Eur. Phys. J. Plus (2019) **134**: 463
DOI 10.1140/epjp/i2019-12866-8

THE EUROPEAN
PHYSICAL JOURNAL PLUS

Regular Article

Distributed optimal control of a tumor growth treatment model with cross-diffusion effect*

P.T. Sowndarrajan[1,a], J. Manimaran[1,b], Amar Debbouche[2,c], and L. Shangerganesh[1,d]

[1] Department of Applied Sciences, National Institute of Technology, Goa, India
[2] Department of Mathematics, Guelma University, Guelma 24000, Algeria

Received: 19 April 2019 / Revised: 26 June 2019
Published online: 25 September 2019

Abstract. In this paper, we examine an optimal control problem of a coupled nonlinear parabolic system with cross-diffusion operators. The system describes the density of tumor cells, effector-immune cells, circulating lymphocyte population and chemotherapy drug concentration. The distributed control has been taken for drug concentration to control the amount of drug to be injected and to evade the side effects of the drug. We prove the existence of a weak solution of the direct problem. Then, the existence of control for the proposed control problem is proved. Further, we derive the optimality conditions and also the existence of a solution of the adjoint problem. The finite element numerical method is implemented for the proposed control problem. Then, theoretical results are illustrated with the help of numerical experiments. Finally, the importance of control function and the cross-diffusion effect are studied for the proposed control problem using numerical computations.

1 Introduction

Cancer is a disease caused by the growth of uncontrolled cells and their division. A cancer cell, or a malignant one, can penetrate the surrounding normal tissues and also reaches other portions of the body. It continuously involves cell separation and irregulates the function of organs. Non-cancerous or benign cells can grow but will not spread. Cancer has become one of the leading causes of death worldwide. The process of cancer cells spread and the extension of secondary tumors is called metastasis, which is the main reason for mortality in patients. For prevention, better diagnosis and suitable treatment, one must understand the mechanism of cancer cell progression. Therefore, mathematical models play a significant role in cancer studies for clinical and research communities via mathematical methods and theories. Many mathematical models have been presented in the literature to interpret and predict how cancer cells emerge and respond to therapy; for reference, see [1–9].

Treatment for cancer cells comes in various types, such as surgery, radiation therapy, chemotherapy and immunotherapy. Each treatment has its advantages and disadvantages. Surgical excision [10] is a treatment performed by removing the solid tumor in a fixed area which may bring high damage to other near organs, severe pain, and infection. Radiation therapy [11] is used to treat (or kill), with high-energy radiations, tumor cells however it also has side-effects and might injure normal healthy tissues. The immunotherapy [12] treatment helps to improve the patient's immune system to fight against tumor cells, also causes side-effects. Chemotherapy uses powerful drugs to kill tumor cells and to control their growth. Depending on the type of tumor and its severity, the patient may be prescribed with one drug or a combination of drugs. Further, treatment as single chemotherapy or with other treatments, such as radiation or surgery, is also possible. de Pillis *et al.* [13,14] developed and analyzed a mathematical model on tumor growth using immunotherapy and drug therapy. Sharma *et al.* [15] considered a tumor growth model with the effect

* Supplementary material in the form of 4 .m files available from the Journal web page at
`https://doi.org/10.1140/epjp/i2019-12866-8`

[a] e-mail: `sowndarrajan@nitgoa.ac.in`
[b] e-mail: `manimaranj@nitgoa.ac.in`
[c] e-mail: `amar_debbouche@yahoo.fr`
[d] e-mail: `shangerganesh@nitgoa.ac.in`

