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Analysis of a tumor growth model with treatments

Analyse d'un modèle de croissance d'une tumeur avec traitements

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ABSTRACT. In this paper, we conduct a mathematical analysis of a tumor growth model with treatments. The model consists of a system that describes the evolution of metastatic tumors and the number of cells present in the primary tumor. The former evolution is described by a 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. We prove an existence result where the main difficulty is to handle the coupling and to take into account the time discontinuities generated by treatment terms. The proof is based on a Banach fixed point theorem in a suitable functional space. We also develop a computational code based on the method of characteristics and present numerical tests that highlight the effects of different therapies.
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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 [3, 12, 16, 22]. In this context, we consider the model of tumor growth introduced in [15]. It is a coupling system between a transport partial differential equation (PDE) and an ordinary differential equation (ODE) with a non local boundary condition. We point out that, in [8], the authors studied the existence, uniqueness, and asymptotic behavior of solution for this model by a semi-group approach. In [1, 25], the authors added a term associated with chemotherapy, proved the existence of a solution, and carried out a thorough numerical analysis justifying the model by clinical trials. In [12], some ODE models with chemo and radiotherapy treatments are analyzed. In [17, 18], the authors considered some conceptual models for the tumor-immune interaction based on dynamic systems; they focused on bifurcation and stability. The parameters' estimation, with the objective of obtaining prognostic models and of finding not observable fields, has also been widely studied in the literature [5, 6].

In this work, we complete the model of [8] by considering a concomitant treatment by radio- and chemotherapy. The radiotherapy term is the one given in [9, 24]. The associated mathematical data are then discontinuous in time. We focus on these irregularities and prove the existence and uniqueness of solution with piecewise regularity in time and Lebesgue integrability in space. The key ingredient in the proof is a Banach fixed point theorem in a suitable fundamental functional space. Our strategy is as follows: we first solve the ODE (decoupled part of the system) within the Caratheodory framework [2, 14], then we plug the solution into the PDE that we solve by a fixed point argument. We also carry out

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some significant numerical tests. To discretize the ODE, we use Runge-Kutta schemes, and for the PDE, we employ the method of characteristics[4]. Our numerical tests suggest that a mixed treatment should be better at reducing the cancer cells for some parameters related to disease progression. However, a significant challenge arises due to the large disparity in biological parameters. The size of the spatial domain is exponentially large, while the time ranges from minutes during treatment to years for disease follow-up. As a result, the choice of temporal and spatial discretization steps is strongly restricted. Finally, the contribution of this work lies both in the modeling, the theoretical analysis and the numerical approach. To our knowledge, the Iwata model has not been used with mixed treatments. Moreover, our proof of existence of the solution is strongly penalized by the discontinuities of the data. At the numerical level, a sophisticated computational code, based on the method of characteristics, is implemented and significant results are obtained. 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 the 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 numerical tests.

1. The mathematical model

1.1. *Growth model and distribution of metastatic tumors*

1.1.1. The primary tumor

To formulate the process of metastases, we consider the model introduced in [15] and taken up in [1, 7, 8, 13]. The authors consider an idealized case 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 presented by the solution of

$$\begin{aligned} \frac{d}{dt}x_p(t) &= g\left(x_p(t)\right); \quad t \geq 0, \\ x_p(0) &= 1, \end{aligned} \tag{1.1}$$

with a Gompertzian growth rate

$$g(x) = ax \ln\left(\frac{b}{x}\right) \tag{1.2}$$

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 (1.1) is

$$x_p(t) = b^{1-\mathrm{e}^{-at}}. \tag{1.3}$$

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.

1.1.2. The model without treatment

Following [15], 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 [15] writes

$$\begin{aligned} \frac{\partial u}{\partial t}(t,x) + \frac{\partial}{\partial x}\big[g(x)u(t,x)\big] &= 0, \qquad t>0,\ x\in]1,b[, && (1.4)\\ u(0,x) &= 0, && (1.5)\\ g(1)u(t,1) &= \int_1^b \beta(x)u(t,x)\mathrm{d}x + \beta\left(x_p(t)\right). && (1.6) \end{aligned}$$

The term $\frac{\partial}{\partial x}(g(x)u(t,x))$ reflects the transport of tumor cells. Equation (1.5) indicates that initially no metastatic tumor exists. Equation (1.6) 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

$$\beta(x) = m.x^{\alpha}, \tag{1.7}$$

where m is the colonization coefficient and α is the fractal dimension of the blood vessels infiltrated into the tumor. Equation (1.7) 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 α expresses how the blood vessels are geometrically distributed in the tumor. We refer to [15] 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. We can find several other applications for this model and other types of coupling in the literature [21].

1.1.3. Consideration of chemo and radiotherapy

In [25], the authors have taken up the model of Iwata et al [15] by considering chemotherapy treatment. We complete here by taking into account concomitant chemo and radiotherapy treatments. The Gompertzian growth rate g is replaced by

$$G(t,x) = g(x) - K_c(x)C(t) - K_r(x)R(t), \tag{1.8}$$

where the term $K_c(x)C(t)$ is associated with chemotherapy, C represents the drug's concentration and K_c measures its efficiency. The expression of K_c is introduced in [25]

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

where H is the Heaviside function, $\overline{x}$ is a threshold from which drugs start and γ 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.

1.1.3.1. Chemotherapy

The term $C(t)$ depends on the pharmacokinetics of administered drugs. We use a model with a central compartment and a peripheral one. The toxic effects of treatment, taken into account in [10, 20], induce a lag in the equations, and are not considered here. 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 [1, 10]

$$\begin{cases} \dot{c_1}(t) &= -k_e c_1(t) + k_{12}(c_2(t) - c_1(t)) + \dfrac{d_c(t)}{V} & \forall t \geq t_0,\ c_1(t_0) = 0, \\ \dot{c_2}(t) &= k_{21}(c_1(t) - c_2(t)) & \forall t \geq t_0,\ c_2(t_0) = 0, \end{cases} \tag{1.9}$$

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

$$d_c = \sum_{i=1}^{n} \frac{d_{i-1}^c}{t_i - t_{i-1}} \chi_{[t_{i-1}, t_i]}, \tag{1.10}$$

d_i^c 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 (1.9) is discontinuous.

1.1.3.2. Radiotherapy

Using a linear-quadratic model, the cell survival probability writes

$$\text{survival probability} = \exp\left(-\alpha_{\text{eff}} d_r\right), \tag{1.11}$$

where d_r is a radiation dose, and α_{eff} is a constant that translates radiations into cell death, said relative effective radiosensitivity parameter [9, 11, 19, 23, 24]. 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

$$R(t) = 1 - \exp\left(-\alpha_{\text{eff}} D_r(t)\right).$$

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, ε and t_i are characteristics of each protocol. Therefore, R writes

$$R(t) = 1 - \exp\left(-\alpha_{\text{eff}} \frac{d_r}{2\varepsilon} \sum_{i=1}^{m} \chi_{[t_{i-\varepsilon}, t_{i+\varepsilon}]}(t)\right).$$

1.2. *Final model*

The model, that we are studying, finally writes

$$\frac{\partial}{\partial t} u(t,x) + \frac{\partial}{\partial x}\left[G(t,x) u(t,x)\right] = 0, \qquad t \in]t_0, T[, \quad x \in]1, b[, \tag{1.12a}$$

$$
\begin{aligned}
(Gu)(t,1) &= \int_1^b \beta(x)u(t,x)\mathrm{d}x + f(t), \quad t \in]t_0, T[, && \text{(1.12b)}\\
(Gu)(t,b) &= 0, \quad t \in]t_0, T[, && \text{(1.12c)}\\
u(t_0,x) &= u_0(x), && \text{(1.12d)}\\
f(t) &= \beta\left(x_p(t)\right), && \text{(1.12e)}\\
\frac{dx_p}{dt}(t) &= G\left(t, x_p(t)\right), \quad t > t_0,\ x_p(t_0) = x_0, && \text{(1.12f)}
\end{aligned}
$$

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 (1.8).

The existence of a solution for the above problem was proven in [25] with $G \in C^2([t_0, T] \times [1, b])$. But taking the treatments into account makes G discontinuous, we focus on the irregularities in time : K_c and K_r will be approached with functions of class $C^2([1, b])$.

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 $\mathcal{Q} = [t_0, T] \times [1, b]$ delimited by the curves $\Sigma_i = \{(t_i, x), x \in [1, b]\},\ i = 1, ..., n$.

2. The ordinary differential equation

In this section, we are interested in the ODE (1.12f). With **Hypothesis H**, this ODE has no classical solution (in the Cauchy sense), we look then for solutions in the Caratheodory sense [2, 14].

Proposition 2.1. *We suppose that G verifies **Hypothesis H**. For all $(s, x) \in \mathcal{Q} = [t_0, T] \times [1, b]$, the differential equation*

$$
\begin{cases}
\frac{d}{dt}\Phi(t) &= G\big(t, \Phi(t)\big) \text{ a.e. in time,}\\
\Phi(s) &= x,
\end{cases}
\tag{2.1}
$$

has a unique solution of class C^1 piecewise on $[t_0, T]$ given by

$$
\Phi_{(s,x)}(t) = x + \int_s^t G\left(r, \Phi_{(s,x)}(r)\right) dr.
$$

Moreover, $\Phi : (t, s, x) \to \Phi_{(s,x)}(t)$ is continuous on $[t_0, T] \times [t_0, T] \times [1, b]$,
$\tilde{\Phi}_t : (s, x) \to \Phi_{(s,x)}(t)$ is of class C^1 in a neighborhood of any point where G is C^1 for all fixed t,
and $\hat{\Phi}_{(t,s)} : x \to \Phi_{(s,x)}(t)$ is of class C^1 on $]1, b[$ for any fixed (t, s).

