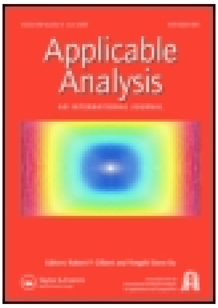


Applicable Analysis: An International Journal
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gapa20

# A solvable hyperbolic free boundary problem modelling tumour regrowth

Dian Yang [a] [b] , Jianjun Paul Tian [a] & Jin Wang [c]

[a] Department of Mathematics, The College of William and Mary, Williamsburg, VA, USA

[b] Harvard School of Engineering and Applied Sciences, Cambridge, MA, USA

[c] Department of Mathematics and Statistics, Old Dominion University, Norfolk, VA, USA

Version of record first published: 29 May 2012

*Applicable Analysis*
2012, 1–18, iFirst



# A solvable hyperbolic free boundary problem modelling tumour regrowth

Dian Yang[ab], Jianjun Paul Tian[a]* and Jin Wang[c]

[a]*Department of Mathematics, The College of William and Mary, Williamsburg, VA, USA;* [b]*Harvard School of Engineering and Applied Sciences, Cambridge, MA, USA;* [c]*Department of Mathematics and Statistics, Old Dominion University, Norfolk, VA, USA*

Communicated by Y. Xu

(*Received 12 March 2012; final version received 29 April 2012*)



Recently, Tian and Friedman et al. developed a mathematical model on brain tumour recurrence after resection [J.P. Tian, A. Friedman, J. Wang and E.A. Chiocca, *Modeling the effects of resection, radiation and chemotherapy in glioblastoma*, J. Neuro-Oncol. 91(3) (2009), pp. 287–293]. The model is a free boundary problem with a hyperbolic system of nonlinear partial differential equations. In this article, we conduct a rigorous analysis on this hyperbolic system and prove the local and global existence and uniqueness of the solution. It is well known that most nonlinear free boundary problems are impossible to solve in terms of explicit analytical solutions. In contrast, the free boundary problem in this study is solvable, and the explicit solution is found using the backward characteristic curve method. This explicit solution is then validated by numerical simulation results. An interesting finding in this study is that the problem can be treated as a hyperbolic system defined on an infinite domain where the initial condition has a first-type discontinuity.

**Keywords:** free broundary problem; tumour growth; characteristic curve method

**AMS Subject Classifications:** 35L50; 35L60; 35Q92

## 1. Introduction

A variety of partial differential equation (PDE) models for tumour growth have been developed over the last few decades. For a recent review, we refer to [1]. These models are generally based on mass conservation laws and reaction–diffusion processes for cell densities. The surface of the tumour is a free boundary which evolves in time, and one central task in tumour modelling is to determine the motion of the free boundary so as to predict the tumour growth pattern.

The brain tumour, i.e. glioblastoma multiforme, is the most aggressive one among solid tumours. The life expectancy from the time when it is diagnosed is typically 1 year. There have been several interesting models to describe its growth

*Corresponding author. Email: jtian@wm.edu

ISSN 0003–6811 print/ISSN 1563–504X online

http://dx.doi.org/10.1080/00036811.2012.692366
http://www.tandfonline.com

pattern and possible therapies (e.g. [2–5]). Each model has its own strength and specific focus. However, a common feature among most (if not all) of these models is that they are not analytically solvable due to the strong nonlinearity of the PDEs and the presence of an unknown moving surface. Meanwhile, the existence and uniqueness of the solutions to these models are usually difficult to establish. Hence, these works have to heavily rely on numerical simulation to obtain essential information on tumour evolution. Design of accurate and stable numerical methods for nonlinear moving boundary problems is generally a nontrivial task; if not carefully implemented, numerical errors from the simulation could easily mask the true effects of the biological processes. Furthermore, since the analytical solutions cannot be found, the only means to validate the numerical results would be the comparison with experimental measurements which are usually limited in scope, and, may not even be available in some situations.

In contrast to the afore-mentioned studies, a glioblastoma regrowth model recently developed in [6] presents an example of solvable hyperbolic free boundary problems. This work integrates different treatments of patients by surgery, radiotherapy and chemotherapy, with model parameters chosen in such a way that the simulation results fit the patient data analysis reported in [7–9]. Based on the numerical prediction, the model suggests certain combinations of treatment protocols that can give patients maximal survival time. However, neither effort was made in [6] to mathematically analyse the model, nor to seek its exact solution, due to the biomedical focus of that work.

In this article, we will conduct a rigorous analysis on the model proposed in [6] so as to improve our understanding of the tumour growth mechanism revealed in this model. Specifically, we will prove the local existence and uniqueness of the solution by the Banach fixed point theorem, and then extend the local solution to the global solution. We will then determine the explicit solution by using the backward characteristic curve method. An interesting finding is that the original free boundary problem can be reformulated as a fixed boundary problem defined on an infinite domain with discontinuous initial condition. To our knowledge, this analytical treatment of nonlinear free boundary problems is new, and the type of the exact solution we obtain in this article has never been published before. This study will not only confirm the numerical prediction in the original work [6], but also shed light on further analysis for problems of this type towards better understanding the complicated phenomena of tumour growth.

We organize the remainder of this article as follows. In Section 2, we present the tumour model and perform a series of transformations to facilitate the analysis. In Section 3, we prove the existence and uniqueness of the solution for both local and global domains. In Section 4, we derive the exact solution in explicit form. In Section 5, we provide numerical simulation results to validate the analytical solution. Finally, we close this article by some discussion.

## 2. Model and transformation

The model in [6] describes a spherical tumour regrowing after surgical resection. The tumour contains tumour cells ($x$) and necrotic cells ($y$). The variable $x$ represents the number density of tumour cells (i.e. the number of tumour cells in $1\,\mathrm{mm}^3$); the variable $y$ represents the number density of necrotic cells. It is assumed that the number density of cells in tumour is a constant [3], that is, $x+y=$ number of cells in $1\,\text{mm}^3$, which is $\theta = 10^6$ [10]. New tumour cells are produced by proliferation, and they transit to necrotic cells by lysis. The proliferation and removal of cells cause a movement of cells within the tumour, with a convection term, for tumour cells $x$, in the form $\frac{1}{r^2}\frac{\partial}{\partial r}[r^2 u(r,t)x(r,t)]$, where $u(r,t)$ is the radial velocity. By mass conservation law,

$$\begin{aligned}\frac{\partial x(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 u(r,t)x(r,t)\right) &= \lambda x(r,t) - \delta x(r,t),\\ \frac{\partial y(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 u(r,t)\,y(r,t)\right) &= \delta x(r,t) - \mu y(r,t).\end{aligned} \tag{1}$$

By adding these two equations together, it gives the equation for the radical velocity:

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

The tumour radius evolves according to

$$\frac{\mathrm{d}R}{\mathrm{d}t} = u(R(t),t). \tag{3}$$

It is assumed that after resection there is a small shell of tumour left,

$$x(r,0) = c\theta, \quad \text{for} \quad R_* \le r \le R_0. \tag{4}$$

The above model does not include radiotherapy and chemotherapy. If the standard radiotherapy is administered over a time period of 6 weeks with $6 \le t \le 12$ and the temozolomide is given during the weeks of $6 \le t \le 40$, equations in (1) are replaced by

$$\begin{aligned}\frac{\partial x(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 u(r,t)x(r,t)\right) &= (\lambda-\delta)x(r,t) - (A\rho(t) + B\tau(t))x(r,t),\\ \frac{\partial y(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 u(r,t)\,y(r,t)\right) &= \delta x(r,t) + (A\rho(t) + B\tau(t))x(r,t) - \mu y(r,t),\end{aligned} \tag{5}$$

where $\rho(t)$ and $\tau(t)$ represent radiotherapy and chemotherapy, respectively, and are prescribed by (see [6]):

$$\rho(t) = \begin{cases} 1, & \text{if } 6 \le t \le 12;\\ 0, & \text{otherwise.}\end{cases} \qquad \tau(t) = \begin{cases} 1, & \text{if } 6 \le t \le 12;\\ 2, & \text{if } 16 \le t \le 20;\\ 8/3, & \text{if } 20 < t \le 28;\\ 0, & \text{otherwise.}\end{cases}$$

Below, we first transform this model for the ease of analysis.

