Analysis of tumor growth model including a PDE-ODE coupling with a nonlocal boundary condition

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Abstract
This paper deals with the analysis of a nonlinear model of tumor growth with treatment. The model consists of a system of equations that describe the evolution of the colony size distribution of the metastatic tumors and the number of cells present in a primary tumor. The former evolution is described by a linear transport equation and the latter by an ordinary differential equation of Gompertzian type. The two dynamics are coupled through a nonlocal boundary condition that takes into account the tumor colonization rate. The model takes into account the presence of treatments by chemo and radiotherapy. We prove an existence result, the main difficulty is to deal with the coupling and to take into account the discontinuities in time that come from the treatment terms.

Keywords
Ordinary differential equations, Partial differential equations, Discontinuous data, Tumor growth.

I INTRODUCTION
In deciding the best treatment for cancer therapy, estimations of the colony size of tumors, predictions of the metastasis propagation and responses to treatments are needed. Given its vitality, this subject is of increasing interest for mathematicians [6, 18, 23, 27]. In this context, we consider the mathematical model of tumor growth introduced in [3]. It is a linear coupling system between a transport partial differential equation (PDE) and an ordinary differential equation (ODE) with a nonlocal boundary condition. We point out that in [8], the authors studied the existence, uniqueness and asymptotic behavior of solution for this model by implementing a semi-group approach. Also in [10, 13, 24], the authors added a term associated with chemotherapy, the resulting problem is then nonlinear. They proved the existence of a solution in a smooth setting and carried out a thorough numerical analysis that justifies the model by clinical trials. We note that in [19], the authors proposed a PDE model of tumor growth that describes the movement of cells generated by the proliferation of cancer cells which exerts pressure on surrounding tissues. Furthermore in [18], the authors extended some mathematical models of cancer with mixed treatments. They presented and analyzed a model, in terms of an ODE system, with chemo and radiotherapy treatments. In [22, 25, 26], the authors propose and analyze some conceptual models for the tumor-immune interaction based on dynamic systems. They focused on bifurcation and stability. The problem of estimating the parameters of a tumor growth model with the objective of obtaining a prognostic model and of finding fields that are not observable, has been widely studied in the literature [14, 15].
In this work, we complete the model studied in [8] by considering a concomitant treatment. The radiotherapy term is the one given in [4, 12]. The associated mathematical data is then discontinuous in time and space. Here, we focus on the irregularities in time. We prove the existence and uniqueness of solution with piecewise regularity in time and Lebesgue integrability in space. Our strategy is the following: we first solve the ODE (decoupled part of the system) within the Caratheodory framework[2, 5], then we plug the solution into the PDE part solving it using a fixed point argument. We also carry out some numerical tests. We discretize the ODE using Runge Kutta schemes and the PDE by the method of characteristics [1]. We notice that there is a large disparity in the parameter scales of the model, which is restrictive for the choice of the discretization parameters. Our numerical tests suggest that a mixed treatment should be better to reduce the population of cancer cells for some parameters related to the progress of the disease.

Finally, the contribution in this work lies at the same time in the modeling, the theoretical analysis and the numerical approach. To the best of our knowledge, Iwata’s model has not been used with mixed treatments. Also, compared to [13], our proof of solution’s existence is strongly penalized by the discontinuities of the data. On the numerical level, a sophisticated calculation code, based on the method of characteristics, is implemented. The numerical results show the interest in a mixed treatment for a clinical combination of parameters linked to the disease.

The paper is sketched as follows. In section 2, we write our model with some details that allow us to understand the origin of irregularities. Section 3 is devoted to the analysis of the ODE’s solution. In section 4, we present an existence result. The proof is based on the construction of an adequate contracting operator which takes into account the different constraints of the problem. Finally in section 5, we present our discretization strategy and some numerical tests.

II THE MATHEMATICAL MODEL

2.1 Growth model and distribution of metastatic tumors

2.1.1 The primary tumor

To formulate the process of metastases, we consider the model introduced in [3] and taken up in [8–10]. The authors consider an idealized case in which a primary tumor is generated from a single cell at time $t = 0$ and grows at rate $g(x)$ per unit time, where $x$ denotes the tumor size represented by the number of cells in the tumor. The number $x_p(t)$ of cells present in a primary tumor at time $t$ is given by the solution of

\[ \frac{d}{dt}x_p(t) = g(x_p(t)) ; \quad t \geq 0, \]

\[ x_p(0) = 1, \]

with a Gompertzian growth rate

\[ g(x) = ax \ln \left( \frac{b}{x} \right) \]

where $b \geq 1$ is the maximal tumor size and $a$ is a positive parameter that measures the rate of clonogenic proliferation. The solution of (1) is

\[ x_p(t) = b^1 - e^{-at}. \]
It increases strictly between 1 and b, the corresponding curve is a sigmoid with three phases: a slow growth phase, an exponential growth phase and a slowdown one. This takes into account the stages of carcinogenesis, namely: the initiation phase corresponding to the transformation of a normal cell into a malignant cell, the phase of promotion corresponding to the accumulation of mutations and the slowing phase which corresponds to cell loss.