Proof. With **Hypothesis H**, the function G verifies the following the Caratheodory's conditions [2]

$$
\begin{aligned}
&1.\ \text{for almost all } t \in [t_0, T],\ G(t, .) \text{ is continuous in } x,\\
&2.\ \text{for almost all } x \in [1, b],\ G(x, .) \text{ is Lebesgue measurable in } t,\\
&3.\ \text{there is a function } m \in L^1([t_0, T]) \text{ such that}\\
&\qquad |G(t, x)| \le m(t) \quad \forall (t, x) \in Q,\\
&4.\ \text{there is a function } l \in L^1([t_0, T]) \text{ such that}\\
&\qquad |G(t, x) - G(t, y)| \le l(t)\,|x - y| \quad \forall t \in [t_0, T],\ \forall x, y \in [1, b],
\end{aligned}
\tag{2.2}
$$

with $m(t) = m = \max_{(t,x)\in\mathcal{Q}} G(t,x)$ and $l(t) = \max_{x\in[1,b]} \frac{\partial G(t,x)}{\partial x}$. Then, the system (2.1) admits a unique global solution in $W^{1,1}([t_0,T])$ given by the integral equation (2.1). In addition, $\frac{d}{dt}\Phi_{(s,x)}(.)$ is continuous for all $t \neq t_i, i = 1, ..., n$. Otherwise, for all $(t, s_1, x_1), (t, s_2, x_2)$ in $[t_0, T]^2 \times [1, b]$, we have for $s_1 < s_2 < t$

$$\begin{aligned}
\left|\Phi_{(s_1,x_1)}(t) - \Phi_{(s_2,x_2)}(t)\right| &\leq |x_1 - x_2| + \left| \int_{s_1}^{t} G\left(\tau, \Phi_{(s_1,x_1)}(\tau)\right) d\tau - \int_{s_2}^{t} G\left(\tau, \Phi_{(s_2,x_2)}(\tau)\right) \mathrm{d}\tau \right| \\
&\leq |x_1 - x_2| + \int_{s_1}^{s_2} \left|G\left(\tau, \Phi_{(s_1,x_1)}(\tau)\right)\right| \mathrm{d}\tau \\
&\quad + \int_{s_2}^{t} \left|G\left(\tau, \Phi_{(s_2,x_2)}(\tau)\right) - G\left(\tau, \Phi_{(s_1,x_1)}(\tau)\right)\right| \mathrm{d}\tau \\
&\leq |x_1 - x_2| + m\,|s_1 - s_2| \\
&\quad + \int_{s_2}^{t} \left|G\left(\tau, \Phi_{(s_2,x_2)}(\tau)\right) - G\left(\tau, \Phi_{(s_1,x_1)}(\tau)\right)\right| \mathrm{d}\tau \\
&\leq |x_1 - x_2| + m\,|s_1 - s_2| \\
&\quad + \|l\|_{L^\infty(t_0,T)} \int_{s_2}^{t} \left|\Phi_{(s_2,x_2)}(\tau) - \Phi_{(s_1,x_1)}(\tau)\right| \mathrm{d}\tau.
\end{aligned}$$

Gronwall's Lemma implies that

$$\left|\Phi_{(s_1,x_1)}(t) - \Phi_{(s_2,x_2)}(t)\right| \leq (|x_1 - x_2| + m\,|s_1 - s_2|)\mathrm{e}^{\|l\|_{L^\infty(t_0,T)}|t-s_2|}. \tag{2.3}$$

Now, for all (t_1, s_1, x_1), (t_2, s_2, x_2) in $[t_0, T] \times [t_0, T] \times [1, b]$, we have

$$\begin{aligned}
|\Phi(t_1, s_1, x_1) - \Phi(t_2, s_2, x_2)| &\leq |\Phi(t_1, s_1, x_1) - \Phi(t_1, s_2, x_2)| &(2.4)\\
&\quad + |\Phi(t_1, s_2, x_2) - \Phi(t_2, s_2, x_2)|\,, &(2.5)
\end{aligned}$$

hence, the function : $(t, s, x) \to \Phi(t, s, x)$ is continuous. The regularity of $\tilde{\Phi}$ and $\hat{\Phi}_{(t,s)}$ derives from Cauchy's theorem. □

We will prove, in the following theorem, that the solutions of (1.12f) allow $Q = [t_0, T] \times [1, b]$ to be partitioned into three areas, each area will be concerned only by one boundary condition in problem (1.12). In particular, we construct regular functions corresponding to the entry of the characteristic curves in each zone.

Theorem 2.2. *We suppose that G verifies* ***Hypothesis H*** *and*

$$G(t,1) > 0,\ \forall t \in [t_0, T], \tag{2.6a}$$
$$G(t_0,x) > 0,\ \forall x \in [1, b[, \tag{2.6b}$$
$$G(t,b) < 0,\ \forall t \in]t_0, T]. \tag{2.6c}$$

We introduce the sets

$$\begin{aligned}\Omega_1 &= \big\{(t,x)\in\mathcal{Q}\,/\,x<\Phi_{(t_0,1)}(t)\big\},\\ \Omega_2 &= \big\{(t,x)\in\mathcal{Q}\,/\,\Phi_{(t_0,1)}(t)<x<\Phi_{(t_0,b)}(t)\big\},\\ \Omega_3 &= \big\{(t,x)\in\mathcal{Q}\,/\,x>\Phi_{(t_0,b)}(t)\big\}.\end{aligned}$$

Then there are a piecewise C^1 function $\varphi:\bar{\Omega}_1\to[t_0,T]$ defined by

$$\Phi\big(t,\varphi(t,x),1\big)=x, \tag{2.7}$$

a piecewise C^1 function $\psi:\bar{\Omega}_2\to]1,b[$ defined by

$$\Phi\big(t,t_0,\psi(t,x)\big)=x,$$

and a piecewise C^1 function $\theta:\bar{\Omega}_3\to[t_0,T]$ defined by

$$\Phi\big(t,\theta(t,x),b\big)=x.$$

Remark 2.3. *The hypotheses (2.6) are verified by the mapping G given by (1.8). They make sure that Ω_1, Ω_2 and Ω_3 cover $[t_0,T]\times[1,b]$ and that each subdomain is concerned by only one boundary condition in the problem (1.12).*

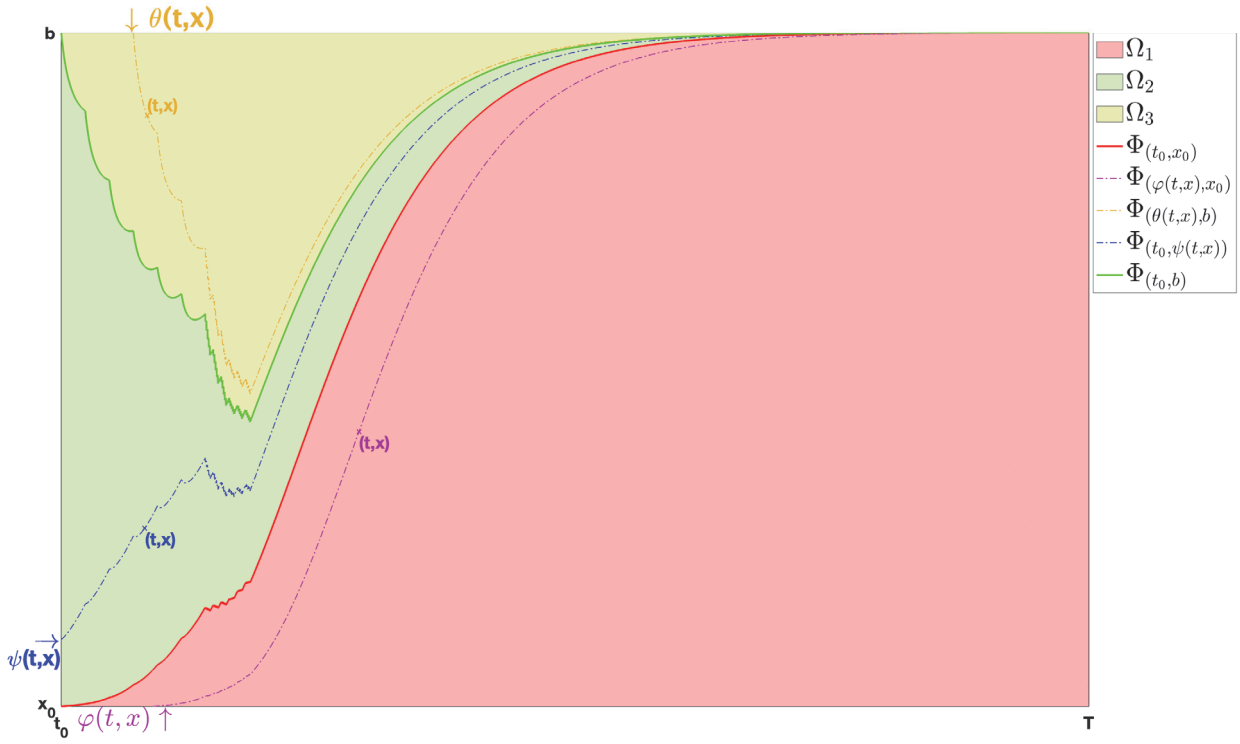

Figure 1. *The characteristic curves Φ on Ω_1, Ω_2 and Ω_3*

Remark 2.4. *The functions φ and θ define the entry time into Ω_1 (resp. Ω_3) of the characteristic curves intersecting Ω_1 (resp. Ω_3). The function ψ defines the entry point in Ω_2 of the characteristic curves intersecting Ω_2 (see Figure 1).*