Notice $\alpha(t) := \lambda - \delta - A\rho(t) - B\tau(t)$. We will treat $\alpha(t)$ as a step function or constant. We apply the following minor change of notations:

$$\tilde{x}(r,t) = x(r,t)/\theta \quad \beta = \lambda + \mu,$$

and the system becomes

$$\begin{cases} \dfrac{\partial \tilde{x}(r,t)}{\partial t} + \dfrac{1}{r^2}\dfrac{\partial}{\partial t}(r^2 u(r,t)\tilde{x}(r,t)) = \alpha \tilde{x}(r,t), & R_* \le r \le R(t), t \ge 0, \\ \dfrac{1}{r^2}\dfrac{\partial}{\partial t}(r^2 u(r,t)) = \beta \tilde{x}(r,t) - \mu, & R_* \le r \le R(t), t \ge 0, \\ u(R_*, t) = 0, & t \ge 0, \\ \dfrac{\mathrm{d}R(t)}{\mathrm{d}t} = u(R(t), t), & t \ge 0, \end{cases}$$

with the initial conditions: $R(0) = R_0$, $\tilde{x}(r,0) = c$, for $R_* \le r \le R(0)$. Here the second equation is also replaced by the sum of the first two equations.

To get rid of all $r^2$ or $r$ terms, we introduce the 'volume speed':

$$v(r,t) := r^2 u(r,t).$$

The system then becomes

$$\begin{cases} \dfrac{\partial \tilde{x}(r,t)}{\partial t} + \dfrac{1}{r^2}\dfrac{\partial}{\partial t}(v(r,t)\tilde{x}(r,t)) = \alpha \tilde{x}(r,t), & R_* \le r \le R(t), t \ge 0, \\ \dfrac{1}{r^2}\dfrac{\partial v(r,t)}{\partial t} = \beta \tilde{x}(r,t) - \mu, & R_* \le r \le R(t), t \ge 0, \\ v(R_*, t) = 0, & t \ge 0, \\ R(t)^2 \frac{\mathrm{d}R(t)}{\mathrm{d}t} = v(R(t), t), & t \ge 0, \end{cases}$$

with the initial conditions: $R(0) = R_0$, $\tilde{x}(r,0) = c$, for $R_* \le r \le R(0)$.

Then we apply the following change of variables:

$$\begin{aligned} s &:= r^3, \\ V(t) &:= R(t)^3, \\ V_* &:= R_*^3, \\ V_0 &:= R_0^3, \\ \omega(s,t) &:= 3v(\sqrt[3]{s}, t). \end{aligned}$$

By abusing notations, we redefine '$x$' as function $\tilde{x}$ in terms of variable $s$:

$$x(s,t) := \tilde{x}\left(\sqrt[3]{s}, t\right).$$

Then we have

$$\begin{aligned} \frac{\partial \omega(s,t)}{\partial s} &= 3\frac{\partial}{\partial s} v\left(\sqrt[3]{s}, t\right) = \frac{\partial v(r,t)}{\partial r} s^{-\frac{2}{3}} = v_r(r,t) r^{-2}, \\ \frac{\partial x(s,t)}{\partial s} &= \frac{1}{3}\frac{\partial \tilde{x}(r,t)}{\partial r} s^{-\frac{2}{3}} = \frac{1}{3}\frac{\partial \tilde{x}(r,t)}{\partial r} r^{-2}, \\ \frac{\mathrm{d}V(t)}{\mathrm{d}t} &= \frac{\mathrm{d}}{\mathrm{d}t}(R(t)^3) = 3R(t)^2 \frac{\mathrm{d}R(t)}{\mathrm{d}t} = 3v(R(t), t) = \omega(V(t), t). \end{aligned}$$

After the change of variables, the system becomes

$$\begin{cases} \dfrac{\partial x(s,t)}{\partial t} + \dfrac{\partial}{\partial s}(\omega(s,t)x(s,t)) = \alpha x(s,t), & V_* \le s \le V(t), t \ge 0, \\ \dfrac{\partial \omega(s,t)}{\partial s} = \beta x(s,t) - \mu, & V_* \le s \le V(t), t \ge 0, \\ \omega(V_*, t) = 0, & t \ge 0, \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \omega(V(t), t), & t \ge 0, \end{cases}$$

with the initial conditions: $V(0) = V_0$, $x(s, 0) = c$, for $V_* \le s \le V(0)$. Substitute the second equation into the first one to obtain

$$\frac{\partial x(s,t)}{\partial t} + \omega(s,t)\frac{\partial x(s,t)}{\partial s} = \beta x(s,t)(K - x(s,t)),$$

where $K := \frac{\alpha+\mu}{\beta}$, and $K < 1$.

Thus, we have transformed the original system into the following system:

$$\begin{cases} \dfrac{\partial x(s,t)}{\partial t} + \omega(s,t)\dfrac{\partial x(s,t)}{\partial s} = \beta x(s,t)(K - x(s,t)), & V_* \le s \le V(t), t \ge 0, \\ \dfrac{\partial \omega(s,t)}{\partial s} = \beta x(s,t) - \mu, & V_* \le s \le V(t), t \ge 0, \\ \omega(V_*, t) = 0, & t \ge 0, \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \omega(V(t), t), & t \ge 0, \end{cases} \tag{6}$$

with the initial conditions: $V(0) = V_0$, $x(s, 0) = \varphi(s)$, for $V_* \le s \le V(0)$. Here a more general initial condition $\varphi(s)$ will be considered.



## 3. Existence and uniqueness of solution

### 3.1. *Landau's transformation*

In the study of free boundary problems, we often find it convenient to transform problems into fixed domains. We transform the system (6) in the unknown domain $\{(s, t)\colon V_* \le s \le V(t), t \ge 0\}$ into a system in the fixed domain $\{(\bar{s}, t)\colon 0 \le \bar{s} \le 1, t \ge 0\}$ by using the following transformation:

$$\bar{s} := \frac{s - V_*}{V(t) - V_*}, \quad s = (V(t) - V_*)\bar{s} + V_*.$$

We introduce the functions

$$\bar{x}(\bar{s}, t) := x((V(t) - V_*)\bar{s} + V_*, t), \quad 0 \le \bar{s} \le 1, t \ge 0,$$

$$\bar{\omega}(\bar{s}, t) := \frac{\omega((V(t) - V_*)\bar{s} + V_*, t)}{V(t) - V_*}, \quad 0 \le \bar{s} \le 1, t \ge 0.$$