of tumor-immune interactions and analyzed its dynamics with chemotherapy and immunotherapy. Similarly, models describe the interactions between the immune system and a growing tumor also developed (see [16–20]). Cattani *et al.* [21] considered a family of nonlinear models to describe the asynchronous process of the tumor and the immune cells. Kuznstsoz *et al.* [22] presented and analyzed a mathematical model of the cytotoxic T lymphocytes (CTL) cells response to the growth of immunogenic tumor and estimated the parameters of the target model. Recently, Pang *et al.* [23] proposed and analyzed an optimal strategy for a tumor model with combination of immunotherapy and chemotherapy. They established that the combination of therapies are the most-effective strategy for tumor treatment. But during the treatment, it also kills the normal cells and induces some side-effects. To avoid the side-effects caused by chemotherapy treatment, oncologists found a new treatment called targeted chemotherapy. It targets the changes in cancer cells that help them to grow, divide and spread [24,25]. Therefore, we consider a mathematical model represents a tumor-immune system with targeted chemotherapy. In this work, we analyse a tumor growth model concerning only the chemotherapy treatment. It means that we use drugs to kill the tumor or to reduce the growth and invasion of the tumor. The analytical study of the cancer invasion mathematical model is very beneficial to understand the dynamics of tumor-immune. Most of the models of chemotherapy in the literature have omitted the spatial effects and therefore ignored an important part in tumor growth treatment model. These spatial displacements can occur naturally due to several factors including social, economic and demographic inequalities. Therefore, it is important to include spatial dimensions in a mathematical model of targeted chemotherapy. Thus, we propose a mathematical model with distributed controls subject to partial differential equations (PDEs) constraints.

Our main aim of the proposed problem is to minimize the tumor burden and the total amount of drugs used during the targeted chemotherapy. Anaya *et al.* [26] investigated a nonlinear reaction-diffusion equation modelling the spread of tumor cells in spatial domain. Many researchers have proposed mathematical models for tumor growth and related studies (see [1,2,5,7–9,27,28]). Further, the gradient in the density of any cells which provokes a flux in either linear or nonlinear form of another density of cells is called cross-diffusion. There has been increasing attention, in recent years, in the research of mathematical models of reaction-diffusion type with cross-diffusion operators, also including cases in cancer invasion modelling, that is, chemotaxis or haptotaxis effect. Therefore, in addition to the reaction-diffusion effect, we also added cross-diffusion terms in our system to examine the mathematical model. In the literature, there are many papers investigating various applications with cross-diffusion effect, see [29–35] and references therein.

In this work, we mainly focus on performing the optimal control analysis constrained by a system of PDEs. Many researchers started analysing the optimal control problems constrained by reaction-diffusion equations. Anderson *et al.* studied the existence of optimal control solutions for tumor invasion model in [36]. They studied the distributed optimal control problem for the two-dimensional mathematical model belonging to the wide class of chemotaxis models. Colli *et al.* studied the distributed optimal control of a diffuse interface model consisting of the Cahn-Hilliard equation for tumor growth in [37]. Optimal radiotherapy fractionations for the low-grade glioma model was studied in [38]. Optimal control for a parabolic-hyperbolic free boundary problem modeling the tumor growth with drug application was studied in [39]. Belmiloudi investigated a mathematical model of tumor-normal cells interaction dynamics on the role of drugs in the brain-tumor–targeted treatment in [40]. He proved the existence and uniqueness of an optimal solution and formulated an optimal control problem to minimize the drug delivery and tumor cell burden in different situations. Also, he derived the necessary conditions for optimality.

Apart from theoretical works, there are numerical investigations proposed in the literature related to an optimal control of the problem for cancer invasion and the related continuum mathematical models, for example, see [41–44] and references therein. Quiroga *et al.* [45] proposed an optimal control problem for the two-dimensional (2D) non-linear reaction diffusion equation of cancer invasion. They solved a parameter estimation problem of the cancer invasion model proposed by [9]. A distributed parameters reaction-diffusion model for brain tumor treatment was presented in [46] using the Galerkin finite element method. The authors formulated an optimal control problem and successfully minimized the density of the tumor cell and also reduced the side-effects of the drugs. Moreover, the work of Knopoff *et al.* [41] showed a PDE constrained optimization for tumor growth model whose spatial domain is the tumor, that changes in size over time. Further, they defined an appropriate functional to compare both the real data and the numerical solution. Recently, Sakine *et al.* [47] proposed and numerically analysed an optimal control problem with four control variables to control the concentration of nutrient and drug on the boundary and inside the tumor. However, there is no paper available to study the mathematical and numerical analysis of distributed control problem constrained by the cancer invasion PDE model with the cross-diffusion process. By taking the above studies as motivation, we have made an attempt in this work to study the optimal control problem proposed for tumor growth model that takes into account the spatial diffusion.

This paper is organized as follows. We present the mathematical model of a tumor-immune non-linear coupled system with cross-diffusion in sect. 2. In sect. 3, using the Faedo-Galerkin scheme, we prove the existence of a weak solution of the state system. In sect. 4, we prove the existence of control. Then, we establish the adjoint problem as well as the first-order optimality conditions for the proposed control problem. Further, we obtain the existence of a weak solution to the derived adjoint problem. In sect. 5, we propose the finite element numerical scheme for our control problem. Then, we perform various numerical simulations associated to our control problem to understand the effect of control in the treatment.

