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Set-Valued Stabilization of Reaction-Diffusion Model by Chemotherapy and or Radiotherapy

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Abstract

This paper aims to control partial differential equations, modeling cancer chemotherapy and or radiotherapy, so in order to asymptotically stabilize the tumor density. Viability kernel of general model on set of initial condition is used to solve the control problem, and characterize the control solution as regulation law of regulation map. Three models from the literature are considered to simulate the results. The first model includes chemotherapy effect on logistic tumor proliferation, while the second one demonstrates radiotherapy effect on exponential tumor increasing, whereas the third one models the effects of the combination of chemotherapy and radiotherapy on Gompertzian tumor growth.

1. Introduction

Partial differential equations are usually used in cancer modeling to describe the tumors progression, and they provide a valuable tool for cancer researchers to understand and predict the behavior of tumors, and to develop new therapies to combat the cancer disease.
The reaction-diffusion equations used in [1, 14] to model cancer, are unified in the general partial derivatives equation

$$u_t = \nabla \cdot (D(x)\nabla u) + f(u,c), (x,t) \in \Omega \times [0,T], \tag{1.1a}$$

where $t \in [0,T] \subset \mathbb{R}_+$ $(0 < T < \infty)$ and $x \in \Omega \subset \mathbb{R}^m$ $(m \in \mathbb{N}^*)$ denote time and position dependent of therapy by the vector valued function $c(x,t) \in \mathbb{R}^\ell$ $(\ell \in \mathbb{N}^*)$ on the tumor density by the scalar valued function $u(x,t) \in \mathbb{R}$,

$$c : \bar{\Omega} \times [0,T] \to \mathbb{R}^\ell \text{ and } u : \bar{\Omega} \times [0,T] \to \mathbb{R},$$

while u_t and ∇ denote the temporal derivative $\partial_t u$ and the spatial gradient operator $(\partial/\partial x_i)_{1 \le i \le m}$, respectively, furthermore $D(x) \in L^\infty(\Omega)$ is the spatially varying scalar diffusion coefficient, as well as the reaction-control term $f(u,c)$ is given.
The partial differential equation (1.1a) is supplied with the boundary condition

$$n \cdot \nabla u = 0, (x,t) \in \partial\Omega \times [0,T], \tag{1.1b}$$

where n is the normal vector on the boundary $\partial\Omega$, and augmented by the initial condition

$$u(x,0) = u_0(x), \text{for almost all } x \in \Omega, \text{where the initial state } u_0 \in L^2(\Omega). \tag{1.1c}$$

Several studies have been conducted on the system (1.1). [1] Uses Crank-Nicolson scheme to solve three models of glioma. [2] Presents an alternative fractional differential equation, to investigate the concentration of glioblastomas by using the theory of

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fractional calculus. [3] Introduces a weighted parameter diffusion of brain glioma. [4] Uses statistical procedures to estimate intra- and inter-patient heterogeneity for tumor growth model. [5] Investigates the stability of the Fisher-Stefan equation. [6] Analyzes a spectral regularization of a time-reversed model problem. [7] Solves a constrained optimization problem to calibrate tumor growth model. [8] Introduces and studies model to explain the dynamics of cancer propagation. [9] Presents numerical scheme driven from Fibonacci wavelets to solve Burgess model of brain tumor growth. [10] Focuses on the Fisher-KPP model of tumor growth. [11] Investigates the bang-bang property under spatio-temporal controls. [12] Uses equation to simulate the growth of the glioblastoma and radiotherapy prevention. [13] Solves equation governing tumor growth in human brain under radiotherapy. [14] Derives a nonlinear conjugate gradient method for identifying treatment parameter of brain tumors under therapy.
The originality of this paper is that the set-valued methods developed to feedback stabilize the tumor density $u(t)$,

$$u(t) \to 0, \text{ when } t \to \infty,$$

subject to the odes [15, 16, 17]

$$\begin{aligned} \dot{u}(t) &= f(t,u,c), u(0) = u_0, \\ \dot{c}(t) &= g(c), \end{aligned}$$

and to the odes [18, 19, 20, 21, 22, 23]

$$\begin{aligned} \dot{u}(t) &= f(u,v,c), u(0) = u_0, \\ \dot{v}(t) &= g(u,v,c), v(0) = v_0, \end{aligned}$$

where the time dependent vector $v = v(t) \in \mathbb{R}^k$ ($k \in \mathbb{N}^*$) denotes densities of interactive cells with the tumor density $u(t)$; will be adapted here to stabilize the tumor density $u(x,t)$, subject to the partial differential equation (1.1), and applied on the following models.