2.1.2 The model without treatment

Following [3], the primary growing tumor emits metastatic cells at rate $\beta(x)$. In turn, each metastatic cell grows into a new tumor which grows at rate $g(x)$ and emits new metastatic nuclei like the primary tumor. Let $u(t, x)$ represents the colony size distribution of metastatic tumors with $x$ cells at time $t$. Assuming the localized colonization nuclei sufficiently distant from each other, so that they do not overlap, the dynamic model proposed in [3] writes

$$\frac{\partial u}{\partial t}(t, x) + \frac{\partial}{\partial x} \left[ g(x)u(t, x) \right] = 0, \quad t > 0, \quad x \in [1, b], \quad (4)$$

$$u(0, x) = 0, \quad (5)$$

$$g(1)u(t, 1) = \int_1^b \beta(x)u(t, x)dx + \beta(x_p(t)). \quad (6)$$

The term $\frac{\partial}{\partial x} (g(x)u(t, x))$ reflects the transport of tumor cells. Equation (5) indicates that initially no metastatic tumor exists. Equation (6) means that the number of metastatic single cells newly created per unit time is the total rate of new metastases due to metastases already present and to the primary tumor. The colonization rate $\beta(x)$ has the form

$$\beta(x) = m.x^\alpha, \quad (7)$$

where $m$ is the colonization coefficient and $\alpha$ is the fractal dimension of the blood vessels infiltrated into the tumor. Equation (7) indicates that the rate of metastases from a tumor of size $x$ is proportional to the number of tumor cells in contact with the blood vessels. The parameter $\alpha$ expresses how the blood vessels are geometrically distributed in the tumor. We refer to [3] for more details on the development of the model and its justification by clinical trials, as well as for an extensive bibliography on the subject.

2.1.3 Consideration of chemo and radiotherapy

In [13], the authors have taken up the model of Iwata et al [3] by considering chemotherapy treatment. We complete here by taking into account concomitant chemo and radiotherapy treatments. The Gompertzian growth rate $g$ is replaced by

$$G(t, x) = g(x) - K_c(x)C(t) - K_r(x)R(t), \quad (8)$$

where the term $K_c(x)C(t)$ is associated with chemotherapy, $C$ represents the drug’s concentration and $K_c$ measures its efficiency. We adopt for $K_c$ the expression introduced in [13]

$$K_c(x) = \gamma(x - \overline{x})H(x - \overline{x}),$$

where $H$ is the Heaviside function, $\overline{x}$ is a threshold from which drugs start and $\gamma$ is a positive constant that quantifies the drug’s effectiveness. Likewise, $R$ represents cell death induced by radiation, and

$$K_r(x) = \gamma_r(x - \hat{x})H(x - \hat{x}),$$

indicates that radiotherapy is applied to tumors larger than $\hat{x}$. The terms $C$, $R$, and the concomitant timeline depend on the types of protocols.
Chemotherapy. The term $C(t)$ depends on the pharmacokinetics of administered drugs. Here, we use a model with a central compartment and a peripheral one. Let $V$ be the volume distribution, $k_e$ the elimination constant and $d_c$ the rate of drug’s infusion into the central compartment. The drugs concentration is modeled by \[ \begin{align*}
  \dot{c}_1(t) &= -k_e c_1(t) + k_{12}(c_2(t) - c_1(t)) + \frac{d_c(t)}{V} & \forall t \geq t_0, \ c_1(t_0) = 0, \\
  \dot{c}_2(t) &= k_{21}(c_1(t) - c_2(t)) & \forall t \geq t_0, \ c_2(t_0) = 0,
\end{align*} \] (9)
where $t_0$ is the start time of treatment, $c_1, c_2$ represent respectively the evolution of drug’s concentration in the central and peripheral compartments, $k_{12}, k_{21}$ are exchange constants between the two compartments and
\[
d_c = \sum_{i=1}^{n} \frac{d_{c_{i-1}}}{t_i - t_{i-1}} \chi_{[t_{i-1}, t_i]},
\]
(10)
$d_{c_i}$ is the dose given during the time $[t_{i-1}, t_i]$. For the following, we notice that the second member of the differential system (9) is discontinuous.

Radiotherapy. Using a linear-quadratic model, the cell survival probability writes
\[
\text{survival probability} = \exp(-\alpha_{\text{eff}} d_r),
\]
(11)
where $d_r$ is a radiation dose, and $\alpha_{\text{eff}}$ is a constant that translates radiations into cell death, said relative effective radiosensitivity parameter [4, 7, 11, 12, 16, 17, 20, 21]. In general, fractions of doses with the same magnitude are administered. We denote by $D_r(t)$ the accumulated dose at time $t$. By not considering any delayed or otherwise toxic effects, the probability of cells death by radiation at time $t$ writes
\[
R(t) = 1 - \exp(-\alpha_{\text{eff}} D_r(t)).
\]
Each radiation session lasts a few minutes, a finite series of pulses is then administered. We assume that during these minutes, the irradiation takes place continuously and uniformly, so that the accumulated dose writes
\[
D_r(t) = \sum_{i=1}^{m} \frac{d_r}{2\varepsilon} \chi_{[t_{i-\varepsilon}, t_{i+\varepsilon}]}(t),
\]
where $m$, $\varepsilon$ and $t_i$ are characteristics of each protocol. Therefore, $R$ writes
\[
R(t) = 1 - \exp\left( -\alpha_{\text{eff}} \frac{d_r}{2\varepsilon} \sum_{i=1}^{m} \chi_{[t_{i-\varepsilon}, t_{i+\varepsilon}]}(t) \right).
\]
2.2 Final model