2 Mathematical model and optimal control problem

In this section, first, we propose the distributed optimal control problem subject to PDEs constraints. The proposed PDEs represent tumor-immune interactions with chemotherapy treatment. It is a highly nonlinear coupled system with cross-diffusion effect. The proposed model is extended from the original ordinary differential equation model proposed in [48]. In this paper, we assume that the interactions of unknowns not only depends on time t but also depends on the space x.

In this paper, we frame an optimal control problem to minimize the tumor cells and also the total amount of drug used to weaken or slow down the growth of tumors. Here, J is the cost functional to minimize and u_1 is the state variable. Then, we use v as the control variable to reduce the tumor burden minimizing total drug administered and v_d denotes some nominal (or expected) control. Further u_{1Q}, u_{1T} are the corresponding desired terminal states belong to $L^2(Q_T)$, $L^2(\Omega)$ respectively. Moreover, $A > 0$, $B > 0$ and $C > 0$ are the corresponding weight parameter. Furthermore, there is no assumption about the control constraints, but v_d works as a physical limitation on the measure and costs of drugs given to the patients.

We consider the optimal control problem governed by the nonlinear system of parabolic equations with cross-diffusion as follows:

$$\min J(u_1, v) = \frac{A}{2}\|u_1 - u_{1Q}\|^2_{L^2(Q_T)} + \frac{B}{2}\|u_1(T) - u_{1T}\|^2_{L^2(\Omega)} + \frac{C}{2}\|v - v_d\|^2_{L^2(Q_T)}, \tag{1}$$

subject to the following PDEs constraints:

$$\begin{aligned}
&\partial_t u_1 = D_1 \Delta u_1 + \nabla\cdot((a_1 u_1 + u_2)\nabla u_1 + u_1 \nabla u_2) + \alpha_1 u_1(1 - b u_1) - c_1 u_2 u_1 - K_T u_4 u_1, \quad \text{in } Q_T,\\
&\partial_t u_2 = D_2 \Delta u_2 + \nabla\cdot(u_2 \nabla u_1 + (u_1 + a_2 u_2)\nabla u_2) + c_2 u_2(1 - d u_2) - \mu u_2 - \rho u_1 u_2 - K_N(1-\nu) u_4 u_2, \quad \text{in } Q_T,\\
&\partial_t u_3 = \nabla\cdot(D_3(u_3)\nabla u_3) + \alpha_2 u_3 - \beta u_3 - K_C(1-\nu) u_4 u_3, \quad \text{in } Q_T,\\
&\partial_t u_4 = \nabla\cdot(D_4(u_4)\nabla u_4) - \gamma u_4 + v - k_T u_1 u_4, \quad \text{in } Q_T.
\end{aligned} \tag{2}$$

Further, we have assumed the following initial and no-flux Neumann boundary conditions for the state system (2):

$$\begin{aligned}
u_i(x,0) &= u_{i,0}(x), \quad \text{in } \Omega,\\
\frac{\partial u_i}{\partial \eta} &= 0, \quad \text{in } \Sigma_T,
\end{aligned}$$

where $i = 1, \cdots, 4$. Here, $Q_T = \Omega \times (0,T)$, $\Sigma_T = \partial\Omega \times (0,T)$, Ω is an open bounded domain in $\mathbb{R}^N$, $(N \le 3)$ and η is the unit outward normal vector on boundary $\partial\Omega$. The given model consists of four physical variables, namely tumor cell density $u_1 = u_1(x,t)$, immune cell density $u_2 = u_2(x,t)$, circulating lymphocyte density $u_3 = u_3(x,t)$ and the chemotherapeutic drug concentration $u_4 = u_4(x,t)$. In (2), D_i, $i = 1,2$ are diffusion coefficients of tumor and immune cells and $D_i(u_i)$, $i = 3,4$ denotes the density-dependent diffusion coefficients of the lymphocyte population and the drug concentration, respectively. Further, a_1 and a_2 are, respectively, the self-diffusion rates of tumor and immune cells. The parameters α_1, b, c_1, c_2, d, K_T, μ, ρ, K_N, ν, α_2, β, K_C, γ, k_T are positive constants, which are shown in table 1. In this model, $v(x,t)$ acts as the control variable for drug concentration in the fourth equation of the model and $u_{i,0}(x)$, $i = 1,2,3,4$ represent the initial conditions of unknown variables u_i, $i = 1,2,3,4$, respectively.

