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EXISTENCE AND OPTIMAL CONTROL ANALYSIS OF ACID-MEDIATED TUMOR INVASION MODEL

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Abstract

The distributed optimal control problem of a highly nonlinear coupled system of reaction-diffusion equations is investigated in the study. Normal cell density, tumor cell density, excess H^+ ion concentration, and chemotherapy drug concentration are all represented by partial differential equations (PDEs) in the coupled system of acid-mediated tumor invasion model. It is a usual factor to formulate an optimal control problem by introducing control interventions while considering the tumor invasion model with drug chemotherapy. However, in our model, we consider a constant drug injection rate as a control variable based on biological motivation. The major goal of our optimal control problem is to reduce the overall amount of medicine

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supplied while minimizing cancer cell proliferation. First, we prove the existence of solutions to the direct problem using the Faedo-Galerkin approximation method, deriving a priori estimates, and then passing to the limit in the approximate solutions using monotonicity and compactness arguments. We introduce a functional to minimize and to establish the existence of optimal control for the proposed optimal control problem. Using the Lagrangian framework, we derive the adjoint problem and necessary optimality condition associated with our problem. Finally, we prove the existence of weak solutions to the adjoint system.

1. Introduction

Cancer is a complex disease that develops into one of the causes of death in humans as of uncontrolled cell development. It can also spread to other organ parts. By creating lumps or masses of aberrant cells, cancer cells engage in continual cell division and disrupt organ processes. Chemotherapy, sometimes known as *chemo*, is a type of cancer treatment used to kill or limit the growth of cancer cells. During treatment, it has harmful side effects and also affects normal and healthy cells. Chemotherapy can stop cancer cells from multiplying and invading. Cells that are normal or non-cancerous do not spread throughout the body, but cancer cells are diffusion. As a result, to make a diagnosis and treat cancer, it is vital to understand how it progresses. Many researchers have constructed mathematical models to understand and determine how cancer cells evolve and respond to therapy in the literature; for example, see [2, 3, 8, 14, 15] and its references.

The acid-mediation hypothesis, in which tumor cell invasion is enhanced by acidification of the region around the tumor-host interface induced by aerobic glycolysis, is discussed in [23]. This acid kills normal cells and spreads the tumor cells to other parts of the body. With a series of reaction-diffusion equations concerns the interaction between the tumor, host, and acid, this model was first investigated theoretically by [8]. Holder and Rodrigo investigated the mathematical model for acid-mediated tumor invasion with chemotherapeutic intervention in [22] with a homogeneous population and with a spatially heterogeneous population in [21].

In this paper, we investigate a highly nonlinear coupled cancer invasion model. According to [21], the coupled system of equations defining the interactions of normal cells, malignant cells, excess H^+ ions, and medication concentration is modelled. The following is a nonlinear reaction-diffusion model that arises in acid-mediated tumor invasion with nonlinear diffusion:

$$\left.\begin{aligned} \partial_t u_1 &= \nabla \cdot (D_1(u_1)\nabla u_1) + r_1 u_1(1 - u_1 - \alpha_1 u_2) - \gamma_1 u_1 u_3 && \text{in } Q_T \\ \partial_t u_2 &= \nabla \cdot (D_2(u_2)\nabla u_2) + r_2 u_2(1 - u_2 - \alpha_2 u_1) - \gamma_2 u_2 u_4 && \text{in } Q_T \\ \partial_t u_3 &= D_3 \Delta u_3 + r_3 u_2 - m_3 u_3 && \text{in } Q_T \\ \partial_t u_4 &= D_4 \Delta u_4 + r_I - m_4 u_4 - \gamma_4 u_2 u_4 && \text{in } Q_T \end{aligned}\right\} \tag{1}$$

with initial and boundary conditions

$$u_i(x, 0) = u_{i,0}(x) \text{ in } \Omega,$$

$$\frac{\partial u_i}{\partial \eta} = 0, \; i = 1, \ldots, 4 \text{ in } \Sigma_T,$$

where $Q_T = \Omega \times (0, T)$, $\Sigma_T = \partial\Omega \times (0, T)$, Ω is an open bounded domain in $\mathbb{R}^N$ with boundary $\partial\Omega$ and η is the unit normal vector on $\partial\Omega$. Normal cell density $u_1(x, t)$, tumor cell density $u_2(x, t)$, excess H^+ ion concentration $u_3(x, t)$, and chemotherapeutic drug concentration $u_4(x, t)$ are the four physical variables involved in acid-mediated tumor cell invasion model with spatial and time evolution. The positive constants r_1, r_2, r_3, α_1, α_2, γ_1, γ_2, γ_4, m_3 and m_4 are shown in Table 1. When considering mathematical modelling of cancer growth with medication chemotherapy, it is common to frame an optimal control problem with the objective of minimizing the total amount of drug administered. We use the control as r_I to reduce tumor burden while decreasing total drug administered, based on biological motives and research such as [3] and [19], and by keeping the biomedical goal in mind.