Hence, we can replace functions in the system (6) with the following:

$$x(s,t) = \bar{x}\left(\frac{s - V_*}{V(t) - V_*}, t\right) = \bar{x}(\bar{s}, t),$$
$$\omega(s,t) = (V(t) - V_*)\bar{\omega}\left(\frac{s - V_*}{V(t) - V_*}, t\right) = (V(t) - V_*)\bar{\omega}(\bar{s}, t).$$

It follows:

$$\begin{aligned}
\frac{\partial x(s,t)}{\partial s} &= \frac{\partial \bar{x}(\bar{s},t)}{\partial \bar{s}} \frac{1}{V(t) - V_*},\\
\frac{\partial x(s,t)}{\partial t} &= \frac{\partial \bar{x}(\bar{s},t)}{\partial t} - \frac{\partial \bar{x}(\bar{s},t)}{\partial \bar{s}} \frac{s - V_*}{(V(t) - V_*)^2} V'(t)\\
&= \frac{\partial \bar{x}(\bar{s},t)}{\partial t} - \frac{\partial \bar{x}(\bar{s},t)}{\partial \bar{s}} \bar{s}\bar{\omega}(1,t),\\
\frac{\partial \omega(s,t)}{\partial s} &= \frac{\partial \bar{\omega}(\bar{s},t)}{\partial \bar{s}}.
\end{aligned}$$

Substituting these expressions into the system (6) we have a new system:

$$\begin{cases}
\dfrac{\partial \bar{x}(\bar{s},t)}{\partial t} + (\bar{\omega}(\bar{s},t) - \bar{s}\bar{\omega}(1,t))\dfrac{\partial \bar{x}(\bar{s},t)}{\partial \bar{s}} = \beta \bar{x}(\bar{s},t)(K - \bar{x}(\bar{s},t)), & 0 \le \bar{s} \le 1, t \ge 0,\\
\dfrac{\partial \bar{\omega}(\bar{s},t)}{\partial \bar{s}} = \beta \bar{x}(\bar{s},t) - \mu, & 0 \le \bar{s} \le 1, t \ge 0,\\
\bar{\omega}(0,t) = 0, & t \ge 0,\\
\dfrac{\partial V(t)}{\partial t} = (V(t) - V_*)\bar{\omega}(1,t), & t \ge 0,
\end{cases} \tag{7}$$

with an initial condition: $V(0) = V_0$, $\bar{x}(\bar{s}, 0) = \bar{\varphi}(\bar{s})$, for $0 \le \bar{s} \le 1$, where we define $\bar{\varphi}(\bar{s}) := \varphi((V(t) - V_*)\bar{s} + V_*)$. We further define

$$l(\bar{s},t) = \bar{\omega}(\bar{s},t) - \bar{s}\bar{\omega}(1,t).$$

Then, the system (7) takes the following form:

$$\begin{cases}
\dfrac{\partial x(s,t)}{\partial t} + l(s,t)\dfrac{\partial x(s,t)}{\partial s} = \beta x(s,t)(K - x(s,t)), & 0 \le s \le 1, t \ge 0,\\
\dfrac{\partial \omega(s,t)}{\partial s} = \beta x(s,t) - \mu, & 0 \le s \le 1, t \ge 0,\\
\omega(0,t) = 0, & t \ge 0,\\
\dfrac{\partial V(t)}{\partial t} = (V(t) - V_*)\omega(1,t), & t \ge 0,
\end{cases} \tag{8}$$

with an initial condition: $V(0) = V_0$, $x(s, 0) = \varphi(s)$. We dropped all bars for simplicity. Notice $\omega(s, t)$ (and hence $l(s, t)$) can be explicitly expressed in terms of $x(s, t)$:

$$\omega(s,t) = \int_0^s (\beta x(\rho,t) - \mu)\mathrm{d}\rho \tag{9}$$

$$l(s,t) = \int_0^s (\beta x(\rho,t) - \mu)\mathrm{d}\rho - \mathrm{s}\int_0^1 (\beta \mathrm{x}(\rho,\mathrm{t}) - \mu)\mathrm{d}\rho. \tag{10}$$

To prove the existence and uniqueness of the solution of the original free boundary system (6), it suffices to prove them for this fixed boundary system (8).

### 3.2. *Local existence and uniqueness*

In this subsection, we shall prove the existence and uniqueness of the solution to the system (8) for a small time $T > 0$. The method we use is the Banach fixed point theorem (i.e. the contraction mapping theorem). We will define a complete metric function space $X_T$, and construct a mapping $\mathcal{F}$ from $X_T$ to itself. We then prove this mapping is a contraction mapping. The fixed point of this mapping is the solution of the system (8). The conclusion is the local existence and uniqueness theorem at the end of this subsection.

We introduce the space $X_T$ of pairs of functions $(V(t), x(s,t))$ defined for $0 \le s \le 1$, $0 \le t \le T$, where $T$ is a fixed positive small number, satisfying the following conditions:

(1) $V(t) \in C[0,T]$, $V(0) = V_0$, $V(t) \ge 0$, and

$$|V(t) - V_0| \le \delta,$$

where $\delta$ is a fixed number between 0 and $V_0 - V_*$ (for instance, one may take $\delta = (V_0 - V_*)/2$);

(2) $x(s,t) \in C([0,1] \times [0,T])$, $x(s,0) = \varphi(s) \ge 0$ and $|\varphi'(s)| = M_0$, and

$$0 \le x(s,t) \le \max_{0 \le s \le 1} \varphi(s) = 1, \quad 0 \le s \le 1, 0 \le t \le T.$$

We take the metric $d$ in $X_T$ to be the uniform metric, i.e.

$$d((V_1, x_1), (V_2, x_2)) = \max_{0 \le t \le T} |V_1(t) - V_2(t)| + \max_{0 \le s \le 1, 0 \le t \le T} |x_1(s,t) - x_2(s,t)|.$$

Obviously, $X_T$ is a complete metric space.

Given a pair $(V(t), x(s,t)) \in X_T$, define $\omega(s,t)$ and $l(s,t)$ according to Equations (9) and (10), respectively, and consider the following two initial value problems:

$$\begin{cases} \dfrac{\partial \tilde{x}(s,t)}{\partial t} + l(s,t)\dfrac{\partial \tilde{x}(s,t)}{\partial s} = \beta \tilde{x}(s,t)(K - \tilde{x}(s,t)), & 0 \le s \le 1, 0 \le t \le T, \\ \tilde{x}(s,0) = \varphi(s), & 0 \le s \le 1; \end{cases} \tag{11}$$

$$\begin{cases} \dfrac{\mathrm{d}\tilde{V}(t)}{\mathrm{d}t} = (\tilde{V}(t) - V_*)\omega(1,t), & 0 \le t \le T, \\ \tilde{V}(0) = V_0. \end{cases} \tag{12}$$

Clearly, there exists a unique nonnegative solution of $\tilde{V}(t) \in C^1[0,T]$:

$$\tilde{V}(t) = (V_0 - V_*)\exp\left(\int_0^t \omega(1,\tau)\mathrm{d}\tau\right) + V_*, \quad 0 \le t \le T.$$

Since

$$\omega(1,t)=\int_0^1(\beta x(\rho,t)-\mu)\mathrm{d}\rho\le\beta+\mu,$$

we have

$$\begin{aligned}|\tilde{V}(t)-V_0| &= |(V_0-V_*)\exp\left(\int_0^t\omega(1,\tau)\mathrm{d}\tau\right)+V_*-V_0| \\ &= (V_0-V_*)|\exp\left(\int_0^t\omega(1,\tau)\mathrm{d}\tau\right)-1| \\ &\le (V_0-V_*)\left(\exp\left(\int_0^t(\beta+\mu)\mathrm{d}\tau\right)-1\right) \\ &= (V_0-V_*)(\exp(\beta+\mu)t-1) \\ &\le (V_0-V_*)(\beta+\mu)t\exp(\beta+\mu)t \\ &\le (V_0-V_*)(\beta+\mu)T\exp(\beta+\mu)T,\end{aligned}$$

which is less than $\delta$ if $T$ is sufficiently small, namely $\tilde{V}(t)$ satisfies condition 1.