We consider the equivalent dimensionless form of system (2) as follows:

$$\begin{aligned}
&\partial_t u_1 = D_1 \Delta u_1 + \nabla\cdot((a_1 u_1 + u_2)\nabla u_1 + u_1 \nabla u_2) + \alpha_1 u_1 - F_1(u_1,u_2,u_4), \quad \text{in } Q_T,\\
&\partial_t u_2 = D_2 \Delta u_2 + \nabla\cdot(u_2 \nabla u_1 + (u_1 + a_2 u_2)\nabla u_2) + c_2 u_2 - \mu u_2 - F_2(u_1,u_2,u_4), \quad \text{in } Q_T,\\
&\partial_t u_3 = \nabla\cdot(D_3(u_3)\nabla u_3) + \alpha_2 u_3 - \beta u_3 - F_3(u_3,u_4), \quad \text{in } Q_T,\\
&\partial_t u_4 = \nabla\cdot(D_4(u_4)\nabla u_4) - \gamma u_4 + v - F_4(u_1,u_4), \quad \text{in } Q_T,
\end{aligned} \tag{3}$$

where

$$\begin{aligned}
F_1(u_1,u_2,u_4) &= u_1(\alpha_1 b u_1 + c_1 u_2 + K_T u_4),\\
F_2(u_1,u_2,u_4) &= u_2(c d u_2 + \rho u_1 + K_N(1-\nu)u_4),\\
F_3(u_3,u_4) &= u_3(K_C(1-\nu)u_4),\\
F_4(u_1,u_4) &= u_4(k_T u_1).
\end{aligned}$$

Table 1. Symbols and description of parameters.

Symbol	Description
u_1	Density of cancer cells
u_2	Density of immune cells
u_3	Density of circulating lymphocytes
u_4	Concentration of chemotherapeutic drug
D_1, D_2	Diffusion coefficients
$D_3(u_3)$, $D_4(u_4)$	Density-dependent coefficients
T	Time
$u_{1,0}$	Initial cancer cells
$u_{2,0}$	Initial immune cells
$u_{3,0}$	Initial circulating lymphocyte
$u_{4,0}$	Initial chemotherapeutic drug
Ω	Spatial domain
Σ_T	Neumann boundary
η	Unit outward normal vector
a_1, a_2	Self diffusion rates
α_1	Tumor growth rate
α_2	Growth rate of circulating lymphocytes
b	$\frac{1}{b}$ is tumor carrying capacity
c_1	Death rate of cancer cells due to immune cells
c_2	Growth rate of immune cells
d	$\frac{1}{d}$ is immune carrying capacity
K_T	Death rate of cancer cells due to chemotherapy
μ	Death rate of immune cells
ρ	Inactive rate of immune cells by cancer cells
K_N	Death rate of immune cells due to chemotherapy
ν	Efficacy of chemotherapy
β	Death rate of circulating lymphocytes
K_C	Death rate of circulating lymphocytes due to chemotherapy
γ	Decay rate of drug
k_T	Combination rate of drug with cancer cells
J	Cost functional
u_{1Q}, u_{1T}	Desired terminal states
v	Control variable
v_d	Expected control
A, B, C	Positive weight constants

For technical reasons, we extend the above-mentioned function in the following form, for $j = 1, 2$:

$$F_j(x,t,u_1,u_2,u_4) = \begin{cases} F_j(x,t,0,u_2,u_4), & \text{if } u_2 \geq 0 \text{ and } u_4 \geq 0, \\ F_j(x,t,u_1,0,u_4), & \text{if } u_1 \geq 0 \text{ and } u_4 \geq 0, \\ F_j(x,t,u_1,u_2,0), & \text{if } u_1 \geq 0 \text{ and } u_2 \geq 0, \end{cases}$$

$$F_3(x,t,u_3,u_4) = \begin{cases} F_j(x,t,0,u_4), & \text{if } u_4 \geq 0, \\ F_j(x,t,u_3,0), & \text{if } u_3 \geq 0, \end{cases}$$

$$F_4(x,t,u_1,u_4) = \begin{cases} F_j(x,t,0,u_4), & \text{if } u_4 \geq 0, \\ F_j(x,t,u_1,0), & \text{if } u_1 \geq 0. \end{cases}$$

First, to prove the existence of weak solutions of (3), we assume that diffusion functions $D_i(s),\ s \in \mathbb{R}$ satisfies following conditions:

H_1) $D_i(s)\zeta\zeta \geq \delta_i|\zeta|^2$ for every $\zeta \in \mathbb{R}^N$, where $\delta_i > 0$, and $i = 3, 4$.
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 $|D_i(s)\zeta| \leq C_k(x,t) + \Lambda_k|\zeta|$, $i = 3, 4$.