Table 1. Symbols and description of parameters

Symbol	Description
u_1	Density of normal cell
u_2	Density of tumor cell
u_3	Excess H^+ ion concentration
u_4	Chemotherapy drug concentration
$D_1(u_1),\ D_2(u_2)$	Density-dependent diffusion coefficients
$D_3,\ D_4$	Constant diffusion coefficients
T	Time
$u_{1,0}$	Initial normal cell
$u_{2,0}$	Initial tumor density
$u_{3,0}$	Initial H^+ ion concentration
$u_{4,0}$	Initial drug concentration
r_1	Normal cell growth rate
r_2	Tumor cell growth rate
α_1	Normal cell death due to tumor cell
α_2	Tumor cell death due to normal cell
γ_1	Normal cell killed by H^+ ions
γ_2	Tumor cell killed by drug
r_3	H^+ ion production rate
m_3	H^+ ion removal rate
m_4	Chemotherapy removal rate
γ_4	Chemotherapy removal by tumor interaction
r_I	Chemotherapy drug infusion

In this model, $r_I = c = c(x, t)$ is the control variable when dealing with the optimal control system and $u_{i,0}(x),\ \ i = 1, ..., 4$ represents the initial conditions of unknown variables $u_i,\ i = 1, ..., 4,$ respectively. We have also assumed Neumann boundary conditions on the Σ_T boundary. The mathematical analysis of an optimal control problem constrained by the system of PDEs (1) is discussed in this work. The study of mathematical analysis of optimal control problems constrained by reaction-diffusion equations has attracted attention in recent years [9, 11, 16-19] and its references. In electro cardiology, Ainseba et al. investigated an optimal control problem constrained by PDEs [1]. The optimal control problem for the Keller-Segel equations to control the aggregate of cells by chemical concentration was investigated. In addition, the existence and uniqueness of the weak solutions have been established in [12, 13], and the references therein.

The existence of solutions and the optimal control problem for the cancer invasion models have been studied in [4, 19, 20], and a large number of references therein. Apart from the theoretical contributions mentioned above, the literature also encompasses some numerical investigations on optimal control problems for the cancer invasion system, for example, see [5, 6, 9-11, 17] and its references. Aside from the existing literature above, it should be highlighted that, to the best of the author's knowledge, there is no work available in the literature for optimal control problems constrained by a system of PDEs (1) with nonlinear diffusion operators. As a result, we attempted to investigate the optimal control problem considering PDEs of the form (1) in this paper.

The paper is structured as follows: We state the basic theorem and introduce the approximation problem for the original system (1) in Section 2. The Faedo-Galerkin method is then used to determine the existence of weak approximation system solutions [7]. We investigate the existence of optimal control in Section 3 and derive the adjoint problem and first-order optimality conditions. Finally, we obtain the existence of a weak solution of the adjoint problem. Conclusion is provided in Section 4.

2. Existence of Solutions for Direct Problem

In this section, we prove the existence of solutions to the direct problem. To do this, we establish an approximation problem for (1) to verify the existence of weak solutions for (1).

Furthermore, throughout the work, we refer to C as the generic constant.

For simplicity, we are considering following equivalent form of the system (1):

$$\left.\begin{aligned} &\partial_t u_1 - \nabla \cdot (D_1(u_1)\nabla u_1) + F_1(u_1, u_2, u_3) = r_1 u_1 && \text{in } Q_T \\ &\partial_t u_2 - \nabla \cdot (D_2(u_2)\nabla u_2) + F_2(u_1, u_2, u_4) = r_2 u_2 && \text{in } Q_T \\ &\partial_t u_3 - D_3 \Delta u_3 = r_3 u_2 - m_3 u_3 && \text{in } Q_T \\ &\partial_t u_4 - D_4 \Delta u_4 + F_4(u_2, u_4) = c - m_4 u_4 && \text{in } Q_T \end{aligned}\right\}, \tag{2}$$

where

$$F_1(u_1, u_2, u_3) = r_1 u_1^2 + r_1 \alpha_1 u_1 u_2 + \gamma_1 u_1 u_3,$$

$$F_2(u_1, u_2, u_3) = r_2 u_2^2 + r_2 \alpha_2 u_1 u_2 + \gamma_2 u_2 u_4,$$

$$F_4(u_2, u_4) = \gamma_4 u_2 u_4.$$

Remark 1. To establish the weak solutions of the given degenerate reaction-diffusion system (1), we assume that the following hypotheses hold true. The Carathéodory functions $D_i(s)\zeta : \mathbb{R} \times \mathbb{R}^N \to \mathbb{R}^N$ are continuous with respect to s and ζ such that

(H_1) $D_i(s)\zeta\zeta \geq \delta_i |\zeta|^2$ for every $\zeta \in \mathbb{R}^N$, where $\delta_i > 0$ and $i = 1, 2$.