Model	Aim	Reference
$u_t = \nabla \cdot (D(x)\nabla u) + \rho u(1-u) - c(x,t)u$	Develops a gradient based algorithm to optimize chemotherapy.	[24]
$u_t = \nabla \cdot (D(x)\nabla u) + \rho u - c(x,t)u$	Extends Swanson's equation to consider the radiotherapy effect.	[25]
$u_t = \nabla \cdot (D(x)\nabla u) - \rho u \ln u - c(x,t)u$	Shows the effects of combined radiotherapy with chemotherapy.	[26]

Table 1: Samples of reaction-diffusion equations with: logistic, exponential, and Gompertz growth laws, under chemotherapy and or radiotherapy.

The structure of this paper is: section 1 introduced preceding papers [1, 14] on cancer modeling and analysis, section 2 proposes to solve the associated stabilizing problem in the viability framework, section 3 applies the obtained results to therapeutic models implying chemotherapy and or radiotherapy, and section 4 concludes by the effectiveness of the combination of chemotherapy and radiotherapy.

2. Problem statement and viability approach

This section considers the general distributed control system (2.1) and associates the corresponding control problem 1, gives the definition 2.1 to the viability property of the state solution, sets the closed subsets (2.4) to express the problem 1 in the viability sens by the proposition 2.2, characterizes the viability property by the regulation map (2.6) in the corollary 2.4, recalls the lemma 2.5 for the contingent cone calculus, and gets useful expression of the regulation law (2.8) in the corollary 2.6 by (2.10).

- State equation

$$u_t = Au + f(u,c), \tag{2.1a}$$

  where A is an elliptic differential operator and f is a function from $\mathbb{R} \times \mathscr{U}$ to $\mathbb{R}$, where $\mathscr{U}$ is a Hilbert space of controls.
- State-dependent feedback controls

$$c(x,t) \in U(x,u(x,t)), \text{ for almost all } (x,t) \in \Omega \times [0,T], \tag{2.1b}$$

  where U is a multifunction from $\Omega \times \mathbb{R}$ to $\mathscr{U}$.
- Dirichlet constraint

$$u(x,t)|_{\partial\Omega} = 0, \text{ for all } t \in [0,T]. \tag{2.1c}$$

- Neumann constraint

$$n \cdot \nabla u(x,t)|_{\partial\Omega} = 0, \text{ for all } t \in [0,T]. \tag{2.1d}$$

- Onset state

$$u(x,0) = u_0(x), \text{ for almost all } x \in \Omega. \tag{2.1e}$$

Problem 1. *Find a control $c \in L^2(\Omega, \mathscr{U})$ rending the tumor density $u \in L^2(\Omega)$ asymptotically stable, i.e.,*

$$u(x,t) \to 0, \text{ when } t \to \infty, \text{ for almost all } x \in \Omega. \tag{2.2}$$

Definition 2.1. *System (2.1) is viable in a closed subset $K \subset L^2(\Omega)$, if for any initial state $u_0 \in K$ the system (2.1) admits viable solution u in K, i.e.,*

$$\forall t \geq 0, u(\cdot,t) \in K. \tag{2.3}$$

Let be the subsets

$$K_\alpha := \{u \in L^2(\Omega), u \geq 0 \text{ and } \psi_\alpha(u) \leq 0, \text{ almost everywhere}\}, \tag{2.4a}$$

where the function ψ_α expression is

$$\psi_\alpha(u)(x,t) = u(x,t) - u_0(x)\exp(-\alpha t), \tag{2.4b}$$

and parameter α is as follows

$$\alpha \in \mathbb{R}_+^*. \tag{2.4c}$$

Proposition 2.2. *If $c \in L^2(\Omega, \mathscr{U})$ rends viable the distributed control system (2.1) in a subset (2.4), then c is solution to the problem 1.*