To solve for $\tilde{x}(s,t)$, we define the backward characteristic curve of Equation (11),

$$\tau=\tau(s,t),\quad 0\le s\le 1, 0\le t\le T, \tag{13}$$

which satisfies:

$$\begin{cases}\dfrac{\mathrm{d}\tau(s,t)}{\mathrm{d}t}=l(\tau(s,t),t), & 0\le s\le 1, 0\le t\le T,\\ \tau(s,0)=s, & 0\le s\le 1.\end{cases} \tag{14}$$

Since $l(s,t)$ is continuous in $(s,t)$ and continuously differentiable in $\tau$, these curves are uniquely defined, satisfying $0<\tau(s,t)<1$ for $0<s<1$, $0\le t\le T$, and $\tau(0,t)=0$, $\tau(1,t)=1$ for $0\le t\le T$. From the system (14), we deduce an initial value problem

$$\begin{cases}\dfrac{\partial}{\partial t}\left(\dfrac{\partial\tau(s,t)}{\partial s}\right)=\dfrac{\partial}{\partial s}\left(\dfrac{\partial\tau(s,t)}{\partial t}\right)=\dfrac{\partial}{\partial s}\left(\dfrac{d\tau(s,t)}{dt}\right)=\dfrac{\partial l(\tau,t)}{\partial\tau}\dfrac{\partial\tau}{\partial s},\\ \dfrac{\partial\tau(s,0)}{\partial s}=1,\end{cases} \tag{15}$$

which has the solution

$$\frac{\partial\tau(s,t)}{\partial s}=\exp\left(\int_0^t\frac{\partial l}{\partial\tau}(\tau(s,\rho),\rho)\mathrm{d}\rho\right).$$

Since

$$\frac{\partial l(s,t)}{\partial s}=\frac{\partial\omega(s,t)}{\partial s}-\omega(1,t)=\beta x(\tau,t)-\mu-\omega(1,t),$$

and $-\mu\le\omega(1,t)\le\beta-\mu$, we have

$$-\beta\le\beta x(\tau,t)-\mu-\omega(1,t)\le\beta,$$

which implies

$$e^{-\beta T} \leq \frac{\partial \tau(s,t)}{\partial s} \leq e^{\beta T}, \quad 0 \leq s \leq 1, 0 \leq t \leq T.$$

It follows that the mapping $(s, t) \mapsto (\tau(s, t), t)$ is a one-one and onto correspondence of the region $[0,1] \times [0,T]$ to itself. Setting $\hat{x}(s,t) = \tilde{x}(\tau(s,t),t)$, the system (11) reduces to the initial value problem

$$\begin{cases} \dfrac{\partial \hat{x}(s,t)}{\partial t} = \beta \hat{x}(s,t)(K - \hat{x}(s,t)), & 0 \leq s \leq 1, 0 \leq t \leq T, \\ \hat{x}(s,0) = \tilde{x}(s,0) = \varphi(s), & 0 \leq s \leq 1, \end{cases} \tag{16}$$

which has the unique solution $\hat{x}(s,t)$ for any initial value $\varphi(s)$. It is easy to see $K < 1$ is a stable equilibrium solution for any given $s$. If $\varphi(s) < K$, then $\hat{x}(s,t)$ increases with $t$ and approaches $K$. Then $0 \leq \hat{x}(s,t) < K$. When $\varphi(s) > K$, then $\hat{x}(s,t)$ decreases and approaches $K$. So, $1 > \hat{x}(s,t) > K$ . Therefore, $0 \leq \hat{x}(s,t) \leq 1$. Now let $\zeta = \zeta(\tau, t)$ be the inverse function of $\tau = \tau(s, t)$ for fixed $0 \leq t \leq T$, and let $\tilde{x}(s,t) = \hat{x}(\zeta(s,t),t)$. It is easy to see $0 \leq \tilde{x}(s,t) \leq 1$. Namely, $\tilde{x}(s,t)$ satisfies condition 2.

We now define a mapping $\mathcal{F}$: $X_T \to X_T$, by $\mathcal{F}(V(t), x(s,t)) = (\tilde{V}(t), \tilde{x}(s,t))$. To prove this mapping is a contraction mapping, we need to estimate the spatial derivative of $\hat{x}(s,t)$. Take the derivative with respect to $s$ on equations in (16), and consider the following initial value problem:

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}\left(\dfrac{\partial \hat{x}(s,t)}{\partial s}\right) = \beta \dfrac{\partial \hat{x}(s,t)}{\partial s}(K - 2\hat{x}(s,t)), & 0 \leq s \leq 1, 0 \leq t \leq T, \\ \dfrac{\partial \hat{x}(s,0)}{\partial s} = \varphi'(s), & 0 \leq s \leq 1. \end{cases} \tag{17}$$

Since $\beta(K-2) \leq \beta(K - 2\hat{x}(s,t)) \leq \beta K$ and $K \leq 1$, the solution to this problem (17) satisfies

$$\begin{aligned} \varphi'(s)e^{\beta(K-2)t} \leq \frac{\partial \hat{x}(s,t)}{\partial s} &= \varphi'(s)e^{\beta \int_0^t (K - 2\hat{x}(s,t))\mathrm{d}\tau} \leq \varphi'(s)e^{\beta K t}, \\ \left|\frac{\partial \hat{x}(s,t)}{\partial s}\right| &\leq |\varphi'(s)|e^{\beta K t} \\ &\leq M_0 e^{\beta K t} \\ &\leq M_0 + M_0 \beta K T e^{\beta K T}. \end{aligned}$$

By our assumption on $T$ before, $T$ is sufficiently small, then it follows that

$$\left|\frac{\partial \hat{x}(s,t)}{\partial s}\right| \leq M_0 + 1. \tag{18}$$

We now prove that $\mathcal{F}$ is a contraction map for a sufficiently small $T$. Let $(V_i, x_i) \in X_T$ for $i = 1$, 2 and set

$$\begin{aligned} \omega_i(s,t) &= \int_0^s (\beta x_i(\rho, t) - \mu)\mathrm{d}\rho, \\ l_i(s,t) &= \omega_i(s,t) - s\omega_i(1,t), \\ (\tilde{V}_i, \tilde{x}_i) &= \mathcal{F}(V_i, x_i), \\ d &= d((V_1, x_1), (V_2, x_2)). \end{aligned}$$

By direct calculations, we have

$$|\omega_1(s,t)-\omega_2(s,t)| = \left|\int_0^s \beta(x_1(s,\rho)-x_2(s,\rho))\mathrm{d}\rho\right| \le \beta d,$$
$$|l_1(s,t)-l_2(s,t)| \le |\omega_1(s,t)-\omega_2(s,t)| + s|\omega_1(1,t)-\omega_2(1,t)| \le 2\beta d.$$