(H_2) For any $k > 0$, there exists $\Lambda_k > 0$ and a function $C_k(x, t) \in L^2(Q_T)$ such that $|D_i(s)\zeta| \leq C_k(x, t) + \Lambda_k |\zeta|$, $i = 1, 2$.

Definition 1. A *weak solution* of the system (2) is a 4-tuple (u_1, u_2, u_3, u_4) such that $u_i \in L^2(0, T; H^1(\Omega)) \cap L^\infty(0, T; L^2(\Omega))$, $\partial_t u_i \in L^2(0, T; (H^1(\Omega))^*)$, $u_i(0) = u_{i,0}$, a.e. in Ω, for $i = 1, ..., 4$, and satisfying the following weak formulation:

$$\int_0^T \langle \partial_t u_1, \phi_1 \rangle dt + \int_{Q_T} D_1(u_1)\nabla u_1 \cdot \nabla \phi_1 dxdt + \int_{Q_T} F_1(u_1, u_2, u_3)\phi_1 dxdt$$

$$= r_1 \int_{Q_T} u_1 \phi_1 dxdt,$$

$$\int_0^T \langle \partial_t u_2, \phi_2 \rangle dt + \int_{Q_T} D_2(u_2)\nabla u_2 \cdot \nabla \phi_2 dxdt + \int_{Q_T} F_2(u_1, u_2, u_4)\phi_2 dxdt$$

$$= r_2 \int_{Q_T} u_2 \phi_2 dxdt,$$

$$\int_0^T \langle \partial_t u_3, \phi_3 \rangle dt + \int_{Q_T} D_3 \nabla u_3 \cdot \nabla \phi_3 dxdt = \int_{Q_T} (r_3 u_2 - m_3 u_3)\phi_3 dxdt,$$

$$\int_0^T \langle \partial_t u_4, \phi_4 \rangle dt + \int_{Q_T} D_4 \nabla u_4 \cdot \nabla \phi_4 dxdt + \int_{Q_T} F_4(u_2, u_4)\phi_4 dxdt$$

$$= \int_{Q_T} (c - m_4 u_4)\phi_4 dxdt,$$

for all $\phi_i \in L^2(0, T; H^1(\Omega))$, $i = 1, ..., 4$. Here, $\langle \cdot, \cdot \rangle$ denotes the duality pairing between $H^1(\Omega)$ and $(H^1(\Omega))^*$.

Remark 2. To find a weak solution of (1), we use the following regularized system. For $\varepsilon > 0$,

$$\left.\begin{array}{ll}
\partial_t u_1^\varepsilon - \nabla \cdot (D_1(u_1^\varepsilon)\nabla u_1^\varepsilon) + F_{1,\varepsilon}(u_1^\varepsilon, u_2^\varepsilon, u_3^\varepsilon) = r_1 u_1^\varepsilon & \text{in } Q_T \\
\partial_t u_2^\varepsilon - \nabla \cdot (D_2(u_2^\varepsilon)\nabla u_2^\varepsilon) + F_{2,\varepsilon}(u_1^\varepsilon, u_2^\varepsilon, u_4^\varepsilon) = r_2 u_2^\varepsilon & \text{in } Q_T \\
\partial_t u_3^\varepsilon - D_3 \Delta u_3^\varepsilon = r_3 u_2^\varepsilon - m_3 u_3^\varepsilon & \text{in } Q_T \\
\partial_t u_4^\varepsilon - D_4 \Delta u_4^\varepsilon + F_{4,\varepsilon}(u_2^\varepsilon, u_4^\varepsilon) = c - m_4 u_4^\varepsilon & \text{in } Q_T \\
u_i^\varepsilon(x, 0) = u_{i,0}(x) & \text{in } \Omega \\
\dfrac{\partial u_1^\varepsilon}{\partial \eta} = 0, \quad i = 1, ..., 4 & \text{in } \Sigma_T
\end{array}\right\}, \tag{3}$$

where $F_{i,\varepsilon} = \frac{F_i}{1+\varepsilon|F_i|}$, $i = 1, 2, 4.$ Therefore, throughout the section, we relabel u_i^{ε} as u_i, $i = 1, 2, 3.$