Definition 1. *A weak solution of* (3) *is a 4-tuple* (u_1, u_2, u_3, u_4)*, such that*

$$\begin{aligned}
&u_1, u_2, u_3, u_4 \in L^2(0,T; H^1(\Omega)) \cap L^\infty(0,T; L^2(\Omega)) \cap C([0,T], L^2(\Omega)),\\
&\partial_t u_1, \partial_t u_2, \partial_t u_3, \partial_t u_4 \in L^2(0,T; (W^{1,\infty}(\Omega))^*),\\
&D_i(u_i) \in L^2(0,T; H^1(\Omega)), \quad i = 3, 4,\\
&u_i(0) = u_{i,0} \quad a.e.\ in\ \Omega, \quad i = 1, 2, 3, 4,
\end{aligned}$$

and satisfies the following weak formulation:

$$\begin{aligned}
&\int_0^T \langle \partial_t u_1, \phi_1 \rangle \mathrm{d}t + D_1 \int_{Q_T} \nabla u_1 \cdot \nabla \phi_1 \mathrm{d}x\,\mathrm{d}t + \int_{Q_T} ((a_1 u_1 + u_2)\nabla u_1 + u_1 \nabla u_2) \cdot \nabla \phi_1 \mathrm{d}x\,\mathrm{d}t =\\
&\alpha_1 \int_{Q_T} u_1 \phi_1 \mathrm{d}x\,\mathrm{d}t - \int_{Q_T} F_1(u_1, u_2, u_4)\phi_1 \mathrm{d}x\,\mathrm{d}t,\\
&\int_0^T \langle \partial_t u_2, \phi_2 \rangle \mathrm{d}t + D_2 \int_{Q_T} \nabla u_2 \cdot \nabla \phi_2 \mathrm{d}x\,\mathrm{d}t + \int_{Q_T} (u_2 \nabla u_1 + (u_1 + a_2 u_2)\nabla u_2) \cdot \nabla \phi_2 \mathrm{d}x\,\mathrm{d}t =\\
&\int_{Q_T} c_2 u_2 \phi_2 \mathrm{d}x\,\mathrm{d}t - \mu \int_{Q_T} u_2 \phi_2 \mathrm{d}x\,\mathrm{d}t - \int_{Q_T} F_2(u_1, u_2, u_4)\phi_2 \mathrm{d}x\,\mathrm{d}t,\\
&\int_0^T \langle \partial_t u_3, \phi_3 \rangle \mathrm{d}t + \int_{Q_T} D_3(u_3)\nabla u_3 \cdot \nabla \phi_3 \mathrm{d}x\,\mathrm{d}t = \int_{Q_T} \alpha_2 u_3 \phi_3 \mathrm{d}x\,\mathrm{d}t - \beta \int_{Q_T} u_3 \phi_3 \mathrm{d}x\,\mathrm{d}t - \int_{Q_T} F_3(u_3, u_4)\phi_3 \mathrm{d}x\,\mathrm{d}t,\\
&\int_0^T \langle \partial_t u_4, \phi_4 \rangle \mathrm{d}t + \int_{Q_T} D_4(u_4)\nabla u_4 \cdot \nabla \phi_4 \mathrm{d}x\,\mathrm{d}t = -\int_{Q_T} \gamma u_4 \phi_4 \mathrm{d}x\,\mathrm{d}t + \int_{Q_T} v(x,t)\phi_4 \mathrm{d}x\,\mathrm{d}t - \int_{Q_T} F_4(u_1, u_4)\phi_4 \mathrm{d}x\,\mathrm{d}t,
\end{aligned}$$

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

We prove the main result, the existence of a weak solution for the direct problem in the following theorem. For simplicity, we use the generic constant c throughout this paper.