Proof. 1. We look for a time $\varphi(t,x)$ (resp. $\theta(t,x)$) such that

$$\begin{aligned}\Phi\big(t,\varphi(t,x),1\big) &= x \qquad (\text{resp. } \Phi\big(t,\theta(t,x),b\big)=x),\\ &\text{or equivalently}\\ \Phi\big(\varphi(t,x),t,x\big) &= 1 \qquad (\text{resp. } \Phi\big(\theta(t,x),t,x\big)=b).\end{aligned}$$

Let (t,x) in Ω_1. The characteristic curve resulting from (t,x) intersects necessarily the line $x=1$ at a unique time $(\varphi(t,x),1)$ so that $(\varphi(t,x),1)$ is the foot of this characteristic curve. Likewise, for (t,x) in Ω_3, the characteristic curve passing through (t,x) intersects necessarily the line $x=b$ at a unique time $\theta(t,x)$. This ensures the existence of continuous functions φ and θ.

Let us prove the regularity of φ and θ.

For (t,x) be in Ω_1, $\varphi(t,x)$ is the entry time in Ω_1. The mapping G may be continuous or not in time at $\varphi(t,x)$.

a . If $G(.,x)$ is continuous at $s=\varphi(t,x)$, we have

$$\Phi_{(t,x)}(s)=1 \Rightarrow G\left(s,\Phi_{(t,x)}(s)\right)>0,$$

and so

$$\frac{\partial\Phi}{\partial s}(s,t,x)\neq 0.$$

The function: $s \to \Phi(s,t,x)$ is then of class C^1 in a neighborhood of $\varphi(t,x)$ and $\frac{\partial\Phi}{\partial s}\big(\varphi(t,x),t,x\big)$ is strictly positive. We deduce from the implicit function theorem that $s=\varphi(t,x)$ and that φ is of class C^1 in a neighborhood of (t,x).

b . If G is not continuous in time at the point $\varphi(t,x)$, the regularity of Φ implies that the curves $\Phi(s,t,x)$ and $\Phi(s,t',x)$ are close and do not intersect themselves for t' close to t

$$t\neq t',\ |t-t'|<\varepsilon \ \Rightarrow\ \varphi(t,x)\neq\varphi(t',x) \text{ and } |\varphi(t,x)-\varphi(t',x)|\ll\varepsilon,$$

$\varphi(t',x)$ is thus a continuity point of $G(.,x)$, and φ admits a right and a left continuous derivative in time at the point (t,x).

In the same way, with x' close to x and the curves $\Phi(s,t,x)$, $\Phi(s,t,x')$, we get that φ is of class C^1 piecewise on Ω_1.

The exactly same approach with

$$\theta_{(t,x)}(s)=b \Rightarrow G\left(s,\Phi_{(t,x)}(s)\right)<0,$$

ensures the regularity of θ.

2. For (t,x) given in $]t_0,T[\times]1,b[$, we look for an entry point $y\in]1,b[$ that satisfies $\Phi(t,t_0,y)=x$. Immediately we have $y=\Phi(t_0,t,x)=\psi(t,x)$ and ψ is of class C^1 piecewise in Ω_2.

□

Remark 2.5. *The mapping φ is of class C^1 on parts of Ω_1 delimited by the curves $\widetilde{\Sigma}_i=\Phi_{(t_i,1)}$, $i=1,...,n$,. The mapping ψ is of class C^1 on the parts of Ω_2 delimited by $\Sigma_i=\{(t_i,x),x\in[1,b]\}$, $i=1,...,n$. And by construction, φ and ψ are constant along the characteristic curves so that*

$$\varphi\big(s,\Phi(s,t,x)\big)=\varphi(t,x)\ ;\ \ \psi\big(s,\Phi(s,t,x)\big)=\psi(t,x)\ \ \forall s,\ t,\ x.$$

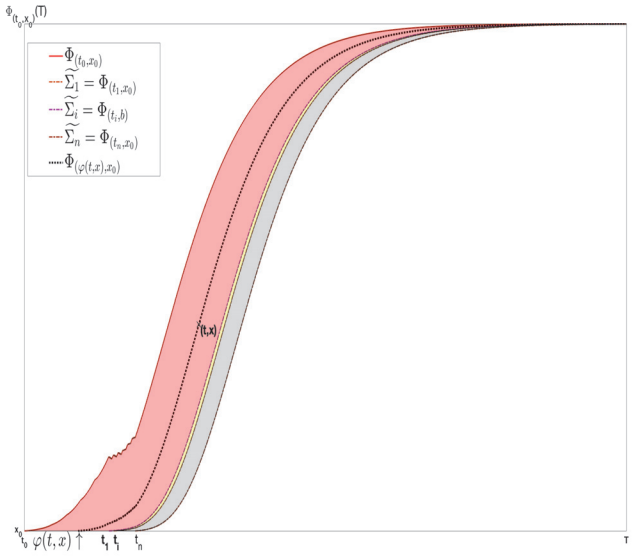

Figure 2. *Regularity domain of φ delimited by $\widetilde{\Sigma}_i$*

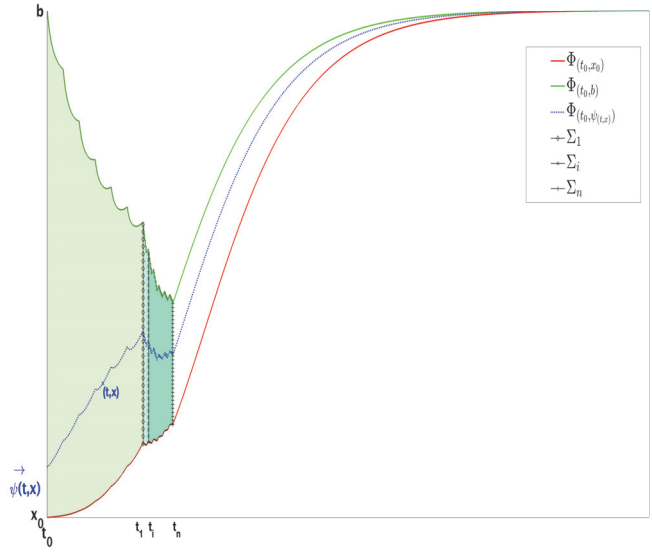

Figure 3. *Regularity domain of ψ delimited by $\Phi_{(t_0,b)}$, $\Phi_{(t_0,x_0)}$ and Σ_i*

3. Existence result

In this section, we focus on the proof of the existence and uniqueness of solution for the problem (1.12).

3.1. *Functional framework*

We denote by $E = \mathcal{C}^1_{MG}([t_0, T],\ L^1([1, b]))$ the set of continuous functions on $[t_0, T]$ with values in $L^1([1, b])$, of class C^1 on $[t_0, T]\backslash\{t_i,\ \ i = 1, ..., n\}$, 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

$$\|w\| = \sup_{t\in[t_0,T]} \|w(t,.)\|_{L^1([1,b])} + \max_{i\in\{0,...,n\}} \sup_{t\in[t_i,t_{i+1}]} \left\| \frac{\partial w}{\partial t}(t,.) \right\|_{L^1([1,b])}.$$

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

$$E(u) = \left\{ w \in \mathcal{C}^1_{MG}([t_0, T],\ L^1([1, b])) \quad w(t_0,\ .) = u \right\}.$$

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

3.2. *The main theorem*

Theorem 3.1. *We suppose that the initial data u_0 belongs to $W^{1,1}(]1, b[)$ and verifies the compatibility conditions*

$$u_0(b) = 0 \quad \textit{and} \quad (Gu_0)(t_0, 1) = \int_1^b \beta(x)u_0(x)dx + f(t_0). \tag{3.1}$$

*We suppose that G verifies **Hypothesis H** and the conditions (2.6) with $G(t, 1)$ constant on $[t_0, T]$.*

Then, there is a unique $u \in E(u_0)$ with $Gu \in \mathcal{C}([t_0,T],\, W^{1,1}(]1,b[))$ that verifies the equations (1.12a), (1.12b) and (1.12c) respectively in $\mathcal{C}_{MG}([t_0,T],\, L^1(]1,b[))$, $\mathcal{C}([t_0,T],\, \mathbb{R})$ and $L^1(]1,b[)$.

Remark 3.2. *The hypothesis $G(t,1)$ constant is verified by G given by (1.8). It reflects the fact that radiotherapy starts only from a threshold $\hat{x}$ greater than* 1.