Definition 2. That $u_{i,n}(x, t) = \sum_{m=1}^{n} c_{i,n,m}(t) e_m(x)$, $i = 1, \ldots, 4$ are called *approximate solutions* to (1) for $m = 1, 2, \ldots, n,$ if it satisfies

$$\left.\begin{array}{l}
\langle \partial_t u_{1,n}, e_m\rangle + \int_{\Omega} D_1(u_{1,n})\nabla u_{1,n}\cdot\nabla e_m dx + \int_{\Omega} F_{1,\varepsilon}(u_{1,n}, u_{2,n}, u_{3,n}) e_m dx \\
= r_1 \int_{\Omega} u_{1,n} e_m dx \\
\langle \partial_t u_{2,n}, e_m\rangle + \int_{\Omega} D_2(u_{2,n})\nabla u_{2,n}\cdot\nabla e_m dx + \int_{\Omega} F_{2,\varepsilon}(u_{1,n}, u_{2,n}, u_{4,n}) e_m dx \\
= r_2 \int_{\Omega} u_{2,n} e_m dx \\
\langle \partial_t u_{3,n}, e_m\rangle + \int_{\Omega} D_3 \nabla u_{3,n}\cdot\nabla e_m dx = \int_{\Omega} (r_3 u_{2,n} - m_3 u_{3,n}) e_m dx \\
\langle \partial_t u_{4,n}, e_m\rangle + \int_{\Omega} D_2 \nabla u_{4,n}\cdot\nabla e_m dx + \int_{\Omega} F_{4,\varepsilon}(u_{2,n}, u_{4,n}) e_m dx \\
= \int_{\Omega} (-m_4 u_{4,n} + c) e_m dx
\end{array}\right\}. \tag{4}$$

Further, $u_{i,n}(x, 0) = u_{i,0,n}(x) := \sum_{m=1}^{n} c_{i,n,m}(0) e_m(x).$ Here, $c_{i,n,m}(t) \in C^1([0, T]).$

Theorem 1. *Suppose that* $u_{i,0}, i = 1, \ldots, 4$ *are in* $L^{\infty}(\Omega)$ *and* c *in* $L^2(Q_T)$. *Then there exists a weak solution for* (1) *in the sense of Definition* 1.

Proof. Rewriting (4) as a system of ordinary differential equations (ODEs) with unknowns $c_{i,n,m}$, $i = 1, \ldots, 4$ and using the standard existence theorem, we show that there exist absolutely continuous functions

$\{c_{1,n,m}\}_{m=1}^{n}$, $\{c_{2,n,m}\}_{m=1}^{n}$, $\{c_{3,n,m}\}_{m=1}^{n}$, $\{c_{4,n,m}\}_{m=1}^{n}$ which satisfy (4) for a.e. $t \in [0, T]$.

Now, we derive the following priori estimates to the approximate solutions. Set $\phi_{i,n}(x, t) = \sum_{m=1}^{n} b_{i,n,m}(t)e_m(x)$, where $\{b_{i,n,m}\}$, $i = 1, ..., 4$ are given absolutely continuous coefficients. Then, from (4), we have

$$\left.\begin{aligned}
\int_\Omega \partial_t u_{1,n}\phi_{1,n}dx &= -\int_\Omega D_1(u_{1,n})\nabla u_{1,n}\cdot\nabla\phi_{1,n}dx \\
&\quad -\int_\Omega F_{1,\varepsilon}(u_{1,n}, u_{2,n}, u_{3,n})\phi_{1,n}dx + r_1\int_\Omega u_{1,n}\phi_{1,n}dx \\
\int_\Omega \partial_t u_{2,n}\phi_{2,n}dx &= -\int_\Omega D_2(u_{2,n})\nabla u_{2,n}\cdot\nabla\phi_{2,n}dx \\
&\quad -\int_\Omega F_{2,\varepsilon}(u_{1,n}, u_{2,n}, u_{4,n})\phi_{2,n}dx + r_2\int_\Omega u_{2,n}\phi_{2,n}dx \\
\int_\Omega \partial_t u_{3,n}\phi_{3,n}dx &= -\int_\Omega D_3\nabla u_{3,n}\cdot\nabla\phi_{3,n}dx + \int_\Omega (r_3u_{2,n} - m_3u_{3,n})\phi_{3,n}dx \\
\int_\Omega \partial_t u_{4,n}\phi_{4,n}dx &= -\int_\Omega D_4\nabla u_{4,n}\cdot\nabla\phi_{4,n}dx - \int_\Omega F_{4,\varepsilon}(u_{2,n}, u_{4,n})\phi_{4,n}dx \\
&\quad + \int_\Omega (-m_4u_{4,n} + c)\phi_{4,n}dx
\end{aligned}\right\}. \tag{5}$$

Setting $\phi_{i,n} = u_{i,n}^{\varepsilon}$, $i = 1, ..., 4$, respectively, in the above equations (5), using Young's inequality and then adding the resulting equations, we get