Proof. For almost all $x \in \Omega$

$$\begin{aligned} \psi_\alpha(u)(x,0) &= u(x,0) - u_0(x)\exp(-\alpha \times 0) \\ &= u(x,0) - u_0(x) \\ &= 0, \end{aligned}$$

which imlplies that $u_0 \in K_\alpha$.
And for all $t \geq 0$

$$\begin{aligned} u \in K_\alpha &\implies u(x,t) - u_0(x)\exp(-\alpha t) \leq 0 \\ &\implies u(x,t) \leq u_0(x)\exp(-\alpha t) \\ &\implies \lim_{t\to\infty} u(x,t) = 0. \end{aligned}$$

The initial state u_0 in (2.1e) is supposed regular enough (for example upper bounded) so that $u_0(x)\exp(-\alpha t)$ admits null limit. □

Remark 2.3. *The non-negative reel parameter α is introduced to further reduce the tumor density $u(x,t)$.*

Assumption 1. *Let introduce the following hypotheses for the next corollary.*

(H0): *The subset Ω is bounded open such that the trace operators*

$$\begin{aligned} \gamma\colon H^1(\Omega) &\to H^{1/2}(\partial\Omega) \\ u(x) &\mapsto u(x)|_{\partial\Omega} \end{aligned}$$

and

$$\begin{aligned} \delta\colon H^1(\Omega) &\to H^{-1/2}(\partial\Omega) \\ u(x) &\mapsto n \cdot \nabla u(x)|_{\partial\Omega} \end{aligned}$$

are surjective continuous linear.

(H1): *The single-valued map f is continuous affine to c and linear growth to c,*

$$\sup_u |f(u,c)| \leq \varsigma(\|c\| + 1). \tag{2.5}$$

(H2): *The set-valued map* $\mathbb{U} : L^2(\Omega) \rightsquigarrow L^2(\Omega, \mathscr{U})$ *defined by*

$$\mathbb{U}(u(\cdot)) := \{c(\cdot) \in L^2(\Omega, \mathscr{U}), c(x) \in U(x, u(x)), \text{ for almost all } x \in \Omega\},$$

is bounded and upper semicontinuous with closed convex images.

Corollary 2.4 ([27, Corollary 13.4.2])**.** *Let* $K \subset L^2(\Omega)$ *be a closed subset such that some* $\|u_0\|_{H_0^1(\Omega)} \leq \kappa$ *belongs to its interior in* $L^2(\Omega)$*. Then* K *is viable when and only when the regulation map*

$$R_K(u) := \{c \in \mathbb{U}(u), Au + f(u,c) \in T_K(u)\}, \tag{2.6}$$

where $T_K(u)$ *is the contingent cone, enjoys non-emptiness property, in the sens that*

$$\forall u \in K, R_K(u) \neq \emptyset, \tag{2.7}$$

and viable solution u *is given by regulation law* c*,*

$$c(x,t) \in R_K(u(x,t)), \text{ for almost all } (x,t) \in \Omega \times [0,T]. \tag{2.8}$$

Lemma 2.5 ([16, Lemma 3.3])**.** *The belonging of directions* $\bar{u}$ *in* $T_{K_\alpha}(u)$ *is characterized by both inequalities*

$$\bar{u} \geq 0 \quad \text{if} \quad u(x,t) = 0, \tag{2.9a}$$
$$D\psi_\alpha(u(x,t))\bar{u} \leq 0 \quad \text{if} \quad \psi_\alpha(u(x,t)) = 0, \tag{2.9b}$$

where D *denotes the differential operator.*

Corollary 2.6. *The regulation law* c *of the regulation map* R_{K_α} *is characterized by*

$$Au(x,t) + f(u(x,t), c(x,t)) \geq 0 \quad \text{if} \quad u(x,t) = 0, \tag{2.10a}$$
$$D\psi_\alpha(u(x,t))(Au(x,t) + f(u(x,t), c(x,t)) \leq 0 \quad \text{if} \quad \psi_\alpha(u(x,t)) = 0. \tag{2.10b}$$

Proof. By definition of the regulation map R_{K_α}

$$c(x,t) \in R_{K_\alpha}(u(x,t)),$$

if and only if

$$Au(x,t) + f(u(x,t), c(x,t)) \in T_{K_\alpha}(u(x,t)),$$

and by characterization (2.9) of contingent cone $T_{K_\alpha}(u(x,t))$ of the subsets K_α at $u(x,t)$

$$Au(x,t) + f(u(x,t), c(x,t)) \geq 0 \quad \text{if} \quad u(x,t) = 0,$$
$$D\psi_\alpha(u(x,t))(Au(x,t) + f(u(x,t), c(x,t)) \leq 0 \quad \text{if} \quad \psi_\alpha(u(x,t)) = 0.$$

