_2 k_2}{1+k_2}e^{(\alpha-1-a-b-\beta)(t-6\delta)},$$

where $c_2 = \frac{c_1}{1+k_1}e^{-6\beta\delta} + \frac{c_1 k_1}{1+k_1}e^{6(\alpha-1-\beta)\delta}$. For $12\delta \le t \le 20\delta$,

$$R_3^3(t) = R_*^3 + \frac{c_3}{1+k_3}e^{-\beta(t-12\delta)} + \frac{c_3 k_3}{1+k_3}e^{(\alpha-1-2b-\beta)(t-12\delta)},$$

where $c_3 = \frac{c_2}{1+k_2}e^{-6\beta\delta} + \frac{c_2 k_2}{1+k_2}e^{6(\alpha-1-a-b-\beta)\delta}$. For $20\delta \le t \le 40\delta$,

$$R_4^3(t) = R_*^3 + \frac{c_4}{1+k_4}e^{-\beta(t-20\delta)} + \frac{c_4 k_4}{1+k_4}e^{(\alpha-1-\frac{8}{3}b-\beta)(t-20\delta)},$$

where $c_4 = \frac{c_3}{1+k_3}e^{-8\beta\delta} + \frac{c_3 k_3}{1+k_3}e^{8(\alpha-1-2b-\beta)\delta}$. When $t \ge 40\delta$,

$$R_5^3(t) = R_*^3 + \frac{c_5}{1+k_5}e^{-\beta(t-40\delta)} + \frac{c_5 k_5}{1+k_5}e^{(\alpha-1-\beta)(t-40\delta)},$$

where $c_5 = \frac{c_4}{1+k_4}e^{-20\beta\delta} + \frac{c_4 k_4}{1+k_4}e^{20(\alpha-1-\frac{8}{3}b-\beta)\delta}$. We denote this solution by $R_w(t)$.
We then state it as a theorem.

Theorem 3.3. *For any initial conditions $0 \le x(0) \le 1$ and $R(0) \ge R_*$, the system of (13)and (14) has a unique weak solution given by $x_w(t)$, $R_w(t)$ for $t \ge 0$. $x_w(t)$ and $R_w(t)$ are continuous, and $0 \le x_w(t) \le 1$ and $R_w(t) \ge R_*$.*

For the biologically meaningful values of the parameters, it is required that $a \ge 0$, $b \ge 0$, $\alpha > 0$. And we require $\alpha - 1 - a - b \ge 0$. From the bifurcation diagram Figure 1, $0 \le x_1(t) \le 1$. So, $0 \le x_2(6\delta) \le 1$. If $0 \le \frac{\alpha-1-a-b}{\alpha} \le x_2(6\delta)$, then $0 \le \frac{\alpha-1-a-b}{\alpha} \le x_2(t) \le 1$ since $\frac{\alpha-1-a-b}{\alpha}$ is a stable equilibrium point for the equation $\frac{dx}{dt} = (\alpha - 1 - a - b)x - \alpha x^2$. If $\frac{\alpha-1-a-b}{\alpha} \le 0$, $0 \le x_2(t) \le 1$ since 0 is a stable equilibrium point. Similarly, $0 \le x_3(t) \le 1$, $0 \le x_4(t) \le 1$, and $0 \le x_5(t) \le 1$. Thus, $0 \le x_w(t) \le 1$. It is easy to see $R_w(t) \ge R_*$.

¿From the construction of the solution, we know $x_w(t)$ and $R_w(t)$ are continuous. The uniqueness still refer to classical meaning. It then is obvious.

With those assumptions about parameter values and the same initial condition, by computation and comparison, we have another theorem.

Theorem 3.4. *$x_s(12\delta) > x_w(12\delta)$, $x_s(20\delta) > x_w(20\delta)$, $x_s(40\delta) > x_w(40\delta)$; $R_s(12\delta) > R_w(12\delta)$, $R_s(20\delta) > R_w(20\delta)$, $R_s(40\delta) > R_w(40\delta)$.*

This verifies that radiation (represented by parameter a) and chemotherapy (represented by parameter b) have suppression effect on tumor growth.

We also want to compare efficacy of radiation and that of chemotherapy. Let $x_a(t)$ and $R_a(t)$ be the tumor cell density and the tumor radius when only radiation therapy is administered, and $x_b(t)$ and $R_b(t)$ be the tumor cell density and the tumor radius when only chemotherapy is administered. Then, we have a comparison theorem.