Theorem 1. *Assume the hypotheses* (H_1) *and* (H_2), $D_j(u_j) > 0$, $D_j(u_j) \in C^1(\mathbb{R})$, *where* $j = 3, 4$ *and if* $u_{i,0} \in L^2(\Omega)$, $i = 1, \cdots, 4$ *and* $v \in L^2(Q_T)$, *then there exists a weak solution for* (2) *in the sense of definition* 1.

The proof of theorem 1 is based on introducing the approximation system to which we apply the Faedo-Galerkin approximation method and the convergence of a weak solution of the approximate solution using monotonicity and compactness methods.

3 Existence of a weak solution for the direct problem

In this section, we prove the existence and nonnegativity of a weak solution. To show the result, first introduce an approximation system for (2). Therefore, we consider the regularized system of (3) as follows: For $\varepsilon > 0$,

$$\begin{aligned}
\partial_t u_1^\varepsilon &= D_1 \Delta u_1^\varepsilon + \nabla \cdot ((a_1 f_\varepsilon^+(u_1^\varepsilon) + f_\varepsilon^+(u_2^\varepsilon))\nabla u_1^\varepsilon + f_\varepsilon^+(u_1^\varepsilon)\nabla u_2^\varepsilon) + \alpha_1 u_1^\varepsilon - F_{1,\varepsilon}(u_1^\varepsilon, u_2^\varepsilon, u_4^\varepsilon), \quad \text{in } Q_T,\\
\partial_t u_2^\varepsilon &= D_2 \Delta u_2^\varepsilon + \nabla \cdot (f_\varepsilon^+(u_2^\varepsilon)\nabla u_1^\varepsilon + (f_\varepsilon^+(u_1^\varepsilon) + a_2 f_\varepsilon^+(u_2^\varepsilon))\nabla u_2^\varepsilon) + c_2 u_2^\varepsilon - \mu u_2^\varepsilon - F_{2,\varepsilon}(u_1^\varepsilon, u_2^\varepsilon, u_4^\varepsilon), \quad \text{in } Q_T,\\
\partial_t u_3^\varepsilon &= \nabla \cdot (D_3(u_3^\varepsilon)\nabla u_3^\varepsilon) + \alpha_2 u_3^\varepsilon - \beta u_3^\varepsilon - F_{3,\varepsilon}(u_3^\varepsilon, u_4^\varepsilon), \quad \text{in } Q_T,\\
\partial_t u_4^\varepsilon &= \nabla \cdot (D_4(u_4^\varepsilon)\nabla u_4^\varepsilon) - \gamma u_4^\varepsilon + v - F_{4,\varepsilon}(u_1^\varepsilon, u_4^\varepsilon), \quad \text{in } Q_T,\\
u_i^\varepsilon(x,0) &= u_{i,0}(x), \quad \text{in } \Omega,\\
\frac{\partial u_i^\varepsilon}{\partial \eta} &= 0, \quad i = 1, 2, 3, 4, \quad \text{in } \Sigma_T,
\end{aligned} \tag{4}$$

where $F_{i,\varepsilon} = \frac{F_i}{1+\varepsilon|F_i|}$, $f_\varepsilon(r) = \frac{r}{1+\varepsilon|r|}$ and $s^+ = \max(0, s)$ for any $r, s \in \mathbb{R}$.

In order to prove theorem 1, we first prove the existence of solutions of the regularized system and then sending the parameter ε to zero, we find a weak solution of our original system (2).

Remark 1. *The diffusion matrix*

$$\mathcal{M} = \begin{pmatrix} a_1 f_\varepsilon^+(u_1^\varepsilon) + f_\varepsilon^+(u_2^\varepsilon) & f_\varepsilon^+(u_1^\varepsilon) \\ f_\varepsilon^+(u_2^\varepsilon) & f_\varepsilon^+(u_1^\varepsilon) + a_2 f_\varepsilon^+(u_2^\varepsilon) \end{pmatrix}$$

is uniformly nonnegative. Using, $a_1 \geq 1$, $a_2 \geq 1$ *and the inequality* $ab \geq -a^2 - b^2$ *for all* $a, b \in \mathbb{R}$ *and* $\xi = (\xi_1, \xi_2) \in \mathbb{R}^N$*, we have*