Since

$$\tilde{V}_i(t) = (V_0 - V_*)\exp\left(\int_0^t \omega_i(1,\tau)\mathrm{d}\tau\right) + V_*, \quad 0 \le t \le T,$$

we have

$$\begin{aligned}
|\tilde{V}_1(t)-\tilde{V}_2(t)| &= (V_0 - V_*)\left|\exp\left(\int_0^t \omega_1(1,\tau)\mathrm{d}\tau\right) - \exp\left(\int_0^t \omega_2(1,\tau)\mathrm{d}\tau\right)\right| \\
&\le (V_0 - V_*)\exp\left(\int_0^t \omega_2(1,\tau\right)\mathrm{d}\tau)\left|\exp\left(\int_0^t (\omega_1-\omega_2)(1,\tau)\mathrm{d}\tau\right) - 1\right| \\
&\le (V_0 - V_*)\exp((\beta+\mu)t)\exp(\beta \mathrm{d}t)\beta\,\mathrm{d}t \\
&\le (V_0 - V_*)\exp((\beta+\mu)T)\exp(\beta \mathrm{d}T)\beta\,\mathrm{d}T
\end{aligned} \tag{19}$$

which is less than $\frac{1}{4}d$ if $T$ is sufficiently small.

Let $y = \tilde{x}_1 - \tilde{x}_2$. Since

$$\begin{cases} \dfrac{\partial \tilde{x}_i(s,t)}{\partial t} + l_i(s,t)\dfrac{\partial \tilde{x}_i(s,t)}{\partial s} = \beta\tilde{x}_i(s,t)(K - \tilde{x}_i(s,t)), & 0 \le s \le 1, 0 \le t \le T, \\ \tilde{x}_i(s,0) = \varphi(s), & 0 \le s \le 1, \end{cases}$$

we have

$$\begin{cases} \dfrac{\partial(\tilde{x}_1-\tilde{x}_2)}{\partial t} + l_1\dfrac{\partial(\tilde{x}_1-\tilde{x}_2)}{\partial s} + (l_1-l_2)\dfrac{\partial \tilde{x}_2}{\partial s} = \beta K(\tilde{x}_1-\tilde{x}_2) - \beta(\tilde{x}_1^2-\tilde{x}_2^2), \\ (\tilde{x}_1-\tilde{x}_2)(s,0) = \varphi(s), \quad 0 \le s \le 1, \end{cases}$$

which is

$$\begin{cases} \dfrac{\partial y}{\partial t} + l_1\dfrac{\partial y}{\partial s} = (l_2-l_1)\dfrac{\partial \tilde{x}_2}{\partial s} + \beta y(K-(\tilde{x}_1+\tilde{x}_2)), \\ y(s,0) = \varphi(s), \quad 0 \le s \le 1. \end{cases} \tag{20}$$

Notice that the right-hand side of Equation (20) is bounded:

$$\begin{aligned}
\left|(l_2-l_1)\frac{\partial \tilde{x}_2}{\partial s} + \beta y(K-(\tilde{x}_1+\tilde{x}_2))\right| &= \left|(l_2-l_1)\frac{\partial \tilde{x}_2}{\partial s} + \beta y(K-(\tilde{x}_1+\tilde{x}_2))\right| \\
&\le |l_2-l_1|\left|\frac{\partial \tilde{x}_2}{\partial s}\right| + \left|\beta y(K-(\tilde{x}_1+\tilde{x}_2))\right| \\
&\le 2\beta(M_0+1)d + 2\beta(K+2)d.
\end{aligned}$$

By integrating (20) along the characteristics determined by the equation $\frac{d\tau}{dt} = l_1(s,t)$ as before, we find

$$|y| \leq (2\beta(M_0+1) + 2\beta(K+2))dT.$$

When $T$ is small enough, we have

$$|\tilde{x}_1 - \tilde{x}_2| = |y| \leq (2\beta(M_0+1) + 2\beta(K+2))dT \leq \frac{1}{4}d. \tag{21}$$

Combining (19) and (21), we have

$$d((\tilde{V}_1, \tilde{x}_1), (\tilde{V}_2, \tilde{x}_2)) \leq \frac{1}{2} d((V_1, x_1), (V_2, x_2)). \tag{22}$$

Therefore, $\mathcal{F}$ is a contraction mapping.

For the completion, we cite the Banach fixed point theorem [11].

THEOREM 3.1 *Let* $(X, d)$ *be a non-empty complete metric space. Suppose* $T: X \to X$ *is a contraction mapping on* $X$, *i.e. there is a positive real number* $q < 1$ *such that*

$$d(T(x), T(y)) \leq q d(x,y)$$

*for all* $x$, $y$ *in* $X$. *Then the mapping* $T$ *admits one and only one fixed point* $x^*$ *in* $X$, *this means* $T(x^*) = x^*$.

Applying the Banach fixed point theorem to the space $(X_T, d)$ with the mapping $\mathcal{F}$, we then have the following theorem of the local existence and uniqueness of solution of the system (8).

THEOREM 3.2 *Given* $0 < \delta \leq (V_0 - V_*) \leq \frac{1}{\delta}$ *and*

$$0 \leq \varphi(s) \leq 1, \quad \max_{0\leq s\leq 1} \varphi'(s) \leq M_0,$$

*the system* (8) *has the unique solution for* $0 \leq s \leq 1$ *and* $0 \leq t \leq T$, *where* $T$ *is sufficiently small and may depend on* $\delta$ *and* $M_0$.

### 3.3. *Global existence and uniqueness*

In this subsection, we will extend the solution of the system (8) for $0 \leq t \leq T$ step-by-step to all $t > 0$. The result is the following theorem.

THEOREM 3.3 *The system* (8) *has the unique solution for* $0 \leq s \leq 1$ *and* $0 \leq t < \infty$, *and it has properties*

$$0 \leq x(s,t) \leq 1, \tag{23}$$

$$V_* + e^{-\mu t} \leq V(t) \leq V_* + e^{(\beta+\mu)t}. \tag{24}$$

The Theorem (3.2) establishes the solution of the system (8) for a small time. If the following proposition can be proved, then the solution can be extended step-by-step to all $t > 0$.

Proposition 3.1 *For arbitrary $T > 0$, if the solution of the system (8) exists for $0 \le t \le T$, then the* a priori *estimates (23), (24) and*

$$\left|\frac{\partial x(s,t)}{\partial s}\right| \le M, \tag{25}$$

*hold for $0 \le s \le 1$, $0 \le t \le T$, where $M$ is a positive constant which may depend on $T$.*

*Proof* The *a priori* estimates (23) is a consequence the initial value problem (16), and the *a priori* estimates (25) is a consequence of the initial value problem (17). We only need to prove *a priori* estimates (24). Since

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} = (V(t) - V_*)\omega(1,t), \quad t \ge 0,$$

we have

$$\frac{\mathrm{d}}{\mathrm{d}t}\ln(V(t) - V_*) = \omega(1,t) = \int_0^1 (\beta x(\rho,t) - \mu)\mathrm{d}\rho,$$

which is bounded by

$$-\mu \le \int_0^1 (\beta x(\rho,t) - \mu)\mathrm{d}\rho \le (\beta + \mu).$$

Therefore,

$$e^{-\mu t} \le (V(t) - V_*) \le e^{(\beta+\mu)t}.$$

■

## 4. Explicit solution

In Section 3, we have proved the global existence and uniqueness of the solution to the system (8)–(10). The existence and uniqueness do not give much information on the property of a solution, particularly, the behaviour of a solution during periods of finite times. It is to our interest to understand how the solutions behave during periods of finite times and their asymptotic behaviours. Fortunately, we can obtain explicit solutions after some transformation of variables. In this section, we will solve the system explicitly.