The key ingredient in the proof of theorem 3.1 is a Banach fixed point theorem in a suitable fundamental functional space. The proof is deduced from the following technical four lemmas. In the first one, we construct an operator on $E(u)$. In the second lemma, we prove that this operator has a fixed point. In the third lemma, we prove that this fixed point is a solution. In the last lemma, we prove the uniqueness.

Lemma 3.3. *Let $u_0 \in W^{1,1}(]1,b[)$ given with $u_0(b) = 0$. We assume that the hypotheses of Theorem 3.1 are satisfied. We define the operator $\mathcal{T}$ by*

$$\mathcal{T}(w)(t,x) = u(t,x) = \begin{cases} R\big(\varphi(t,x)\big) \exp\left(-\displaystyle\int_{\varphi(t,x)}^{t} \partial_x G\left(s, \Phi_{(t,x)}(s)\right)\, \mathrm{d}s\right) & \text{in } \Omega_1, \\ u_0\big(\psi(t,x)\big) \exp\left(-\displaystyle\int_{t_0}^{t} \partial_x G\left(s, \Phi_{(t,x)}(s)\right)\, \mathrm{d}s\right) & \text{in } \Omega_2, \\ 0 & \text{in } \Omega_3, \end{cases} \tag{3.2}$$

where

$$R(t) = \frac{1}{G(t,1)} \left(\int_1^b \beta(y) w(t,y)\, dy + f(t) \right).$$

Then $\mathcal{T}$ is well defined from $E(u_0)$ into $E(u_0)$.

Proof. Let w be given in $E(u_0)$.

Step 1 . The function u defined by (3.2) satisfies

$$\int_1^b |u(t,x)| \mathrm{d}x \;\leq\; M_0 \left(C_1 (\|\beta\|_\infty \sup_{[t_0,T]} \|w(t,.)\|_{L^1} + \sup_{t\in[t_0,T]} |f(t)|) + \|u_0\|_{L^1} \right) < \infty \tag{3.3}$$

where

$$M_0 = \sup_{\mathcal{Q}} \exp\left(-\int_{t_0}^{t} \partial_x G\left(s, \Phi_{(t,x)}(s)\right)\, \mathrm{d}s \right) \text{ and } C_1 = \frac{b-1}{G(t,1)}. \tag{3.4}$$

So, $u(t,.)$ is in $L^1(]1,b[)$. In addition, it is clear that u is continuous on Q deprived of the characteristics curves $\Phi_{(t_0,1)}$ and $\Phi_{(t_0,b)}$. We also have, for any sequence $(\hat{t}_n)_{n\in\mathbb{N}}$ that converges to t

$$\begin{aligned} \|u(\hat{t}_n,.) - u(t,\,.)\|_{L^1} \;\leq\; & M_0 \Big[C_1 \|\beta\|_\infty \|w(\varphi(\hat{t}_n),.) - w(\varphi(t),\,.)\|_{L^1} + \\ & C_1 |f(\hat{t}_n) - f(t)| + \|u_0(\psi(\hat{t}_n,.)) - u_0(\psi(t,\,.))\|_{L^1} \Big]. \end{aligned}$$

As $w \in \mathcal{C}([t_0,T],\, L^1(]1,b[))$, $u_0 \in W^{1,1}(]1,b[)$, $f \in \mathcal{C}([t_0,T])$ and $\varphi,\, \psi$ are continuous, we get

$$\|u(\hat{t}_n,\,.) - u(t,\,.)\|_{L^1} \xrightarrow[n\to+\infty]{} 0.$$

Step 2 . Let us prove that u is continuous on the characteristic curves $\Phi_{(t_0,1)}$ and $\Phi_{(t_0,b)}$. Let (τ, x_0) be a point on the curve $\Phi_{(t_0,1)}$. Due to the continuity of u_0, φ and the fact that $\varphi(\tau, x_0) = t_0$, we have

$$\begin{aligned}\lim_{\substack{(t,x)\to(\tau,x_0)\\(t,x)\in\Omega_1}} u(t,x) &= R\big(\varphi(\tau,x_0)\big)\exp\left(\int_{\varphi(\tau,x_0)}^{t}\partial_x G\left(s,\Phi_{(\tau,x_0)}(s)\right)\,\mathrm{d}s\right)\\ &= u_0(1)\exp\left(-\int_{t_0}^{\tau}-\partial_x G\left(s,\Phi_{(\tau,x_0)}(s)\right)\,\mathrm{d}s\right)\\ &= \lim_{\substack{(t,x)\to(\tau,x_0)\\(t,x)\in\Omega_2}} u(t,x).\end{aligned}$$

Now, let (τ, x_0) be a point on the curve $\Phi_{(t_0,b)}$. As $u_0(b) = 0$, ψ is continuous and $\psi(\tau, x_0) = b$, we get

$$\begin{aligned}\lim_{\substack{(t,x)\to(\tau,x_0)\\(t,x)\in\Omega_2}} u(t,x) &= u_0\big(\psi(\tau,x_0)\big)\exp\left(-\int_{t_0}^{\tau}\partial_x G\left(s,\Phi_{(t,x)}(s)\right)\,\mathrm{d}s\right)\\ &= u_0(b)\exp\left(-\int_{t_0}^{\tau}\partial_x G\left(s,\Phi_{(t,x)}(s)\right)\,\mathrm{d}s\right)\\ &= \lim_{\substack{(t,x)\to(\tau,x_0)\\(t,x)\in\Omega_3}} u(t,x)\\ &= 0.\end{aligned}$$

Step 3 . We prove here that $\partial_t u \in \mathcal{C}^0_{MG}([t_0,T], L^1(]1,b[))$.

1 . Let $(t,x) \in \Omega_1$.

1 . If (t,x) belongs to one of the open connected components delimited by $\cup_{i=1,\dots,n}(\Sigma_i \cup \widetilde{\Sigma}_i)$, $\widetilde{\Sigma}_i = \Phi_{(t_i,1)}$, $\Sigma_i = \{t_i\}\times[1,b]$, then φ and $\Phi(.,.,s)$ are of class C^1 at (t,x). The characteristics starting from the points $(t_i,1)$ and those of foot $(\varphi(t,x),1)$ do not intersect. But, may be, there exist points of discontinuity of G between $\varphi(t,x)$ and t (see Figure 2). So the functions $s \to \Phi_{(t,x)}(s)$ and $s \to \partial_x G(s,\Phi_{(t,x)}(s))$ are of class C^1 piecewise on the segment $[\varphi(t,x),t]$. By deriving the Lebesgue integral, u is differentiable in time at the point (t,x) and

$$\begin{aligned}\partial_t u(t,x) &= \exp\left(-\int_{\varphi(t,x)}^{t}\partial_x G\left(s,\Phi_{(t,x)}(s)\right)\mathrm{d}s\right)\times\Big[R'\big(\varphi(t,x)\big)\partial_t\varphi(t,x)+\\ &\quad R\big(\varphi(t,x)\big)\big(\partial_t\varphi(t,x)\partial_x G\big(\varphi(t,x),1\big)-\partial_x G(t,x)\big)-\\ &\quad R\big(\varphi(t,x)\big)\int_{\varphi(t,x)}^{t}\partial_x^2 G\left(s,\Phi_{(t,x)}(s)\right)\partial_t\Phi_{(t,x)}(s)\mathrm{d}s\Big].\end{aligned}$$

2 . If $t \notin \{t_i, i = 1,...,n\}$ and $\varphi(t,x) = t_j$ with $t_j < t$, φ is not derivable in time at the point (t,x). There is a finite number, at most equal to n, of such points. The function $\partial_t u(t,.)$ is thus defined almost everywhere on $[1,\Phi_{(t_0,1)}(t)]$ (see Figure 3).

3 . If $t = t_i$ for one $i \in \{1,2,...n\}$, φ is not derivable in time over the entire curve $\{(x,t_i), x \in [1,\Phi_{(t_0,1)}(t)]$ and admits right and left derivatives in time.
Finally, the function $\partial_t u$ is defined for any $t \in [t_0,T]\backslash\{t_i,\ i = 1,...,n\}$ and almost everywhere in x in Ω_1.

2 . Let $(t,x) \in \Omega_2$.

a . If $t \notin \{t_i, i = 1, ..., n\}$, then ψ and $\Phi(.,.,s)$ are of class C^1 at the point (t,x). The function $s \to \Phi_{(t,x)}(s)$ is of class C^1 piecewise on $[t_0, T]$. By derivation, u is differentiable in time at the point (t,x) and

$$\begin{aligned} \partial_t u(t,x) \;=\; & \exp\left(-\int_{t_0}^{t} \partial_x G\left(s, \Phi_{(t,x)}(s)\right) \mathrm{d}s\right) \times \\ & \Big[\partial_t \psi(t,x) u_0'\big(\psi(t,x)\big) - u_0\big(\psi(t,x)\big)\partial_x G(t,x) \\ & -u_0(\psi(t,x) \int_{t_0}^{t} \partial_x^2 G\left(z, \Phi_{(t,x)}(s)\right) \partial_t \Phi_{(t,x)}(s)\, \mathrm{d}s\Big]. \end{aligned} \tag{3.5}$$

b . If $t \in \{t_i,\, i = 1, ..., n\},\ u$ admits a right and a left derivative in time on (t,x) just like ψ and Φ.