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\int_\Omega\left(\sum_{i=1}^{4}|u_{i,n}|^2\right)dx + \int_\Omega\left(\sum_{i=1}^{2}\delta_i|\nabla u_{i,n}|^2 + \sum_{i=3}^{4}D_i|\nabla u_{i,n}|^2\right)dx \\
&+ \int_\Omega (F_{1,\varepsilon}(u_{1,n}, u_{2,n}, u_{3,n})u_{1,n} + F_{2,\varepsilon}(u_{1,n}, u_{2,n}, u_{4,n})u_{2,n})dx \\
&+ \int_\Omega (F_{4,\varepsilon}(u_{2,n}, u_{4,n})u_{4,n})dx \le C\int_\Omega\left(\sum_{i=1}^{4}|u_{i,n}|^2\right)dx,
\end{aligned} \tag{6}$$

for some constant $C > 0$ independent of n. Then, application of Gronwall's inequality proves that

$$\| (u_{1,n}, u_{2,n}, u_{3,n}, u_{4,n}) \|_{L^\infty(0,T;L^2(\Omega))} + \| (u_{1,n}, u_{2,n}, u_{3,n}, u_{4,n}) \|_{L^2(0,T;H^1(\Omega))} \leq C, \tag{7}$$

and

$$\left.\begin{aligned} \| F_{1,\varepsilon}(u_{1,n}, u_{2,n}, u_{3,n}) u_{1,n} \|_{L^1(Q_T)} \leq C \\ \| F_{2,\varepsilon}(u_{1,n}, u_{2,n}, u_{4,n}) u_{2,n} \|_{L^1(Q_T)} \leq C \\ \| F_{4,\varepsilon}(u_{2,n}, u_{4,n}) u_{4,n} \|_{L^1(Q_T)} \leq C \end{aligned}\right\}, \tag{8}$$

where $C > 0$ is a constant depending only on the given data and is independent of n. Moreover, we can show that

$$\| (\partial_t u_{1,n}, \partial_t u_{2,n}, \partial_t u_{3,n}, \partial_t u_{4,n}) \|_{L^2(0,T;(H^1(\Omega))^*)} \leq C, \tag{9}$$

where the constant C is independent of n. Further, using the standard compactness arguments, the sequences have convergent subsequences. Then, there exist limit functions $u_{i,n}$, $i = 1, ..., 4.$ Therefore, as $n \to \infty$, we get

$(u_{1,n}, u_{2,n}, u_{3,n}, u_{4,n}) \rightharpoonup (u_1, u_2, u_3, u_4)$ weakly-* in $L^\infty(0, T; L^2(\Omega))$,

$(u_{1,n}, u_{2,n}, u_{3,n}, u_{4,n}) \rightharpoonup (u_1, u_2, u_3, u_4)$ weakly in $L^2(0, T; H^1(\Omega))$,

$F_{1,\varepsilon}(u_{1,n}, u_{2,n}, u_{3,n}) \rightharpoonup F_{1,\varepsilon}(u_1, u_2, u_3)$ weakly in $L^2(Q_T)$,

$F_{2,\varepsilon}(u_{1,n}, u_{2,n}, u_{4,n}) \rightharpoonup F_{2,\varepsilon}(u_1, u_2, u_4)$ weakly in $L^2(Q_T)$,

$F_{4,\varepsilon}(u_{2,n}, u_{4,n}) \rightharpoonup F_{4,\varepsilon}(u_2, u_4)$ weakly in $L^2(Q_T)$,

$D_i(u_{i,n})\nabla u_{i,n} \rightharpoonup \xi_i$ weakly in $L^2(Q_T)$, $i = 1, 2$,

$\partial_t u_{i,n} \rightharpoonup \partial_t u_i$ weakly in $L^2(0, T; (H^1(\Omega))^*)$, $i = 1, ..., 4$.

The results (7)-(9) are also true for approximation solutions u_i^ε, $i = 1, ..., 4.$ Therefore, we can prove the convergence results replacing $u_{i,n}$ by u_i^ε when $\varepsilon \to 0$ instead of $n \to \infty$, and obtain

$$(u_1^\varepsilon, u_2^\varepsilon, u_3^\varepsilon, u_4^\varepsilon) \rightharpoonup (u_1, u_2, u_3, u_4) \text{ weakly-* in } L^\infty(0, T; L^2(\Omega)),$$

$$(u_1^\varepsilon, u_2^\varepsilon, u_3^\varepsilon, u_4^\varepsilon) \rightharpoonup (u_1, u_2, u_3, u_4) \text{ weakly in } L^2(0, T; H^1(\Omega)),$$

$$F_{1,\varepsilon}(u_1^\varepsilon, u_2^\varepsilon, u_3^\varepsilon) \rightharpoonup F_1(u_1, u_2, u_3) \text{ weakly in } L^2(Q_T),$$

$$F_{2,\varepsilon}(u_1^\varepsilon, u_2^\varepsilon, u_4^\varepsilon) \rightharpoonup F_2(u_1, u_2, u_4) \text{ weakly in } L^2(Q_T),$$

$$F_{4,\varepsilon}(u_2^\varepsilon, u_4^\varepsilon) \rightharpoonup F_4(u_2, u_4) \text{ weakly in } L^2(Q_T),$$

$$D_i(u_i^\varepsilon)\nabla u_i^\varepsilon \rightharpoonup \xi_i \text{ weakly in } L^2(Q_T),\ i = 1, 2,$$