At the end of Section 2, we have transformed the original system to the system (6):

$$\begin{cases} \dfrac{\partial x(s,t)}{\partial t} + \omega(s,t)\dfrac{\partial x(s,t)}{\partial s} = \beta x(s,t)(K - x(s,t)), & V_* \le s \le V(t), t \ge 0, \\ \dfrac{\partial \omega(s,t)}{\partial s} = \beta x(s,t) - \mu, & V_* \le s \le V(t), t \ge 0, \\ \omega(V_*,t) = 0, & t \ge 0, \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \omega(V(t),t), & t \ge 0, \end{cases}$$

with the initial conditions: $V(0) = V_0$, $x(s, 0) = \varphi(s)$, for $V_* \leq s \leq V_0$. Similar to the approach in Section 3, we define the 'characteristic' curve of the first equation in the system (6),

$$\gamma = \gamma(s,t), \quad V_* \leq s \leq V_0, t \geq 0, \tag{26}$$

which satisfies:

$$\begin{cases} \dfrac{\mathrm{d}\gamma(s,t)}{\mathrm{d}t} = \omega(\gamma(s,t),t), & V_* \leq s \leq V_0, t \geq 0, \\ \gamma(s,0) = s, & V_* \leq s \leq V_0. \end{cases} \tag{27}$$

Since $\omega(s,t)$ is continuous in $(s,t)$ and continuously differentiable in $\gamma$, these curves are uniquely defined, satisfying $V_* < \gamma(s,t) < V(t)$ for $V_* < s < V_0$, $t \geq 0$, and $\gamma(V_*, t) = V_*$, $\gamma(V_0, t) = V(t)$ for $t \geq 0$. Setting $\hat{x}(s,t) := x(\gamma(s,t),t)$, $\hat{\omega}(s,t) := \omega(\gamma(s,t),t)$, the system (6) reduces to

$$\begin{cases} \dfrac{\partial \hat{x}(s,t)}{\partial t} = \beta \hat{x}(s,t)(K - \hat{x}(s,t)), & V_* \leq s \leq V_0, t \geq 0, \\ \dfrac{\partial \hat{\omega}(s,t)}{\partial s} = (\beta \hat{x}(s,t) - \mu)\dfrac{\partial \gamma(s,t)}{\partial s}, & V_* \leq s \leq V_0, t \geq 0, \\ \dfrac{\mathrm{d}\gamma(s,t)}{\mathrm{d}t} = \hat{\omega}(s,t), & V_* \leq s \leq V_0, t \geq 0, \end{cases} \tag{28}$$

with the initial conditions $\hat{x}(s,0) = x(s,0) = \varphi(s)$ for $V_* \leq s \leq V_0$.

The first equation of the system (28) is a logistic equation, which has a standard solution

$$\hat{x}(s,t) = \begin{cases} \dfrac{K\varphi(s)e^{\beta K t}}{K + \varphi(s)(e^{\beta K t} - 1)}, & \text{if } K \neq 0; \\ \dfrac{\varphi(s)}{\varphi(s)\beta t + 1}, & \text{if } K = 0. \end{cases} \tag{29}$$

Combining the second and the third equations in the system (28), we get an ordinary differential equation of $\frac{\partial \gamma}{\partial s}(s,t)$,

$$\begin{cases} \dfrac{\partial}{\partial t}\left(\dfrac{\partial \gamma(s,t)}{\partial s}\right) = (\beta \hat{x}(s,t) - \mu)\dfrac{\partial \gamma(s,t)}{\partial s}, \\ \dfrac{\partial \gamma(s,0)}{\partial s} = 1, \end{cases}$$

which has the solution

$$\frac{\partial \gamma(s,t)}{\partial s} = \exp\left(\int_0^t (\beta \hat{x}(s,\rho) - \mu)\mathrm{d}\rho\right).$$

Hence

$$\gamma(s,t) = V_* + \int_{V_*}^{s} \exp\left(\int_0^t (\beta \hat{x}(\sigma,\rho) - \mu)\mathrm{d}\rho\right)\mathrm{d}\sigma, \tag{30}$$

where $\hat{x}(s,t)$ is given by the formula (29). Since $\frac{\partial\gamma(s,t)}{\partial s}=\exp\big(\int_0^t(\beta\hat{x}(s,\rho)-\mu)d\rho\big)>0$, we can solve the inverse of $\gamma(s,t)$ for fixed $t$. Denote the inverse of $\gamma(s,t)$ by $\eta(s,t)$. It follows that

$$\begin{cases} x(s,t)=\hat{x}(\eta(s,t),t),\\ \omega(s,t)=\int_{V_*}^{s}(\beta x(\sigma,t)-\mu)\mathrm{d}\sigma. \end{cases}$$

The free boundary is given by

$$V(t)=\gamma(V_0,t)=V_*+\int_{V_*}^{V_0}\exp\left(\int_0^t(\beta\hat{x}(\sigma,\rho)-\mu)\mathrm{d}\rho\right)\mathrm{d}\sigma,$$
$$R(t)=\sqrt[3]{V(t)}=\sqrt[3]{R_*^3+\int_{R_*^3}^{R_0^3}\exp\left(\int_0^t(\beta\hat{x}(\sigma,\rho)-\mu)\mathrm{d}\rho\right)\mathrm{d}\sigma}, \tag{31}$$

where $\hat{x}(s,t)$ is calculated by formula (29).

In order to solve the system, we assumed $\alpha$ to be a constant. If $\alpha$ is a step function, the solution can be given piece-wise by applying the formula (29) piece by piece. Let $\alpha(t)=\alpha_i$, $t\in[t_{i-1},t_i)$, $i=1,2,\dots,n$, $\hat{x}_0(s,0):=\varphi(s)$, $K_i:=\frac{\alpha_i+\mu}{\beta}$, then the solution in (29) changes to $\hat{x}(s,t)=\hat{x}_i(s,t)$, $t\in[t_{i-1},t_i)$, $i=1,2,\dots,n$, where

$$\hat{x}_i(s,t)=\begin{cases} \dfrac{K_i\hat{x}_{i-1}(s,t_{i-1})e^{\beta K_i(t-t_{i-1})}}{K_i+\hat{x}_{i-1}(s,t_{i-1})(e^{\beta K_i(t-t_{i-1})}-1)}, & \text{if } K_i\neq 0\,;\\ \dfrac{\hat{x}_{i-1}(s,t_{i-1})}{\hat{x}_{i-1}(s,t_{i-1})\beta(t-t_{i-1})+1}, & \text{if } K_i=0\,, \end{cases} \tag{32}$$

whereas the formula (31) will also be given piece by piece.

Here we look at several interesting cases or applications of this explicit solution. First, we look at how tumour regrows after the surgical resection without any treatment. In this case, $K=\frac{\lambda+\mu-\delta}{\lambda+\mu}$, where $\lambda$ is the tumour cell proliferation rate, $\delta$ is the death rate of tumour cells (the rate at which the tumour cells becomes necrotic), $\mu$ is the removal rate of necrotic cells.