Hence, for all $t \notin \{t_i,\, i = 1, ..., n\}$, the mapping: $x \to \partial_t u(t,x)$ is defined almost everywhere on $[1, b]$ and verifies

$$\begin{aligned} \int_1^b |\partial_t u(t,x)|\, \mathrm{d}x \le M_0 \Bigg[& C_1 \sup_{\Omega_1} \big(|F(t,x)| + |\partial_t \varphi(t,x)|\big) \left(\|\beta\|_\infty \|w\|_{E(u_0)} + \|f\|_{\mathcal{C}^1_{MG}}\right) \\ & + \sup_{\Omega_2} \big(|S(t,x)| + |\partial_t \psi(t,x)|\big) \|u_0\|_{W^{1,1}} \Bigg] \end{aligned}$$

where

$$F(t,x) = \partial_t \varphi(t,x) \partial_x G\big(\varphi(t,x), 1\big) - \partial_x G(t,x) - \int_{\varphi(t,x)}^{t} \partial_x^2 G\left(s, \Phi_{(t,x)}(s)\right) \partial_t \Phi_{(t,x)}(s) \mathrm{d}s, \tag{3.6}$$

and

$$S(t,x) = \partial_x G(t,x) + \int_{t_0}^{t} \partial_x^2 G\left(z, \Phi_{(t,x)}(s)\right) \partial_t \Phi_{(t,x)}(s)\ \mathrm{d}s. \tag{3.7}$$

Thus $\partial_t u(t,.) \in L^1(]1, b[)$.

In addition, the mapping: $t \to \partial_t u(t,.)$ is continuous almost everywhere from $[t_0, T]$ in $L^1(]1, b[)$. Indeed, for any $t \in [t_0, T] \setminus \cup_{i=1}^n \{t_i\}$ and any sequence $(\hat{t}_n)_{n \in \mathbb{N}} \subset [t_0, T] \setminus \cup_{i=1}^n \{t_i\}$ converging to t, we have

$$\begin{aligned} \left\|\partial_t u(\hat{t}_n, .) - \partial_t u(t,\ .)\right\|_{L^1} \le M_0 C_1 \Bigg[& \sup_{\Omega_1} |F(t,x)| \left(\|\beta\|_\infty \left\|w(\hat{t}_n, .) - w(t,.)\right\|_{L^1} + \left|f(\hat{t}_n) - f(t)\right| \right) \\ & + \sup_{\Omega_1} |\partial_t \varphi(t,x)| \left(\left|f'(\hat{t}_n) - f'(t)\right| + \|\beta\|_\infty \left\|\partial_t w(\hat{t}_n, .) - \partial_t w(t,.)\right\|_{L^1} \right) \Bigg]. \end{aligned}$$

We conclude by using the regularity of f and w.

□

Lemma 3.4. *Under the hypothesis of Theorem 3.1, the operator $\mathcal{T}$ admits a unique fixed point.*

Proof.

Step 1 . Let $w_1,\ w_2$ be given in $E(u_0)$. We have

$$\mathcal{T}(w_1) - \mathcal{T}(w_2) = 0 \text{ on } \Omega_2 \cup \Omega_3,$$

and then for all $(t,x) \in \mathcal{Q}$ we have

$$\left|\left(\mathcal{T}(w_1) - \mathcal{T}(w_2)\right)(t,x)\right| \leq \frac{M_0 C_1}{b-1}\|\beta\|_\infty \|w_1\big(\varphi(t,x),.\big) - w_2\big(\varphi(t,x),.\big)\|_{L^1} \mathbb{1}_{\Omega_1}(t,x),$$

where M_0 and C_1 are given by (3.4). It follows that

$$\begin{aligned}\|\left(\mathcal{T}(w_1) - \mathcal{T}(w_2)\right)(t,.)\|_{L^1} &\leq \frac{M_0 C_1}{b-1}\|\beta\|_\infty \times \int_1^{\Phi_{(t_0,1)}(t)} \|\left(w_1 - w_2\right)\left(\varphi(t,x),.\right)\|_{L^1} \mathrm{d}x \\ &\leq M_0 C_1 \|\beta\|_\infty \|w_1 - w_2\|_{E(u_0)}.\end{aligned}$$

On another hand, a technical calculation gives for almost all (t,x)

$$\begin{aligned}\partial_t\left(\mathcal{T}(w_1) - \mathcal{T}(w_2)\right)(t,x) &= \frac{C_1}{b-1}\exp\left(-\int_{\varphi(t,x)}^{t} \partial_x G\left(s, \Phi_{(t,x)}(s)\right)\mathrm{d}s\right) \times \\ &\quad \Bigg[\partial_t\varphi(t,x)\int_1^b \beta(y)\partial_t(w_1 - w_2)\big(\varphi(t,x),y\big)\mathrm{d}y \\ &\quad + F(t,x)\int_1^b \beta(y)(w_1 - w_2)\big(\varphi(t,x),y\big)\,\mathrm{d}y\Bigg] \times \mathbb{1}_{\Omega_1}(t,x),\end{aligned}$$

where F is defined by (3.6). It follows that

$$\|\partial_t\left(\mathcal{T}(w_1) - \mathcal{T}(w_2)\right)(t,.)\|_{L^1} \leq \frac{M_0 C_1\left(C_2 + C_3\right)}{b-1}\|\beta\|_\infty \Phi_{(t_0,1)}(t)\|w_1 - w_2\|_{E(u_0)},$$

with $C_2 = \sup_Q\{1,\ |\partial_t\varphi(t,x)|\}$ and $C_3 = \sup_Q |F(t,x)|$.
For t' such that $\Phi_{(t_0,1)}(t') = \frac{b-1}{2M_0C_1\|\beta\|_\infty(1+C_2+C_3)} + 1$, we get

$$\|\mathcal{T}(w_1) - \mathcal{T}(w_2)\|_{E(u_0)} \leq C\|\beta\|_\infty\left(\Phi_{(t_0,1)}(t') - 1\right)\|w_1 - w_2\|_{E(u_0)},$$

where $C = \frac{M_0C_1(1+C_2+C_3)}{b-1}$. Let $\tilde{t} = \Phi^{-1}_{(t_0,1)}\left(\frac{1}{2C\|\beta\|_\infty} + 1\right)$ and $t^* = \min(\tilde{t}, T)$. The operator $\mathcal{T}$ is a contracting operator on

$$E_{t^*}(u_0) = \left\{w \in \mathcal{C}^1_{MG}([t_0,t^\star],\ L^1([1,b]))\ ;w(t_0,\ .) = u_0\right\}.$$

So it admits a unique fixed point.

Step 2 . The contraction constant, in the step 1, do not depend on u_0. We can therefore repeat the process of the first step, with an initial condition $u_0^* = u(t^*, .)$, and the compatibility condition at t^*. We obtain a new point t^{2*} such that the operator $\mathcal{T}$ is contracting on

$$E_{t^{2*}}(u_0^*) = \big\{ w \in \mathcal{C}^1_{MG}([t^\star, t^{2\star}],\, L^1([1,b]))\; w(t^\star,\, .) = u(t^\star,\, .) \big\},$$

so it admits a unique fixed point on $[t^*,\, t^{2*}]$. We iterate the process until we cover $[t_0, T]$ (bootstrap in time as in [21]).

□

Lemma 3.5. *Under the hypothesis of Theorem 3.1, the fixed point u of the two previous lemma is solution of the problem (1.12).*

Proof. By the construction (3.2) and by taking into account the respective regularities, we have

$$\begin{aligned}
\partial_x(Gu)(t,x) &= 0, \text{ in } \Omega_3,\\
\partial_x(Gu)(t,x) &= \exp\left(-\int_{\phi(t,x)}^t \partial_x G\left(s, \Phi_{(t,x)}(s)\right) \mathrm{d}s\right) \times \Big[R\big(\phi(t,x)\big)\partial_x G(t,x)\\
&\quad + G(t,x)\Big(\partial_x\phi(t,x) R'\big(\phi(t,x)\big) + R\big(\phi(t,x)\big)\Big(\partial_x\phi(t,x)\partial_x G\big(\phi(t,x),1\big)\\
&\quad - \int_{\phi(t,x)}^t \partial_x^2 G\left(s, \Phi_{(t,x)}(s)\right) \partial_x \Phi_{(t,x)}(s) \mathrm{d}s\Big)\Big)\Big], \quad \text{in } \Omega_1,\\
\partial_x(Gu)(t,x) &= \exp\left(-\int_{t_0}^t \partial_x G\left(s, \Phi_{(t,x)}(s)\right) \mathrm{d}s\right) \times \Big[u_0\big(\psi(t,x)\big)\partial_x G(t,x)\\
&\quad - G(t,x)\Big(u_0\big(\psi(t,x)\big) \int_{t_0}^t \partial_x^2 G\left(s, \Phi_{(t,x)}(s)\right) \partial_t \Phi_{(t,x)}(s) \mathrm{d}s\\
&\quad - \partial_x\psi(t,x) u_0'\big(\psi(t,x)\big)\Big)\Big], \quad \text{in } \Omega_2.
\end{aligned}$$