$$(\partial_t u_1^\varepsilon, \partial_t u_2^\varepsilon, \partial_t u_3^\varepsilon, \partial_t u_4^\varepsilon) \rightharpoonup (\partial_t u_1, \partial_t u_2, \partial_t u_3, \partial_t u_4)$$

$$\text{weakly in } L^2(0, T; (H^1(\Omega))^*). \qquad \square$$

3. Optimal Control Problem

The existence of optimal control, the derivation of the adjoint equation, and the optimality conditions are all examined in this section. Further, the existence of weak solution for the adjoint problem is also demonstrated. To begin, we show that there is a solution to the following optimal control problem:

$$\hat{J}(u_2, c) = \frac{\alpha}{2}\int_{Q_T} | u_2 - u_{2d} |^2 dxdt + \frac{\beta}{2}\int_{Q_T} | c |^2 dxdt \tag{10}$$

subject to the control constraints

$$c \in C_{ad} = \{c \in L^2(Q_T) : c_a \le c \le c_b \text{ a.e. in } Q_T\}, \tag{11}$$

where J is the cost functional, u_2 is the state variable, u_{2d} is the desired state and $c \in C_{ad}$ is the control variable. Here, c_a and c_b are given functions satisfying $c_a \leq c_b$ in Q_T. Moreover, α and β are the positive parameters used to change the relative importance of the terms that appear in the definition of the functional. The goal is to minimize the functional (10) subject to state equations with respect to input rate.

Introduce the reduced cost functional as follows:

$$J(c) := \hat{J}(u_2, c). \tag{12}$$

3.1. Existence of optimal control

In this subsection, we prove the existence of an optimal solution for the problem (10) subject to (1).

Theorem 2. *Suppose* (u_1, u_2, u_3, u_4) *is a weak solution of* (1), $u_{2d} \in L^2(Q_T)$, $c \in C_{ad}$. *Then there exists an optimal solution* c^* *such that* $J(c^*) = \inf_{c \in C_{ad}} J(c)$ *of the optimal control problem* (12).

Proof. From the definition, the functional is nonnegative and therefore, it has the greatest lower bound. Let (c_n) be the minimizing sequence. Since (u_{2n}) is bounded in $L^2(Q_T)$ (from Theorem 1), the functional (12) is bounded. Since J is bounded, there exists an infimum m such that $\inf_{c \in C_{ad}} J(c) = m.$ Thus there exists a bounded sequence $(c_n)_n$ such that $J(c_n) \to m$ as m is a nonnegative integer and also

$$m \leq J(c_n) \leq m + \frac{1}{n}.$$

Moreover, since the sequence (c_n) is bounded in $L^2(Q_T)$, there exists a function c^* and extracting a subsequence $(c_n)_n$, again denoted by c_n

such that c_n is weakly convergent to c^* in $L^2(Q_T)$. Furthermore, replacing (u_1, u_2, u_3, u_4, c) in (1) by $(u_{1,n}, u_{2,n}, u_{3,n}, u_{4,n}, c_n)$ and passing the limits, we have that $(\tilde{u}_1, \tilde{u}_2, \tilde{u}_3, \tilde{u}_4, \tilde{c})$ satisfies (1). Further, using the strong convergence, we get

$$J(c^*) \leq \lim_{n\to\infty} \inf J(c_n) = \min_{c\in C_{ad}} J(c),$$

since the functional J is weakly lower-semicontinuity on L^2-norm. Therefore, $c^* := c$ is the optimal solution of (12). □

3.2. First-order optimality condition and dual problem

Define the Lagrangian function as follows:

$$\begin{aligned}
&L(u_1, u_2, u_3, u_4, p_1, p_2, p_3, p_4, c) \\
&= \frac{\alpha}{2}\int_{Q_T} | u_2 - u_{2d} |^2 dxdt + \frac{\beta}{2}\int_{Q_T} | c |^2 dxdt \\
&- \int_{Q_T} p_1[\partial_t u_1 - \nabla \cdot (D_1(u_1)\nabla u_1) - r_1 u_1(1 - u_1 - \alpha_1 u_2) + \gamma_1 u_1 u_3] \\
&- \int_{Q_T} p_2[\partial_t u_2 - \nabla \cdot (D_2(u_2)\nabla u_2) - r_2 u_2(1 - u_2 - \alpha_2 u_1) + \gamma_2 u_2 u_4] \\
&- \int_{Q_T} p_3[\partial_t u_3 - D_3\Delta u_3 - r_3 u_2 + m_3 u_3] \\
&- \int_{Q_T} p_4[\partial_t u_4 - D_3\Delta u_4 + m_4 u_4 + \gamma_4 u_2 u_4 - c].
\end{aligned}$$