When $K=0$, that is, $\delta=\lambda+\mu$, the growth of the tumour radius $R(t)$, or scaled volume $V(t)=R^3(t)$ will follow the following curve:

$$V(t)=\left(\beta\int_{V_*}^{V_0}\varphi(s)\mathrm{d}s\right)e^{-\mu t}t+V_0e^{-\mu t}+V_*(1-e^{-\mu t}).$$

From this expression, we find there is a time $T$, approximately $T=\frac{1}{\mu}$, such that the tumour radius will increase before $T$ and decrease after it. When time goes to infinity, the tumour shrinks to the size $V_*$.

When $K\neq 0$, we have

$$V(t)=V_0+\frac{(e^{\beta Kt}-1)e^{-\mu t}}{K}\int_{V_*}^{V_0}\varphi(s)\mathrm{d}s. \tag{33}$$

Since $\int_{V_*}^{V_0}\varphi(s)\mathrm{d}s$ is a constant, the growth of the radius depends on $\frac{(e^{\beta Kt}-1)e^{-\mu t}}{K}$. Substituting original parameters, we have $(e^{\beta Kt}-1)e^{-\mu\ t}=e^{(\beta K-\mu)t}-e^{-\mu t}=e^{(\lambda-\delta)t}-e^{-\mu t}$. Hence, if $\lambda>\delta$, the tumour will grow infinitely. If $\lambda<\delta$, the tumour will shrink to the size $V_0$. If $\lambda = \delta$, the tumour radius will reach a stationary solution

$$V_s = V_0 + \frac{\lambda + \mu}{\mu} \int_{V_*}^{V_0} \varphi(s)\mathrm{d}s.$$

Second, we consider radiotherapy and chemotherapy. After the surgical resection, the patient has to rest for a period of time, usually 6 weeks, and is then treated by radiotherapy and chemotherapy. Set the rest period to be $0 \le t \le t_1$. Then, the tumour grows from $V_0$ to $V(t_1)$, where $V(t_1)$ is given by (33) at $t = t_1$, or explicitly

$$V(t_1) = V_0 + \frac{(\lambda + \mu)(e^{(\lambda-\delta)t_1} - e^{-\mu t_1})}{\lambda + \mu - \delta} \int_{V_*}^{V_0} \varphi(s)\mathrm{d}s.$$

Let the treatment period of radiotherapy with chemotherapy be $t_1 \le t \le t_2$, then the tumour growth follows

$$V(t) = V_0 + \frac{(\lambda + \mu)(e^{(\lambda-\delta-A-B)t} - e^{-\mu t})}{\lambda + \mu - \delta - A - B} \int_{V_*}^{V_0} \varphi(s)\mathrm{d}s, \quad t_1 \le t \le t_2. \tag{34}$$

Let the treatment period of chemotherapy be $t_2 \le t \le t_3$, then the tumour growth follows

$$V(t) = V_0 + \frac{(\lambda + \mu)(e^{(\lambda-\delta-B)t} - e^{-\mu t})}{\lambda + \mu - \delta - B} \int_{V_*}^{V_0} \varphi(s)\mathrm{d}s, \quad t_2 \le t \le t_3. \tag{35}$$

These solutions clearly give the tumour growth pattern in any finite period of time. They provide some information for treatments. We will discuss this issue in the next section.

## 5. Numerical validation and discussion

### 5.1. *Numerical validation*

The analytical solution derived in this article has been thoroughly validated by numerical simulation results. A typical set of results are presented in Figure 1, where we compare the analytical and numerical solutions in three different cases, depending on the choice of the parameters $A$ and $B$ (Equation (5)). The parameter values and initial conditions are taken from [6], specifically, $\lambda = 0.02$, $\delta = 0.0189$ and $\mu = 1/72$. The initial number density of tumour cells is $x(r, 0) = c\ \theta$ with $c = 0.9$. The initial outer radius of the tumour is $R_0 = 20$ and the inner radius (which measures the residual tumour after resection) is $R_* = 18$. The following three choices of $A$ and $B$ are numerically investigated in [6], and also examined here:

(1) $A = 0$, $B = 0$. Neither radiotherapy nor chemotherapy is applied.
(2) $A = 1$, $B = 0$. Only radiotherapy is applied at regular strength.
(3) $A = 1$, $B = 0.03$. Both therapies are applied at regular strength.

In each case, we compare our analytical solution of $R(t)$ to the numerical solution obtained by numerically simulating the free boundary problem (3,5). Note that in Cases 2 and 3, $\alpha(t)$ is a step function and the analytical solution of $R(t)$ is provided by the piecewise form of Equation (31). Figure 1 clearly shows that the analytical and numerical solutions perfectly match each other in all the three cases.

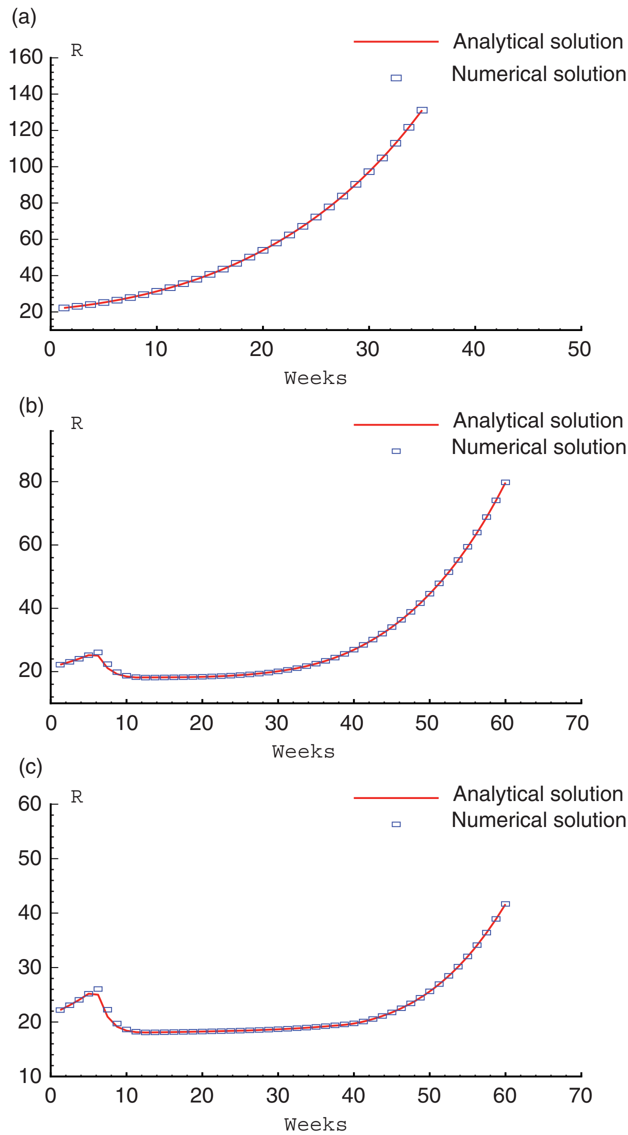


Figure 1. Comparison between the analytical solution of $R(t)$, given in Equation (31), and the numerical solution of $R(t)$, obtained by simulating the free boundary problem (3,5). (a) $A=0$, $B=0$ ; (b) $A=1$, $B=0$; (c) $A=1$, $B=0.03$ . Results show that the analytical and numerical solutions exactly match each other in all the three cases.