□

3. Therapy application

This section is a numerical application of the theoretical results in the previous section 2, for chemotherapy and or radiotherapy, we consider the three representative models in the Table 1, with the regular domain $\Omega =]0,1[$ for the hypothesis $(H0)$, and the Neumann boundary condition (2.1d) (even (1.1b)), without any state-constraint controls (2.1b) (no need to check hypothesis $(H2)$). For all given simulations the parameter $\alpha = 1$ (2.4c).

3.1. Chemotherapy

Let consider the numerical model [24]

$$u_t = \nabla \cdot (0.65\nabla u) + 0.012(1-u)u - c(x,t)u, \quad (x,t) \in]0,1[\times[0,T], \tag{3.1a}$$
$$n \cdot \nabla u = 0, \quad (x,t) \in \{0,1\} \times [0,T], \tag{3.1b}$$
$$u(x,0) = 0.5 + 0.5\cos^2(\pi x), \quad \text{for almost all } x \in]0,1[, \tag{3.1c}$$

for $(H1)$ hypothesis

$$\begin{aligned} \sup_{u \in K_1} |f(u,c)| &= \sup_{u \in K_1} |0.012(1-u)u - cu| \\ &\leq 1 + \|c\| \max_{x \in]0,1[} u(x,0) \\ &\leq \|c\| + 1, \end{aligned}$$

as for (2.10a)

$$\nabla \cdot (0.65\nabla u(x,t)) + 0.012(1-u(x,t))u(x,t) - c(x,t)u(x,t) = 0 \text{ if } u(x,t) = 0,$$

only (2.10b) is used to simulate chemotherapy control $c(x,t)$ in Figure 3.3.

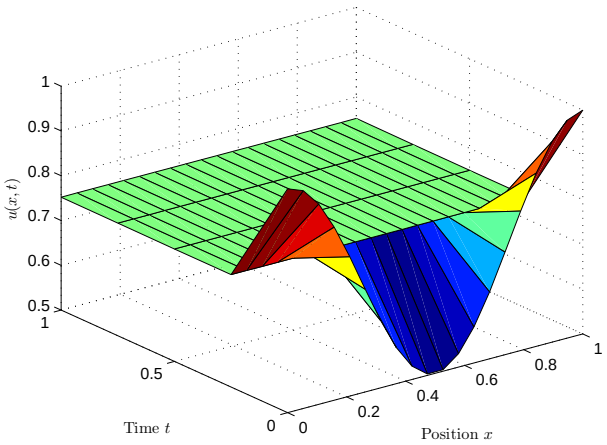

Figure 3.1: Spatio-temporal tumor evolution $u(x,t)$ subject to (3.1).

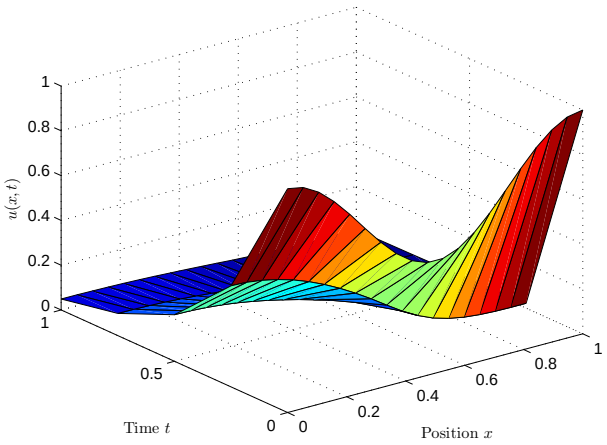

Figure 3.2: Spatio-temporal tumor response $u(x,t)$ subject to (3.1) by spatio-temporal chemotherapy control $c(x,t)$ in Figure 3.3.