Theorem 3.5. *$\frac{\alpha-1-a}{\alpha-1-b} \le \frac{x_a(t)}{x_b(t)} \le 1$ and $\frac{R_a^3(t)-R_*^3}{R_b^3(t)-R_*^3} \le \frac{\alpha-1-b}{\alpha x_0}e^{-(a-b)t}$.*

The proof is a computation by using a weak solution. Let start the therapy at $t = 0$ when tumor has already grown a certain period of time after resection. Then, $\frac{x_a(t)}{x_b(t)} = \frac{\alpha-1-a}{\alpha}\frac{k_a e_{(\alpha-1-a)t}}{1+k_a e^{(\alpha-1-a)t}}\frac{\alpha}{\alpha-1-b}\frac{1+k_b e^{(\alpha-1-b)t}}{k_b e^{(\alpha-1-b)t}}$, where k_a and k_b are coefficients determined by initial conditions. We can take a limit for this ratio although it is

valid within a finite period of time. Since $\alpha - 1 - a \geq 0$, $\alpha - 1 - b \geq 0$, and $a \leq b$, this ratio is decreasing, and we have $\frac{x_a(t)}{x_b(t)} \geq \frac{\alpha-1-a}{\alpha-1-b}$. Since two therapies start at the same initial condition, the ratio is one at the initial time.

Since $\alpha - 1 - a \geq 0$, $\alpha - 1 - b \geq 0$, and $a \geq b$, so $\alpha - 1 - b \geq a - b$. We therefore have the following estimate.

$$\frac{R_a^3(t) - R_*^3}{R_b^3(t) - R_*^3}$$

$$= \left(\frac{c}{1+k_a}e^{-\beta t} + \frac{ck_a}{1+k_a}e^{(\alpha-1-a-\beta)t}\right) \div \left(\frac{c}{1+k_b}e^{-\beta t} + \frac{ck_b}{1+k_b}e^{(\alpha-1-b-\beta)t}\right)$$

$$\leq \left(\frac{c}{1+k_a}e^{-(\alpha-1-b)t} + \frac{ck_a}{1+k_a}e^{-(a-b)t}\right) \div \frac{ck_b}{1+k_b}$$

$$\leq \frac{1+k_b}{k_b}e^{-(a-b)t} = \frac{\alpha-1-b}{\alpha x_0}e^{-(a-b)t}.$$

¿From this theorem, We may conclude that the efficacy of radiotherapy and efficacy of chemotherapy on tumor cells can be measured by the ratio of the number densities of tumor cells, which is bigger than $\frac{\alpha-1-a}{\alpha-1-b}$. The efficacy of radiotherapy and efficacy of chemotherapy on tumor growth in terms of the tumor radius can be measured by the ratio of the $R^3 - R_*^3$, which is smaller than $\frac{\alpha-1-b}{\alpha x_0}e^{-(a-b)t}$. Therefore, radiation has much profound effect on tumor growth.

4. **Discussion.** ¿From the computation of the solution $x_w(t)$ and $R_w(t)$, if the initial value $\frac{\alpha-1}{\alpha} < x_0 < 1$, the lowest value of x that can be reached by these two therapies is in between $\frac{\alpha-1-a-b}{\alpha}$ and $\frac{\alpha-1-\frac{8}{3}b}{\alpha}$, we also suppose radiation parameter a is bigger than $\frac{5}{3}b$. The tumor will eventually grow again until it reaches a fatal size.

If we take a risk to increase radiation amount, namely increase the parameter a value, such $\alpha - 1 - a - b$ is almost zero or even negative, we have a chance to kill all tumor cells within some finite period of time. For example, we can have $x_w(m\delta) = 0$ for some m. Then, there will not be a source for the increasing of the radius $R_w(t)$. Rather, the regrowth will stop after a delayed period of time.

Since the chemotherapy only has very small effect on tumor growth comparing with radiotherapy, only has 1 to 10 percent efficacy of radiation treatment [6], it can not change the dynamics of the system. However, if we first use chemotherapy with different protocols to gradually bring down the tumor cell density $x(t)$ from the initial value x_0, and then use radiation, radiation will sharply decrease the x value. The lowest value of $x(t)$ can certainly be reached.

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