Theorem 3. *If* $u^* = (u_1^*, u_2^*, u_3^*, u_4^*)$ *is an optimal state solution and* c^* *is an optimal control variable for the optimal control problem* (10)-(11), *then there exists an adjoint* (*or*) *dual variable* $p = (p_1, p_2, p_3, p_4)$ *satisfying*

$$\left.\begin{aligned}
&-\partial_t p_1 - \nabla\cdot(D_1(u_1)\nabla p_1) + D_1'(u_1)\nabla u_1 \nabla p_1 - r_1(1-2u_1-\alpha_1 u_2)\,p_1 \\
&\qquad\qquad + \gamma_1 u_3 p_1 + r_2\alpha_2 u_2 p_2 = 0 \quad in\ Q_T \\
&-\partial_t p_2 - \nabla\cdot(D_2(u_2)\nabla p_2) + D_2'(u_2)\nabla u_2 \nabla p_2 - r_2(1-2u_2-\alpha_2 u_1)\,p_2 \\
&\qquad\qquad + \gamma_2 u_4 p_2 + r_1\alpha_1 u_1 p_1 - r_3 p_3 + \gamma_4 u_4 p_4 - \alpha(u_2 - u_{2d}) = 0 \quad in\ Q_T \\
&-\partial_t p_3 - D_3\Delta p_3 + m_3 p_3 + \gamma_1 u_1 p_1 = 0 \quad in\ Q_T \\
&-\partial_t p_4 - D_4\Delta p_4 + m_4 p_4 + \gamma_4 u_2 p_4 + \gamma_2 u_2 p_2 = 0 \quad in\ Q_T
\end{aligned}\right\} \tag{13}$$

with following boundary conditions

$$\frac{\partial p_i}{\partial \eta} = 0, \quad i = 1, \ldots, 4 \ on\ \Sigma_T, \tag{14}$$

and final conditions

$$p_i(T) = 0, \quad i = 1, \ldots, 4 \ on\ \Omega. \tag{15}$$

Further, the optimal control c^* *is given as*

$$c^* = \min\left(c_b, \max\left(c_a, \frac{-p_4}{\beta}\right)\right). \tag{16}$$

Proof. The first-order optimality system is given by the Karush-Kuhn-Tucker (KKT) conditions which results from equating the partial derivatives of the Lagrangian $L(u_1, u_2, u_3, u_4, p_1, p_2, p_3, p_4, c)$ with respect to u_1, u_2, u_3 and u_4 equal to zero. Now,

$$\left.\begin{aligned}
\left(\frac{\partial L}{\partial u_1}, \delta u_1\right) &= \int_{Q_T} \{-\partial_t p_1 - \nabla \cdot (D_1(u_1)\nabla p_1) + D_1'(u_1)\nabla u_1 \nabla p_1 \\
&\quad - r_1(1 - 2u_1 - \alpha_1 u_2) p_1 + \gamma_1 u_3 p_1 + r_2 \alpha_2 u_2 p_2\} \delta u_1 dxdt \\
\left(\frac{\partial L}{\partial u_2}, \delta u_2\right) &= \int_{Q_T} \{-\partial_t p_2 - \nabla \cdot (D_2(u_2)\nabla p_2) + D_2'(u_2)\nabla u_2 \nabla p_2 \\
&\quad - r_2(1 - 2u_2 - \alpha_2 u_1) p_2 + \gamma_2 u_4 p_2 + r_1 \alpha_1 u_1 p_1 - r_3 p_3 \\
&\quad + \gamma_4 u_4 p_4 - \alpha(u_2 - u_{2d})\} \delta u_2 dxdt \\
\left(\frac{\partial L}{\partial u_3}, \delta u_3\right) &= \int_{Q_T} \{-\partial_t p_3 - D_3 \Delta p_3 + m_3 p_3 + \gamma_1 u_1 p_1\} \delta u_3 dxdt \\
\left(\frac{\partial L}{\partial u_4}, \delta u_4\right) &= \int_{Q_T} \{-\partial_t p_4 - D_4 \Delta p_4 + m_4 p_4 + \gamma_4 u_2 p_4 + \gamma_2 u_2 p_2\} \delta u_4 dxdt
\end{aligned}\right\} \tag{17}$$

with boundary and final conditions

$$\left.\begin{aligned}
&\frac{\partial p_i}{\partial \eta} = 0,\ i = 1, ..., 4 \text{ on } \Sigma_T \text{ and} \\
&p_i(T) = 0,\ i = 1, ..., 4 \text{ on } \Omega
\end{aligned}\right\}. \tag{18}$$

From (17) and (18), we get the required adjoint system (13)-(15) for the given optimal control problem (2). Further, to find the optimality conditions, we have

$$\frac{\partial L}{\partial c} = p_4 + \beta c^* = 0 \text{ at } c^* = c.$$

Therefore, using the properties of control space for c^*, we get

$$c^* = \begin{cases} \dfrac{-p_4}{\beta} & \text{if } c_a \le \dfrac{-p_4}{\beta} \le c_b, \\ c_a & \text{if } \dfrac{-p_4}{\beta} \le c_a, \\ c_b & \text{if } \dfrac{-p_4}{\beta} \ge c_b. \end{cases} \tag{19}$$

Finally, in the compact notation, the optimality condition is written as

$$c^* = \min\left(c_b, \max\left(c_a, \frac{-p_4}{\beta}\right)\right). \qquad \square$$

3.3. Existence of the solution of adjoint problem

In this subsection, we prove the existence of weak solution for the adjoint system. First, we give the definition of weak solutions of adjoint system (13)-(14).