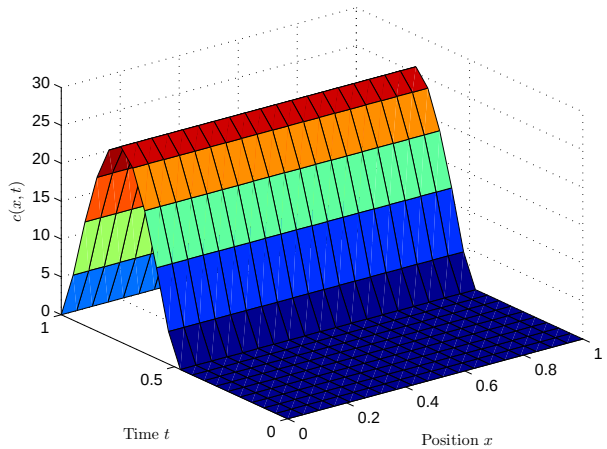

Figure 3.3: Spatio-temporal chemotherapy control $c(x,t)$ given by (2.10b).

3.2. Radiotherapy

Let consider the numerical model [25]

$$\begin{aligned} u_t &= \nabla\cdot(1.43\nabla u)+16.25u-c(x,t)u, \quad (x,t)\in]0,1[\times[0,T], && \text{(3.2a)}\\ n\cdot\nabla u &= 0, \quad (x,t)\in\{0,1\}\times[0,T], && \text{(3.2b)}\\ u(x,0) &= 20^3\exp(-100x^2), \quad \text{for almost all } x\in]0,1[, && \text{(3.2c)} \end{aligned}$$

as for $(H1)$ hypothesis

$$\begin{aligned} \sup_{u\in K_1}|f(u,c)| &= \sup_{u\in K_1}|16.25u-cu|\\ &\leq 16.25\max_{x\in]0,1[}u(x,0)+\|c\|\max_{x\in]0,1[}u(x,0)\\ &\leq 16.25\times 20^3(\|c\|+1), \end{aligned}$$

as for (2.10a)

$$\nabla\cdot(1.43\nabla u(x,t))+16.25u(x,t)-c(x,t)u(x,t)=0 \text{ if } u(x,t)=0,$$

only (2.10b) is used to simulate radiotherapy control $c(x,t)$ in Figure 3.6.

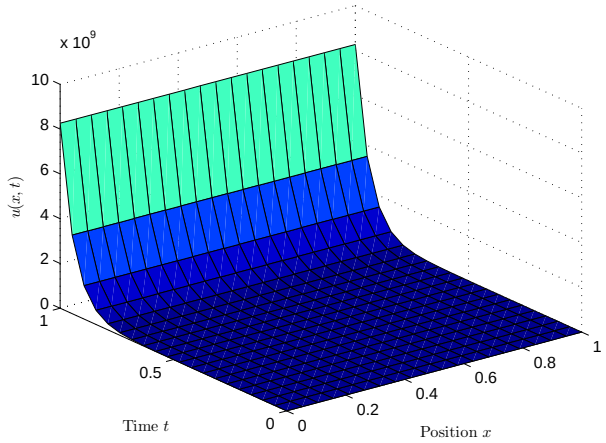

Figure 3.4: Spatio-temporal tumor evolution $u(x,t)$ subject to (3.2).

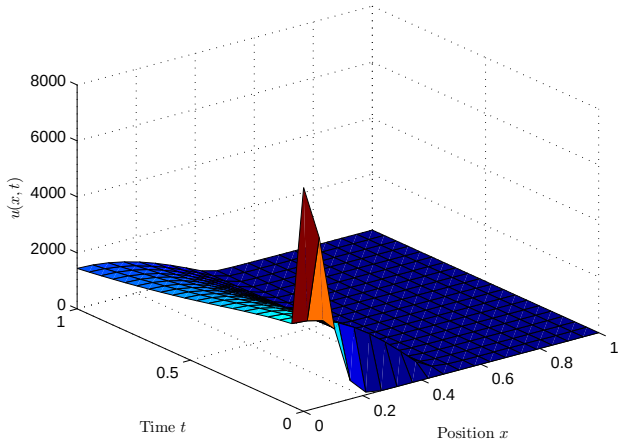

Figure 3.5: Spatio-temporal tumor response $u(x,t)$ subject to (3.2) by spatio-temporal radiotherapy control $c(x,t)$ in Figure 3.6.