The model that we are studying, finally writes

\[
\frac{\partial}{\partial t} u(t, x) + \frac{\partial}{\partial x} [G(t, x)u(t, x)] = 0, \quad t \in [t_0, T[, \quad x \in [1, b[. \tag{12}
\]

\[
(Gu)(t, 1) = \int_1^b \beta(x)u(t, x)dx + f(t), \quad t \in [t_0, T[, \tag{13}
\]

\[
(Gu)(t, b) = 0, \quad t \in [t_0, T[, \tag{14}
\]

\[
u(t_0, x) = u_0(x), \tag{15}
\]

\[
f(t) = \beta(x(t)), \tag{16}
\]

\[
\frac{dx_p}{dt}(t) = G(t, x_p(t)), \quad t > t_0, \quad x_p(t_0) = x_0, \tag{17}
\]

where \(t_0\) and \(T\) are the start and end times of treatment, \(u_0\) is the density in size at \(t_0\) and \(G\) is given by (8).

We notice that the non local boundary condition makes this problem non-classical. The existence of a solution was proven in [13] with \(G \in C^2([t_0, T] \times [1, b])\). But taking the treatments into account makes \(G\) discontinuous in time and space. In this work, we focus on the irregularities in time : \(K_r(t, .)\) and \(K_c(t, .)\) will be approached with functions of class \(C^2([1, b])\) for all \(t\).

Hypothesis H.

We will assume, in a generic framework, that \(G\) is of class \(C^2\) in \(x\) for all \(t\), has a finite number of discontinuities denoted by \(t_i, \ i = 1, ..., n\), and is of class \(C^2\) on the connected components of \(Q = [t_0, T] \times [1, b]\) delimited by the curves \(\Sigma_i = \{(t_i, x), x \in [1, b]\}, \ i = 1, ..., n\). These hypothesis will be called Hypothesis H.

2.3 The main theorem

We denote by \(E = C_{MG}^1([t_0, T[, L^1([1, b])]\) the set of continuous functions on \([t_0, T]\) with values in \(L^1([1, b])\), of class \(C^1\) on \([t_0, T]\setminus\{t_i, \ i = 1, ..., n\} and admitting right and left derivatives in time on each point. We take note that \(E\) is different from the set of class \(C^1\) piecewise in time functions. The index \(G\) reminds that the set of derivative discontinuity points is fixed, finite, and is associated with the set of time discontinuities of \(G\). We provide \(E\) with its natural norm

\[
\|w\| = \sup_{t \in [t_0, T]} \|w(t, .)\|_{L^1([1, b])} + \max_{i \in \{1, ..., n\}} \sup_{t \in [t_i, t_{i+1}]} \left\| \frac{\partial w}{\partial t}(t, .) \right\|_{L^1([1, b])}.
\]

We define, for \(u \in L^1([1, b]),\) the set

\[
E(u) = \{ w \in C_{MG}^1([t_0, T[, L^1([1, b])] : w(t_0, .) = u \}.
\]

It is obvious that \((E, \|, \|)\) is a Banach space and that the metric space \(E(u)\) is closed in \(E\) for each \(u \in L^1([1, b])\).

Theorem 1: Ben Abdejlil, Ben Essid, and Mani-Aouadi [24]

We suppose that the initial data \(u_0\) belongs to \(W^{1,1}([1, b])\) and verifies the compatibility conditions

\[
u_0(b) = 0 \quad \text{and} \quad (Gu_0)(t_0, 1) = \int_1^b \beta(x)u_0(x)dx + f(t_0). \tag{18}
\]
We suppose that $G$ verifies Hypothesis H and the conditions

$$G(t, 1) > 0, \forall t \in [t_0, T], \quad (19)$$

$$G(t_0, x) > 0, \forall x \in [1, b], \quad (20)$$

$$G(t, b) < 0, \forall t \in [t_0, T]. \quad (21)$$

with $G(t, 1)$ constant on $[t_0, T]$.

Then, there is a unique $u \in E(u_0)$ with $G_u \in \mathcal{C}([t_0, T], W^{1,1}([1, b]))$ that verifies the equations (12), (13) and (14) respectively in $\mathcal{C}([t_0, T], L^1([1, b]), \mathcal{C}([t_0, T], \mathbb{R})$ and $L^1([1, b])$.

REFERENCES