$$\begin{aligned}\xi^T \mathcal{M} \xi &= (a_1 f_\varepsilon^+(u_1^\varepsilon) + f_\varepsilon^+(u_2^\varepsilon))\xi_1^2 + f_\varepsilon^+(u_2^\varepsilon)\xi_1\xi_2 + f_\varepsilon^+(u_1^\varepsilon)\xi_1\xi_2 + (a_2 f_\varepsilon^+(u_2^\varepsilon) + f_\varepsilon^+(u_1^\varepsilon))\xi_2^2 \\ &\geq (a_1 - 1) f_\varepsilon^+(u_1^\varepsilon)\xi_1^2 + (a_2 - 1) f_\varepsilon^+(u_2^\varepsilon)\xi_2^2 \geq 0.\end{aligned}$$

Theorem 2. *Assume that theorem 1 holds true. Then there exists a weak solution of* (4) *as follows:*

$$u_1^\varepsilon, u_2^\varepsilon, u_3^\varepsilon, u_4^\varepsilon \in L^2(0,T; H^1(\Omega)) \cap L^\infty(0,T; L^2(\Omega)) \cap C([0,T], L^2(\Omega)),$$

with $\partial_t u_i^\varepsilon \in L^2(0,T;(H^1(\Omega))^*)$ *such that for any* $\phi_i \in L^2(0,T;H^1(\Omega))$, $i = 1, \cdots, 4$,

$$\begin{aligned}&\int_0^T \langle \partial_t u_1^\varepsilon, \phi_1 \rangle \mathrm{d}t + D_1 \int_{Q_T} \nabla u_1^\varepsilon \cdot \nabla \phi_1 \mathrm{d}x\,\mathrm{d}t + \int_{Q_T} ((a_1 f_\varepsilon^+(u_1^\varepsilon) + f_\varepsilon^+(u_2^\varepsilon))\nabla u_1^\varepsilon + f_\varepsilon^+(u_1^\varepsilon)\nabla u_2^\varepsilon) \cdot \nabla \phi_1 \mathrm{d}x\,\mathrm{d}t = \\ &\alpha_1 \int_{Q_T} u_1^\varepsilon \phi_1 \mathrm{d}x\,\mathrm{d}t - \int_{Q_T} F_{1,\varepsilon}(u_1^\varepsilon, u_2^\varepsilon, u_4^\varepsilon)\phi_1 \mathrm{d}x\,\mathrm{d}t, \\ &\int_0^T \langle \partial_t u_2^\varepsilon, \phi_2 \rangle \mathrm{d}t + D_2 \int_{Q_T} \nabla u_2^\varepsilon \cdot \nabla \phi_2 \mathrm{d}x\,\mathrm{d}t + \int_{Q_T} (f_\varepsilon^+(u_2^\varepsilon)\nabla u_1^\varepsilon + (f_\varepsilon^+(u_1^\varepsilon) + a_2 f_\varepsilon^+(u_2^\varepsilon))\nabla u_2^\varepsilon) \cdot \nabla \phi_2 \mathrm{d}x\,\mathrm{d}t = \\ &\int_{Q_T} (c_2 - \mu) u_2^\varepsilon \phi_2 \mathrm{d}x\,\mathrm{d}t - \int_{Q_T} F_{2,\varepsilon}(u_1^\varepsilon, u_2^\varepsilon, u_4^\varepsilon)\phi_2 \mathrm{d}x\,\mathrm{d}t, \\ &\int_0^T \langle \partial_t u_3^\varepsilon, \phi_3 \rangle \mathrm{d}t + \int_{Q_T} D_3(u_3^\varepsilon)\nabla u_3^\varepsilon \cdot \nabla \phi_3 \mathrm{d}x\,\mathrm{d}t = \int_{Q_T} (\alpha_2 - \beta) u_3^\varepsilon \phi_3 \mathrm{d}x\,\mathrm{d}t - \int_{Q_T} F_{3,\varepsilon}(u_3^\varepsilon, u_4^\varepsilon)\phi_3 \mathrm{d}x\,\mathrm{d}t, \\ &\int_0^T \langle \partial_t u_4^\varepsilon, \phi_4 \rangle \mathrm{d}t + \int_{Q_T} D_4(u_4^\varepsilon)\nabla u_4^\varepsilon \cdot \nabla \phi_4 \mathrm{d}x\,\mathrm{d}t = -\int_{Q_T} \gamma u_4^\varepsilon \phi_4 \mathrm{d}x\,\mathrm{d}t + \int_{Q_T} v(x,t)\phi_4 \mathrm{d}x\,\mathrm{d}t - \int_{Q_T} F_{4,\varepsilon}(u_1^\varepsilon, u_4^\varepsilon)\phi_4 \mathrm{d}x\,\mathrm{d}t, \end{aligned} \tag{5}$$

hold. Here, $\langle \cdot, \cdot \rangle$ *represents the duality pairing between* $H^1(\Omega)$ *and* $(H^1(\Omega))^*$.