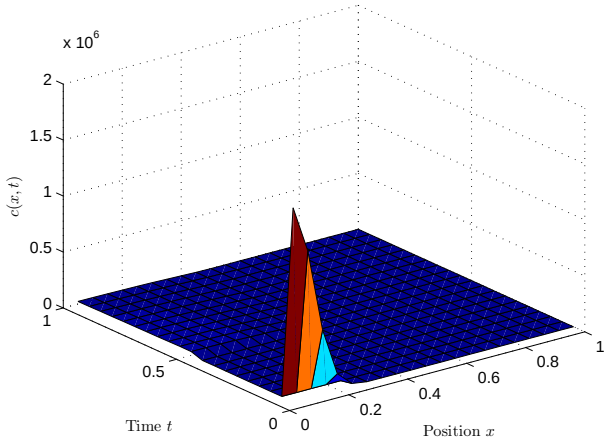

Figure 3.6: Spatio-temporal radiotherapy control $c(x,t)$ given by (2.10b).

3.3. Combination therapy

Let consider the numerical model [26]

$$\begin{aligned} u_t &= \nabla\cdot(\nabla u) - 0.012u\ln(u) - 0.0552c_1(x,t)u - c_2(x,t)u, \quad (x,t)\in]0,1[\times[0,T], && \text{(3.3a)}\\ n\cdot\nabla u &= 0, \quad (x,t)\in\{0,1\}\times[0,T], && \text{(3.3b)}\\ u(x,0) &= 1.25\exp\left(\frac{-x^2}{0.65}\right), \quad \text{for almost all } x\in]0,1[, && \text{(3.3c)} \end{aligned}$$

as for $(H1)$ hypothesis

$$\begin{aligned} \sup_{u\in K_1}|f(u,c)| &= \sup_{u\in K_1}|-0.012u\ln(u) - 0.0552c_1u - c_2u|\\ &\leq 1 + \|c\|\max_{x\in]0,1[}u(x,0)\\ &\leq 1.25(\|c\|+1), \end{aligned}$$

as for (2.10a)

$$\nabla\cdot(\nabla u(x,t)) - 0.012u(x,t)\ln(u(x,t)) - 0.0552c_1(x,t)u(x,t) - c_2(x,t)u(x,t) = 0 \text{ if } u(x,t) = 0, (\lim_{u\to 0^+} u\ln u = 0)$$

only (2.10b) is used to simulate chemotherapy control $0.0552c_1(x,t)$ in Figure 3.9 and radiotherapy control $c_2(x,t)$ in Figure 3.10.

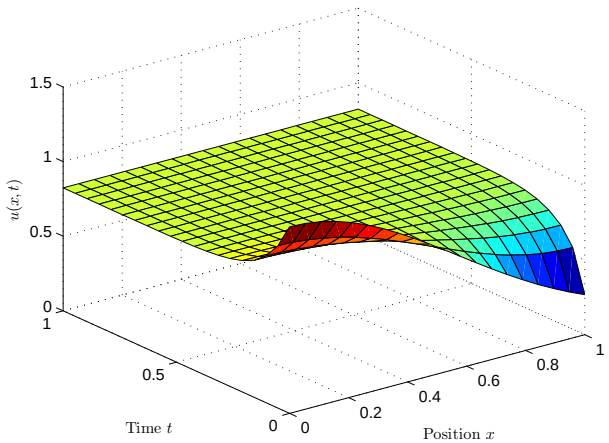

Figure 3.7: Spatio-temporal tumor evolution $u(x,t)$ subject to (3.3).

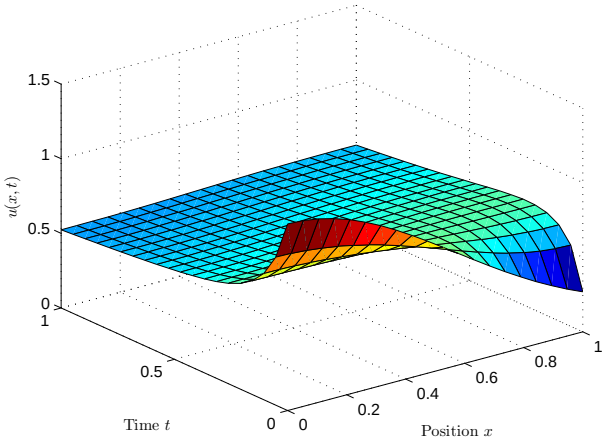

Figure 3.8: Spatio-temporal tumor response $u(x,t)$ subject to (3.3) by spatio-temporal chemotherapy control $0.0552c_1(x,t)$ in Figure 3.9 combined with radiotherapy control $c_2(x,t)$ in Figure 3.10.