Using the derivative in time (3.5)-(3.5), we get

$$\partial_t u + \partial_x(Gu) = \begin{cases}
R'\big(\varphi(t,x)\big) \exp\left(-\displaystyle\int_{\varphi(t,x)}^t \partial_x G\left(s, \Phi_{(t,x)}(s)\right) \mathrm{d}s\right) \times & \\
\Big[\partial_t\varphi(t,x) + G(t,x)\partial_x\varphi(t,x)\Big], & (t,x) \in \Omega_1\\
u_0\big(\psi(t,x)\big) \exp\left(-\displaystyle\int_{t_0}^t \partial_x G\left(s, \Phi_{(t,x)}(s)\right) \mathrm{d}s\right) \times & \\
\Big[\partial_t\psi(t,x) + G(t,x)\partial_x\psi(t,x)\Big], & (t,x) \in \Omega_2\\
0. & (t,x) \in \Omega_3
\end{cases} \tag{3.8}$$

Moreover, since the functions φ and ψ are constant along the characteristics curves, we have

$$\frac{d}{ds}\varphi\big(s, \Phi(s;t,x)\big) = 0 \quad \text{and} \quad \frac{d}{ds}\psi\big(s, \Phi(s;t,x)\big) = 0. \tag{3.9}$$

Then, we get

$$\partial_s\varphi\big(s, \Phi(s;t,x)\big) + G\big(t, \Phi(s;t,x)\big)\partial_x\varphi\big(s, \Phi(s;t,x)\big) = 0 \tag{3.10}$$

and

$$\partial_s\psi\big(s,\Phi(s;t,x)\big)+G\big(t,\Phi(s;t,x)\big)\partial_x\psi\big(s,\Phi(s;t,x)\big)=0.$$

Using (3.8), (3.9) and (3.10), we deduce that

$$\partial_t u(t,x)+\partial_x(G(t,x)u(t,x))=0. \tag{3.11}$$

Finally, since $\partial_t u\in L^1(]1,b[)$, we get $\partial_x(Gu)=-\partial_t u\in\mathcal{C}([t_0,t_1],L^1(]1,b[))$ and u is a solution of our problem. □

Lemma 3.6. *Under hypothesis of Theorem 3.1, the problem (1.12) has a unique solution.*

Proof. Let u be a solution of (1.12). We decompose u in the form

$$u=u_1+u_2, \tag{3.12}$$

where u_1 and u_2 are solutions of (1.12a)–(1.12c) with respectively $f=f_1=0$, $u_1(0,.)=u_0$ and $f_2=f$, $u_2(0,.)=0$. For $n\in\mathbb{N}^*$, we introduce the function Γ_n defined on $\mathbb{R}$ by

$$\Gamma_n(x)=\begin{cases}1 & \text{if } x\geq\frac{1}{n},\\ -1, & \text{if } x\leq-\frac{1}{n}\\ x & \text{if } -\frac{1}{n}\leq x\leq\frac{1}{n}.\end{cases}$$

Multiplying $\partial_t u_i+\partial_x\left[Gu_i\right]$, for $i=1,2$, by $\Gamma_n(u_i(t,x))$ and integrating on $[1,b]$, we get

$$\int_1^b\partial_t u_i(t,x)\Gamma_n\big(u_i(t,x)\big)+\partial_x\left[G(t,x)u_i(t,x)\right]\Gamma_n\big(u_i(t,x)\big)\mathrm{d}x=0.$$

Integrating by parts, making n tend towards infinity and applying the dominated convergence theorem, we get for $i=1,2$

$$\begin{aligned}\partial_t\|u_i(t,.)\|_{L^1(1,b)} &\leq\Big|\int_1^b\beta(x)u_i(t,x)\,\mathrm{d}x\Big|+\big|f_i(t)\big|\\ &\leq\|\beta\|_\infty\|u_i(t,.)\|_{L^1(1,b)}+\big|f_i(t)\big|\end{aligned}.$$

Integrating with respect to t, for all $i=1,2$, we obtain

$$\|u_i(t,.)\|_{L^1(1,b)}\leq\|\beta\|_\infty\int_{t_0}^t\|u_i(s,.)\|_{L^1(1,b)}\,\mathrm{d}s+\int_{t_0}^t\big|f_i(s)\big|\,\mathrm{d}s+\|u_i(0,x)\|_{L^1(1,b)}.$$

Then by applying the Gronwall's Lemma, for $i=1,2$, we get

$$\|u_i(t,.)\|_{L^1(1,b)}\leq\mathrm{e}^{\|\beta\|_\infty(T-t_0)}\big(\|f_i\|_{L^1(t_0,T)}+\|u_i(0,x)\|_{L^1(1,b)}\big). \tag{3.13}$$

We denote by $\mathcal{T}_{u_0,f}$ the operator constructed in Lemma 3.3. Hence for $u_0\in W^{1,1}(]1,b[)$ verifying the compatibility condition $(Gu_0)(t_0,1)=\int_1^b\beta(x)u_0(x)dx$, the operator $\mathcal{T}_1=\mathcal{T}_{u_0,0}:u_0\mapsto u_1$ satisfies

$$\|\mathcal{T}_{u_0,0}u_0\|_{\mathcal{C}([t_0,T],L^1(1,b))}\leq\mathrm{e}^{\|\beta\|_\infty(T-t_0)}\|u_0\|_{L^1(1,b)}. \tag{3.14}$$

Now, for $f\in\mathcal{C}^1_{MG}([t_0,T])$ such that $f(t_0)=0$, the function still denoted by f defined by $f(t,x)=f(t)$, belongs to $E(u_0=0)$ and the operator $\mathcal{T}_2$ defined by $\mathcal{T}_2=\mathcal{T}_{0,f}:f\mapsto u_2$ verifies

$$\|\mathcal{T}_2 f\|_{\mathcal{C}([t_0,T],L^1(1,b))}\leq\mathrm{e}^{\|\beta\|_\infty(T-t_0)}\|f\|_{L^1(t_0,T)}. \tag{3.15}$$

Finally, if there exist two solutions v_1 and v_2 of (1.12a)–(1.12c), then $u = v_1 - v_2$ is a solution with initial data u_0 and second member f null. We decompose u as in (3.12) and we deduce from (3.14, 3.15) that $u_1 = u_2 = 0$ and the uniqueness follows. □

4. Numerical analysis

In this section, we will present some numerical tests that would show the interest of drugs on tumor growth. With G given by (1.8), it is not possible to compute an exact solution for the system (1.12), except in very special cases. So, it is necessary to implement an approximation strategy. We use the method of characteristics to solve the transport equation, a 4th order Runge Kutta scheme for the ODE, and a trapezoidal quadrature formula to approximate the integrals. To follow the evolution of the disease, we introduce as in [8], the metastatic index defined by

$$MI_{b_{\min}}(t) = \int_{b_{\min}}^{b} u(t,x)\mathrm{d}x. \tag{4.1}$$

It evaluates the number of metastases at different times and for different minimal sizes $b_{\min}$. If $b_{\min} = 1$, all the metastases present are measured. For $b_{\min} \geq 10^8$, only detectable tumors by medical imaging are considered [8]. To measure the influence of drugs, we will present the evolution of this index without treatment, with chemotherapy, and with mixed treatments.

4.1. *Method of characteristics*

4.1.1. Time discretization

We consider a time interval $[0,T]$ and an interval $[t_0,\overline{T}]$ strictly included in $[0,T]$, where t_0 and $\overline{T}$ are respectively the start and the end of treatments. We notice that we are in the presence of large variations in time scales: the radiation time is of the order of minutes, the chemo time is counted in hours, the treatment lasts several months, and the disease is monitored for a few years. We then opt for a time discretization with variable steps. Let $(t_n)_{0\leq n\leq N}$ be a nonuniform subdivision of $[0,T]$ with steps $k_n = t_{n+1} - t_n$. Care will be taken to consider the points of discontinuity of G as nodes of the mesh.

4.1.2. Space discretization

The spatial discretization is based on the resolution of the differential equation

$$\left\{\begin{array}{lcl} \frac{d}{dt}\Phi(t) & = & G(t,\Phi(t)), \\ \Phi(s) & = & x. \end{array}\right. \tag{4.2}$$

Along this curve, the solution of the EDP is given by

$$u(t,\Phi_{(s,x)}(t)) = u(s,x)\exp\left(-\int_s^t \partial_x G(\tau,\Phi_{(s,x)}(\tau))\,\mathrm{d}\tau\right). \tag{4.3}$$

To simplify the notations, we introduce the function $y_p(t)$ defined by

$$y_p(t) = \left\{\begin{array}{ll} x_p(t) = b^{1-\mathrm{e}^{-at}} & \text{if } t\in[0,\,t_0], \\ \Phi_{(t_0,1)}(t) & \text{if not.} \end{array}\right.$$

We define a spacial mesh $(x_i^n)_{i\geq 1}$ at time t_n by

$$\begin{aligned} x_i^n &= \Phi_{(t_{n-1},x_{i-1}^{n-1})}(t_n), \ \ \forall i \geq 2, \ \ n \in [[2, N+1]], && (4.4)\\ x_1^n &= 1, \ \ \forall\, n, && (4.5)\\ x_i^0 &= y_p(t_i), \ \ \forall i. && (4.6) \end{aligned}$$