### 5.2. *Discussion*

In the proof of the local existence and uniqueness of the solution, we define the backward characteristic curve when a pair $(V(t), x(s,t))$ is given. The curve is defined in terms of $V(t)$ and $x(s,t)$. Then the system can be solved along the characteristic curve. To obtain the explicit solution, we also define a 'characteristic' curve in a similar way. However, this curve is a part of the solution. It is actually a domain transformation. One may be tempted to think that the existence of the solution can be proven under this transformation. However, it turns out that such an idea is not easy to work out. Since we prove the global existence and uniqueness of the solution by a different way in Section 2, it is safe to use any transformation in order to find the solution.

There is an interesting feature of the solution. Observing the solution formula, we see that the dependent domain of $\hat{x}(s, t)$ is one point $\{s\}$ and the dependent domain of $\gamma(s, t)$, as calculated by the formula (30), is the interval $[V_*, s]$; hence the dependent domain of the tumour radius $R(t)$, or $V(t)$, is the interval $[V_*, V_0]$. Therefore, if we extend the domain of $\varphi(s)$ from $[V_*, V_0]$ to $[V_*, +\infty)$ by assigning arbitrary values to the extended part of $\varphi(s)$, the solution will not be affected.

Due to this property of the solution, the original free boundary problem can be reformulated as a fixed boundary problem defined on an infinite domain $[V_*, +\infty) \times [0, +\infty)$ with a discontinuous initial condition. That is, the solution of the system (6) on its domain coincides with that of the following system:

$$\begin{cases} \dfrac{\partial x(s,t)}{\partial t} + \omega(s,t)\dfrac{\partial x(s,t)}{\partial s} = \beta x(s,t)(K - x(s,t)), & V_* \le s, t \ge 0, \\ \dfrac{\partial \omega(s,t)}{\partial s} = \beta x(s,t) - \mu, & V_* \le s, t \ge 0, \\ \omega(V_*, t) = 0, & t \ge 0, \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \omega(V(t), t), & t \ge 0, \end{cases} \tag{36}$$

with the initial conditions: $V(0) = V_0$, $x(s, 0) = \psi(s)$, for $V_* \le s$, where

$$\psi(s) = \begin{cases} \varphi(s), & s \le V_0; \\ 0, & s > V_0. \end{cases} \tag{37}$$

For the hyperbolic free boundary problem obtained by the mass conversation law where the free boundary moves only because of the expansion of the inside mass, this property of the solution seems true. Conceptually, we can change this type of free boundary problem to a fixed boundary problem. Moreover, the methods developed in this article can be used in the analysis of more general free boundary problems.

We now discuss some biological significance of our solutions. Based on the solution (33) where there is no treatment after the surgical resection, if tumour cell proliferation rate $\lambda$ is greater than the tumour cell death rate $\delta$, the tumour will grow until the patient dies. If the tumour cell proliferation rate $\lambda$ is smaller than the tumour cell death rate $\delta$, the tumour will shrink, and the patient survives. If the the tumour cell proliferation rate $\lambda$ is equal to the tumour cell death rate $\delta$, the tumour will grow to a certain size and then stop growing, so that it reaches a stationary state. This threshold phenomenon is biologically reasonable. Unfortunately, the tumour cell proliferation rate $\lambda$ is always greater than the tumour cell death rate $\delta$ in reality; otherwise, there will be no tumour. According to solution (34), the tumour is treated by the combined radiotherapy and chemotherapy after the tumour regrows to a size of $V(t_1)$. Theoretically, we can make the combined parameter $\lambda - \delta - A - B$ as small as we want by increasing $A$ and $B$. This means, we need to increase the strength of the radiotherapy and chemotherapy. Within the tolerable toxicity of these therapies, $\lambda - \delta - A - B$ may be negative. It is obvious that the longer the tumour is treated by the combined radiotherapy and chemotherapy, the more the tumour cells are killed.

However, the radiotherapy cannot be applied too long because of its side effects and toxicity. Then, the chemotherapy has to be applied individually as the solution (35) shows. It may be the case where the density of tumour cells drops to such a low level that is beyond the detection after these treatments. A condition on which the tumour could be eradicated is $\lambda < \delta + B$, and then it is automatically true that $\lambda < \delta + A + B$. Since these are the parameters of exponential functions, there is no guarantee that all tumour cells are killed with a period of finite time. However, these solutions can be used to compute the survival time when different protocols of radiotherapy and chemotherapy are applied.

**Acknowledgements**

The authors would like to thank Avner Friedman for useful discussion. D. Yang was supported by Monroe Scholarship of undergraduate summer research from the Roy R. Charles Center at the College of William and Mary.



## References

[1] N. Bellomo, N.K. Li, and P.K. Maini, *On the foundations of cancer modelling: selected topics, speculations, and perspectives*, Math. Mod. Meth. Appl. S. 18 (2008), pp. 593–646.

[2] S.E. Eikenberry, T. Sankar, M.C. Preul, E.J. Kostelich, C.J. Thalhauser, and Y. Kuang, *Virtual glioblastoma: Growth, migration and treatment in a three-dimensional mathematical model*, Cell Prolif. 42 (2009), pp. 511–528.

[3] A. Friedman, J.P. Tian, G. Fulci, E.A. Chiocca, and J. Wang, *Glioma virotherapy: The effects of innate immune suppression and increased viral replication capacity*, Cancer Res. 66 (2006), pp. 2314–2319.

[4] K.R. Swanson, C. Bridge, J.D. Murray, and E.C. Alvord, *Virtual and real brain tumours: Using mathematical modelling to quantify glioma growth and invasion*, J. Neurol. Sci. 216 (2003), pp. 1–10.

[5] D.E. Woodward, J. Cook, P. Tracqui, G.C. Cruywagen, J.D. Murray, and E.C. Alvord, *A mathematical model of glioma growth: The effect of extent of surgical resection*, Cell Prolif. 29 (1996), pp. 269–288.

[6] J.P. Tian, A. Friedman, J. Wang, and E.A. Chiocca, *Modeling the effects of resection, radiation and chemotherapy in glioblastoma*, J. Neuro-Oncol. 91(3) (2009), pp. 287–293.

[7] F.K. Albert, M. Forsting, K. Sartor, H.P. Adams, and S. Kunze, *Early postoperative magnetic resonance imaging after resection of malignant glioma: Objective evaluation of residual tumour and its influence on regrowth and prognosis*, Neurosurgery 34 (1994), pp. 45–61.

[8] M. Lacroix, D. Abi-Said, D.R. Fourney, Z.L. Gokaslan, W. Shi, F. DeMonte, F.F. Lang, I.E. McCutcheon, S.J. Hassenbusch, E. Holland, K. Hess, C. Michael, D. Miller, and R. Sawaya, *A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection, and survival*, J. Neurosurg. 95 (2001), pp. 190–198.

[9] S. Stupp, W.P. Mason, M.J. van den Bent, M. Weller, B. Fisher, M.J. Taphoorn, K. Belanger, A.A. Brandes, C. Marosi, U. Bogdahn, J. Curschmann, R.C. Janzer, S.K. Ludwin, T. Gorlia, A. Allgeier, D. Lacombe, J.G. Cairncross, E. Eisenhauer, and R.O. Mirimanoff, *Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma*, N. Engl. J. Med. 352 (2005), pp. 987–96.

[10] J.A. O'Donoghue, M. Bardies, and T.E. Wheldon, *Relationships between tumour size and curability for uniformly targeted therapy with beta-emitting radionuclides*, J. Nucl. Med. 36 (1995), pp. 1902–1909.

[11] A. Granas and J. Dugundji, *Fixed Point Theory*, Springer-Verlag, New York, 2003.