Definition 3. A *weak solution* of (13) is a 4-tuple (p_1, p_2, p_3, p_4) such that $(p_1, p_2, p_3, p_4) \in L^2(0, T; H^1(\Omega)) \cap L^\infty(0, T; L^2(\Omega))$, $(\partial_t p_1, \partial_t p_2, \partial_t p_3, \partial_t p_4) \in L^2(0, T; (H^1(\Omega))^*)$,

$$-\int_0^T \langle \partial_t p_1, \phi_1 \rangle dt + \int_{Q_T} D_1(u_1) \nabla p_1 \cdot \nabla \phi_1 dxdt + \int_{Q_T} D_1'(u_1) \nabla u_1 \nabla p_1 \phi_1 dxdt$$

$$- r_1 \int_{Q_T} (1 - 2u_1 - \alpha_1 u_2) p_1 \phi_1 dxdt + \int_{Q_T} (\gamma_1 u_3 p_1 + r_2 \alpha_2 u_2 p_2) \phi_1 dxdt = 0,$$

$$-\int_0^T \langle \partial_t p_2, \phi_2 \rangle dt + \int_{Q_T} D_2(u_2) \nabla p_2 \cdot \nabla \phi_2 dxdt$$

$$+ \int_{Q_T} D_2'(u_2) \nabla u_2 \nabla p_2 \phi_2 dxdt - r_2 \int_{Q_T} (1 - 2u_2 - \alpha_2 u_1) p_2 \phi_2 dxdt$$

$$+ \int_{Q_T} (\gamma_2 u_4 p_2 + r_1 \alpha_1 u_1 p_1) \phi_2 dxdt$$

$$- \int_{Q_T} (r_3 p_3 + \gamma_4 u_4 p_4) \phi_2 dxdt - \alpha \int_{Q_T} (u_2 - u_{2d}) \phi_2 dxdt = 0,$$

$$-\int_0^T \langle \partial_t p_3, \phi_3 \rangle dt + \int_{Q_T} D_3 \nabla p_3 \cdot \nabla \phi_3 dxdt + m_3 \int_{Q_T} p_3 \phi_3 dxdt$$

$$+ \int_{Q_T} \gamma_1 u_1 p_1 \phi_3 dxdt = 0,$$

$$-\int_0^T \langle \partial_t p_4, \phi_4 \rangle dt + \int_{Q_T} D_4 \nabla p_4 \cdot \nabla \phi_4 dxdt + m_4 \int_{Q_T} p_4 \phi_4 dxdt$$

$$+ \int_{Q_T} \gamma_4 u_2 p_4 \phi_4 dxdt + \int_{Q_T} \gamma_2 u_2 p_2 \phi_4 dxdt = 0,$$

for all $\phi_i \in L^2(0, T; H^1(\Omega)), i = 1, ..., 4.$ Here, $\langle \cdot, \cdot \rangle$ denotes the duality pairing between $H^1(\Omega)$ and $(H^1(\Omega))^*.$

Theorem 4. *Assume that the hypotheses of Theorem* 1 *are true and a* 4-*tuple* (u_1, u_2, u_3, u_4) *is a weak solution of* (1). *Then*, *there exists a weak solution to the adjoint system* (13)-(14) *in the sense of Definition* 3.

The Faedo-Galerkin method is used to prove the aforementioned theorem. The approximation system is then used to prove the existence of a solution to the adjoint system (13) with (15). As a result, we prove the existence solution interval $(0, T]$ for the Faedo-Galerkin solution as well as the global existence of the Faedo-Galerkin weak solution, as in Theorem 1, so we excluded the proof details (see [16, 17] and the references therein).

4. Conclusion

In this paper, we investigated a model for acid-mediated tumor progression with chemotherapeutic intervention that was bounded by a distributed optimal control problem constrained by coupled PDEs. The primary goal of this study was to optimize drug concentration in a mathematical model of tumor invasion where the concentration is directly regulated by the control rate. Using the Faedo-Galerkin approximation method, we first showed the existence of the solution to the direct problem. We also addressed an optimal control problem and proved that an optimal control solution exists that minimizes the performance measure. Using the Lagrangian framework associated to the optimal control problem for the primal and dual variables, we next obtained the first-order optimality conditions satisfied by the optimal control. Finally, we proved the existence of a weak solution of the adjoint problem.

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