Equality (4.5) means that $(t, 1)$ is the entry point for all the characteristic curves in

$$\Omega_1 = \big\{(t,x) \in \mathcal{Q} \,/\, x < \Phi_{(t_0,1)}(t)\big\}.$$

We denote the step of the space discretization by

$$h_i^n = x_i^n - x_{i-1}^n.$$

Using a trapezoidal quadrature formula in the expression (4.3), we get

$$\begin{cases} u_1^1 = \dfrac{\beta(y_p(0))}{G(1,1)}, & \\ u_i^n = 0, & i \geq n, \\ u_i^n = u_{i-1}^{n-1} \mathrm{e}^{-\mathfrak{S}\left(t_{n-1},t_n,x_{i-1}^{n-1},x_i^n,\partial_x G\right)}, & n = 2,...,N, i = 2,...,n, \\ u_1^n = \dfrac{1}{G(t_n,1)}\left(\beta(y_p(t_n)) + \mathfrak{Q}\left((h_i^n)_{i\geq 2},(u_i^n)_{i\geq 2}\right)\right), & n = 2,...,N, \end{cases} \tag{4.7}$$

where

$$\begin{aligned} \mathfrak{S}\left(t_{n-1},t_n,x_{i-1}^{n-1},x_i^n,\partial_x G\right) &= \frac{1}{2}k_n\Big(\partial_x G(t_n,x_i^n) + \partial_x G(t_{n-1},x_{i-1}^{n-1})\Big), \\ &\text{and} \\ \mathfrak{Q}\left((h_i^n)_{i\geq 2},(u_i^n)_{i\geq 2}\right) &= h_2^n\beta(x_2^n)u_2^n + \sum_{i=3}^{n}\left(\frac{1}{2}h_i^n(\beta(x_i^n)u_i^n + \beta(x_{i-1}^n)u_{i-1}^n\right), \end{aligned}$$

are respectively the quadrature formula in $\displaystyle\int_{t_{n-1}}^{t_n} \partial_x G(z, \Phi_{(t_{n-1},x_{i-1}^{n-1})}(z))\,\mathrm{d}z$ and in the nonlocal boundary condition. The second equation of (4.7) means that the solution vanishes on

$$\Omega_3 = \big\{(t,x) \in \mathcal{Q} \,/\, x > \Phi_{(t_0,b)}(t)\big\}.$$

4.2. *Numerical results*

It is worthy to note that all our calculations are carried out with MATLAB software. The time step varies between 3 min and 1 hour. The spatial variable is a matrix of the order of 2×10^5 with coefficients varying between 1 and 10^{12}, depending on whether one is in the regions with or without treatment.

4.2.1. Validation tests

In order to measure the performance of our numerical strategy, we consider two tests with known analytical solutions.

4.2.1.1. First test : Without treatment

The characteristics curves are solutions of (1.12f) and are given by

$$\Phi(t,s,x) = b\left(\frac{x}{b}\right)^{\mathrm{e}^{-a(t-s)}}. \tag{4.8}$$

We present in Figure 4 the exact and approximate metastatic index, we observe that the numerical solution is in perfect agreement with the exact one.

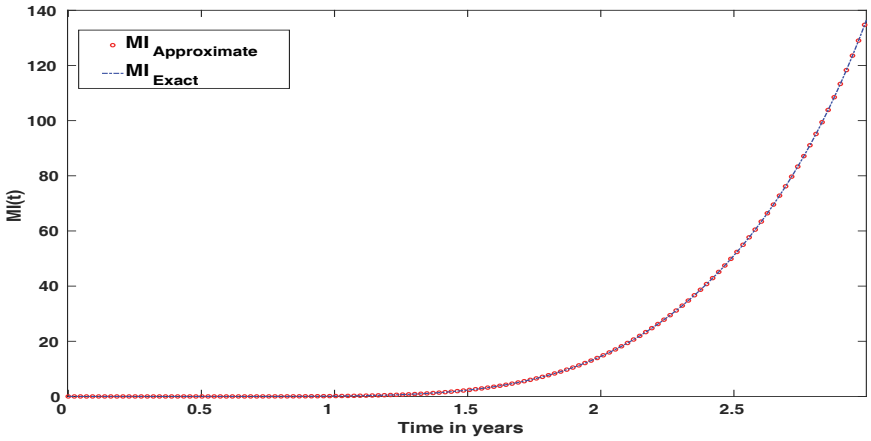

Figure 4. *Exact and approximate MI without treatment.* $a = 0.00286$, $b = 10^{12}$, $b_{min} = 1$, $m = 5.3 \times 10^{-8}$, $\alpha = \frac{2}{3}$, $k_n = 1$ *hour for all* n.

4.2.1.2. Second test : Only chemotherapy

We consider the case with with

$$K(x) = x, \quad \Gamma(t) = \gamma C(t) \quad \text{and} \quad C(t) = c_1(t),$$

where $c_1(t)$ is the drug's concentration defined by (1.9). The exact solution for the ODE (1.12f) is

$$\Phi(t,s,x) = b\left(\frac{x}{b}\right)^{\mathrm{e}^{-a(t-s)}} \mathrm{e}^{-\gamma \mathrm{e}^{-at}(I(t)-I(s))}, \tag{4.9}$$

with $I(t) = \int_0^t C(\tau)\mathrm{e}^{a\tau}\mathrm{d}\tau$. Using the following parameters

$$a = 0.00286, \quad b = 10^{12}, \quad m = 5.3 \times 10^{-8}, \quad \alpha = 0.55,$$

we present in Figure 5 and Figure 6, the approximation error on the metastatic index MI, respectively for detectable and total tumors. We can see the performance of our methodology despite the disparity in the parameters and the size of the matrix. We also see that MI is larger with $b_{min} = 1$, which highlights the existence of not detectable metastases by imaging. In Figure 7 and Figure 8, we highlight the positive effect of the treatments on the metastatic indexes. The difference is of order of 27% for all metastasis and 33% for detectable metastasis. All the results of this test are consistent with those of [25], and confirm the validation of our calculation code.

4.2.2. Significant tests

We consider the effect of concomitant treatments on the evolution of a primary and a metastatic growing tumors. Our numerical tests highlight the effect of mixed protocols. This could assist the oncologists

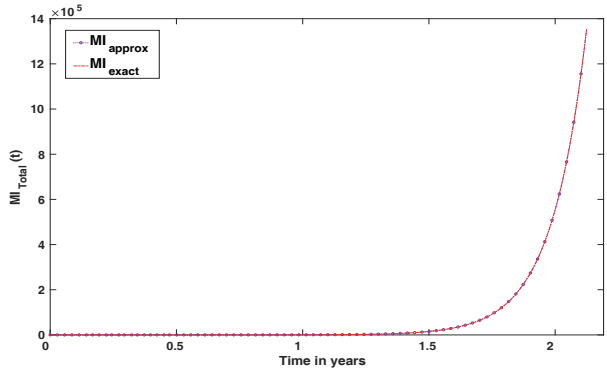

Figure 5. *Exact and approximate total metastatic index with Chemotherapy* ($a = 0.0231,\ b_{min} = 1$)

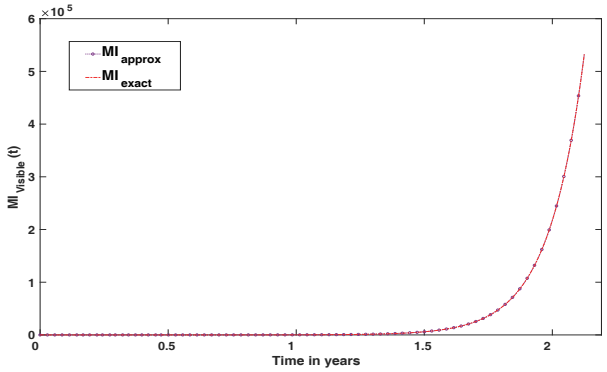

Figure 6. *Exact and approximate visible metastatic index with Chemotherapy* ($a = 0.0231,\ b_{min} = 10^8$)

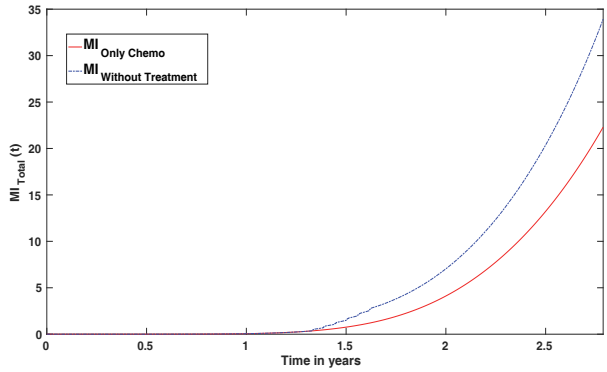

Figure 7. *Total MI with and without chemotherapy.*

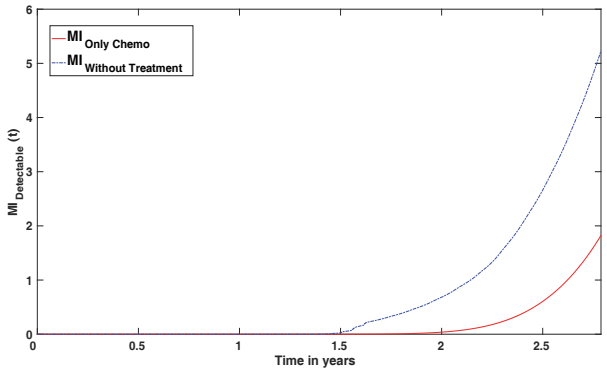

Figure 8. *Detectable MI with and without chemotherapy.*

in their decision-making regarding the optimal regression strategy, considering the size of the primary tumor and the number of metastases. It is important to note that our model does not consider the toxic effects or the overall condition of the patient. We consider the following parameters [25, 10].

$$a = 0.0231,\quad b = 10^{12},\quad m = 5.3 \times 10^{-8},\quad \alpha = 0.55,\quad \alpha_{\text{eff}} = 0.45. \tag{4.10}$$

4.2.2.1. Primary tumor

In Figure 9, we compare the number of cells in a primary tumor, with and without treatment. In Figure 10, we focus on the regression of the primary tumor after the different treatments. The advantage of the mixed treatment is highlighted. To measure the sensitivity to radiation, we vary α_{eff}, and describe the impact of this variation on the primary tumor in Figure 11.