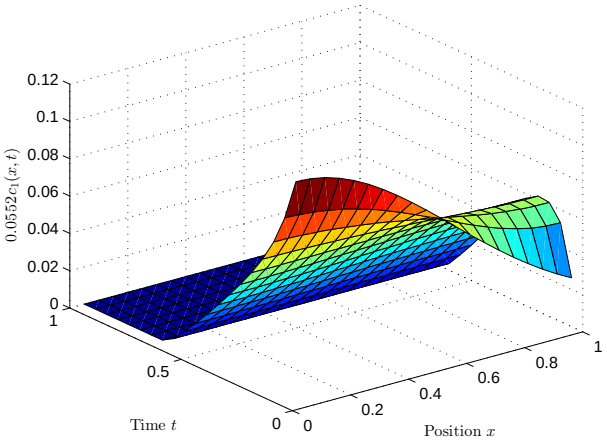

Figure 3.9: Spatio-temporal chemotherapy control $0.0552c_1(x,t)$, where c_1 is given by (2.10b).

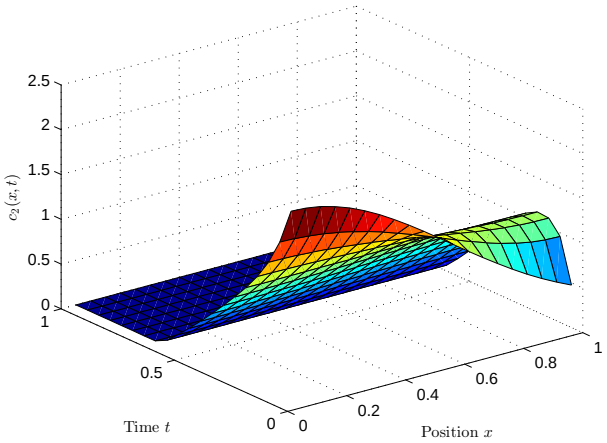

Figure 3.10: Spatio-temporal radiotherapy control $c_2(x,t)$ given by (2.10b).

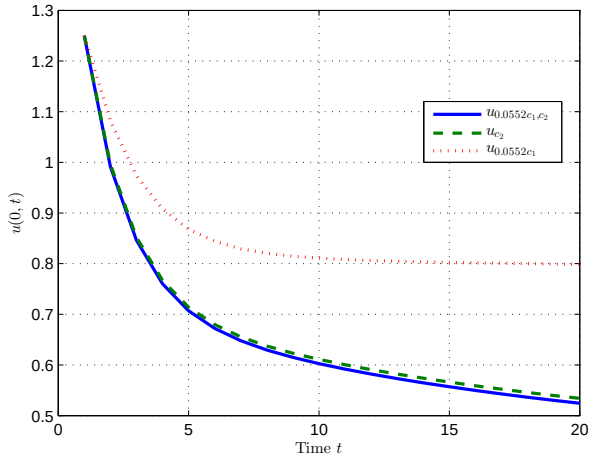

Figure 3.11: Temporal tumor response $u(0,t)$ subject to (3.3) by temporal chemotherapy control $0.0552c_1(0,t)$ in Figure 3.9 and or radiotherapy control $c_2(0,t)$ in Figure 3.10.

4. Conclusion

The control problem 1 is associated to the general system (1.1) in order to stabilize tumor density (2.2). Proposition 2.2 proves that any control rending the system (2.1) viable in a subset of the type (2.4) is a solution to the problem 1. Such control is obtained as the regulation law (2.10) of the regulation map (2.6). Simulation results in Figures 3.2, 3.5 and 3.8 show the effectiveness to stabilize the tumor densities, by the regulation laws in Figures 3.3, 3.6 and 3.9-3.10, on the models (3.1), (3.2) and (3.3) in Figures 3.1, 3.4 and 3.7 respectively. Furthermore, Figure 3.11 shows that chemotherapy and radiotherapy combination $0.0552c_1(x,t)+c_2(x,t)$, is more effective to reduce tumor density than using either treatment alone $0.0552c_1(x,t)$ or $c_2(x,t)$. Overall, this paper is a contribution to the field of cancer treatment, and proposes an effective control to stabilize the class of cancer models (2.1).

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