4.2.2.2. Growing tumor

We present, respectively in Figure 12 and Figure 13, the effect of treatments on the number of metastatic tumors, detectable and not by medical imaging. The ratio of metastatic indexes, with and without treatments, is presented in Figure 14 and Figure 15. We notice the advantage of the concomitant treatment for our selected parameters.

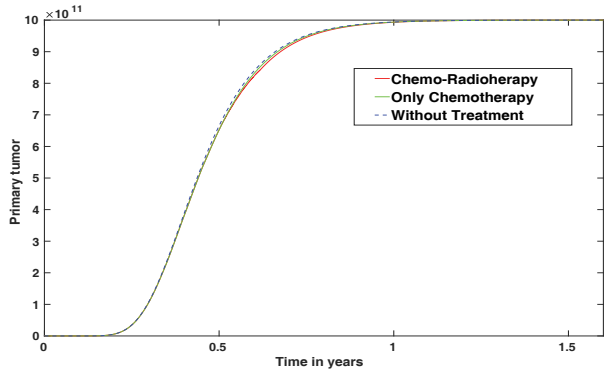

Figure 9. *Primary tumor with and without treatment*

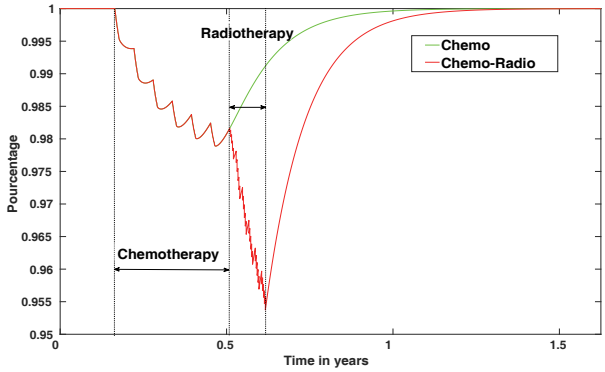

Figure 10. *The ratio of the number of cells*

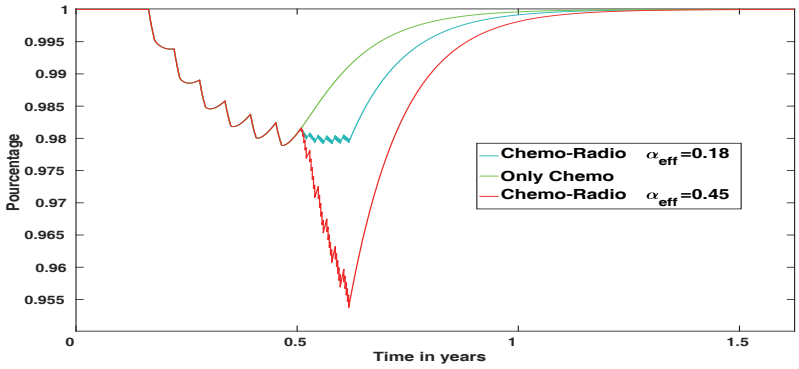

Figure 11. *Influence of the parameter* α_{eff}

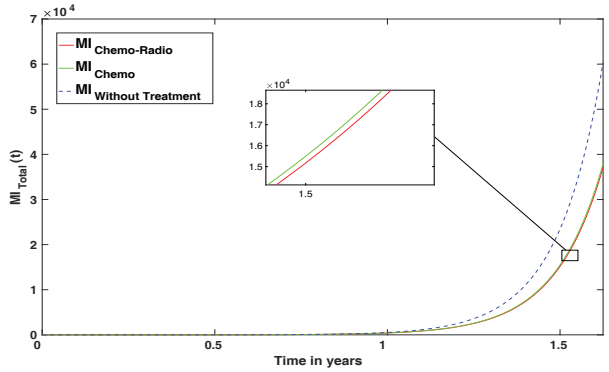

Figure 12. *Total MI with and without treatment*

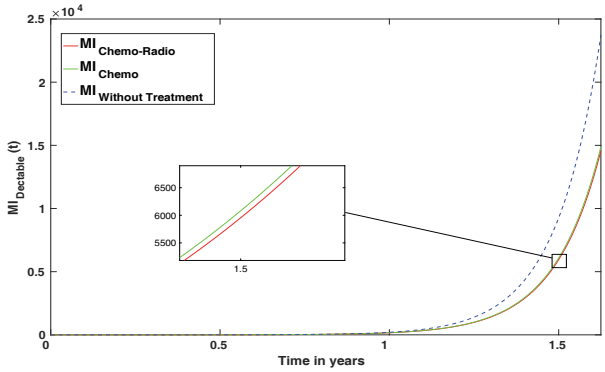

Figure 13. *Detectable MI with and without treatment*

Table 1 shows the evolution of the metastatic index, with and without treatment, at the times of the beginning and the end of treatments, and one years later. It is observed that, one year after the end of the treatment, the variation in the number of metastases between the chemotherapy and the mixed treatment is of the order of 8×10^2 cells and 3×10^2 cells respectively. We see clearly in Figure 14 and Figure 15 the effect of concomitant treatment to reduce tumor size.

In conclusion, the metastatic index should enable to better predict the risk of invasive cancer, even it cannot be seen with standard imaging techniques. We notice that the effect of the treatment is strictly linked to the choice of parameters associated to the disease and to the treatments, namely, the pharmacokinetic and pharmacodynamic parameters for chemotherapy and the radiosensitivity parameters for radiotherapy.

Table 1. *Evolution of the metastatic index at the time points: start of treatment (t_0), end of treatment (T_1) and one years after the end of treatment ($T = T_1 + 1$)*

	Time		
	$t = t_0$	$t = T_1$	$t = T$
Total Metastatic Index			
$\mathrm{MI}_{\text{Without Treat}}$	0.0441	30.028	6.032e04
$\mathrm{MI}_{\text{Chemo-Radio}}$	0.0441	27.078	3.714e04
$\mathrm{MI}_{\text{Only Chemo}}$	0.0441	27.591	3.793e04
Detectable Metastatic Index			
$\mathrm{MI}_{\text{Without Treat}}$	$8.187\text{e}-6$	11.807	2.371e04
$\mathrm{MI}_{\text{Chemo-Radio}}$	$8.187\text{e}-6$	10.615	1.457e04
$\mathrm{MI}_{\text{Only Chemo}}$	$8.187\text{e}-6$	10.807	1.488e04

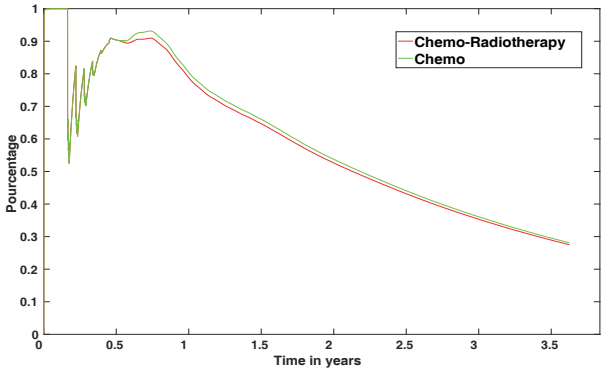

Figure 14. *The ratio of the total MI*

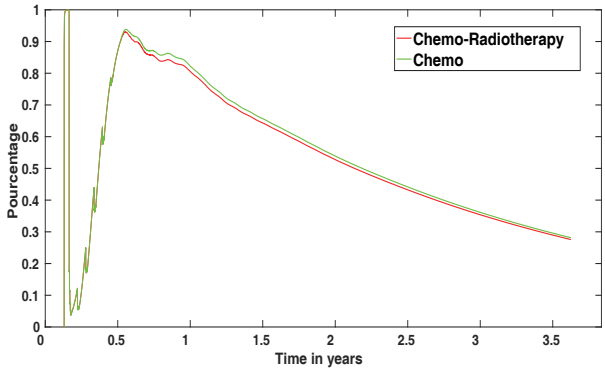

Figure 15. *The ratio of the detectable MI*

5. Conclusion

In this work, We have presented an analysis of a simplified model of tumor growth with treatment. The data associated with the treatments are irregular in time. Our model and existence result could be valid for other problems of population dynamics. We have carried out some numerical tests that could help in the analysis of the treatment effect. Many points remain to be treated. In particular, the inverse problems relating to some parameters of the model are interesting both theoretically, numerically and clinically.

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