Proof. We consider the appropriate spectral problem as in [49]. Then the identified eigenfunctions $e_l(x)$ orthogonal in $H^1(\Omega)$ and orthonormal in $L^2(\Omega)$. Here, we look to find the finite dimensional approximation solutions for the system (4) as sequences $\{u_i^\varepsilon\}$, $i = 1, \cdots, 4$ and v defined for $t \geq 0$ and $x \in \bar{\Omega}$ by

$$u_{i,n}^\varepsilon(x,t) = \sum_{l=1}^n c_{i,n,l}(t) e_l(x) \quad \text{and} \quad v_n(x,t) = \sum_{l=1}^n (v, e_l)_{L^2(Q_T)} e_l(x).$$

The goal is to find the set of coefficients $\{c_{i,n,l}\}_{l=1}^n$, $i = 1, \cdots, 4$, such that, for $m = 1, 2, \ldots, n$,

$$\begin{aligned}&(\partial_t u_{1,n}^\varepsilon e_m)_{L^2(\Omega)} + D_1 \int_\Omega \nabla u_{1,n}^\varepsilon \cdot \nabla e_m \mathrm{d}x + \int_\Omega ((a_1 f_\varepsilon^+(u_{1,n}^\varepsilon) + f_\varepsilon^+(u_{2,n}^\varepsilon))\nabla u_{1,n}^\varepsilon + f_\varepsilon^+(u_{1,n}^\varepsilon)\nabla u_{2,n}^\varepsilon) \cdot \nabla e_m \mathrm{d}x = \\ &\alpha_1 \int_\Omega u_{1,n}^\varepsilon e_m \mathrm{d}x - \int_\Omega F_{1,\varepsilon}(u_{1,n}^\varepsilon, u_{2,n}^\varepsilon, u_{4,n}^\varepsilon) e_m \mathrm{d}x, \\ &(\partial_t u_{2,n}^\varepsilon e_m)_{L^2(\Omega)} + D_2 \int_\Omega \nabla u_{2,n}^\varepsilon \cdot \nabla e_m \mathrm{d}x + \int_\Omega (f_\varepsilon^+(u_{2,n}^\varepsilon)\nabla u_{1,n}^\varepsilon + (f_\varepsilon^+(u_{1,n}^\varepsilon) + a_2 f_\varepsilon^+(u_{2,n}^\varepsilon))\nabla u_{2,n}^\varepsilon) \cdot \nabla e_m \mathrm{d}x = \\ &\int_\Omega (c_2 - \mu) u_{2,n}^\varepsilon e_m \mathrm{d}x - \int_\Omega F_{2,\varepsilon}(u_{3,n}^\varepsilon, u_{2,n}^\varepsilon, u_{4,n}^\varepsilon) e_m \mathrm{d}x, (\partial_t u_{3,n}^\varepsilon e_m)_{L^2(\Omega)} + \int_\Omega D_3(u_{3,n}^\varepsilon)\nabla u_{3,n}^\varepsilon \cdot \nabla e_m \mathrm{d}x = \\ &\int_\Omega (\alpha_2 - \beta) u_{3,n}^\varepsilon e_m \mathrm{d}x - \int_\Omega F_{3,\varepsilon}(u_{3,n}^\varepsilon, u_{4,n}^\varepsilon) e_m \mathrm{d}x, (\partial_t u_{4,n}^\varepsilon e_m)_{L^2(\Omega)} + \int_\Omega D_4(u_{4,n}^\varepsilon)\nabla u_{4,n}^\varepsilon \cdot \nabla e_m \mathrm{d}x = \\ &- \int_\Omega (\gamma u_{4,n}^\varepsilon - v) e_m \mathrm{d}x - \int_\Omega F_{4,\varepsilon}(u_{1,n}^\varepsilon, u_{4,n}^\varepsilon) e_m \mathrm{d}x,\end{aligned} \tag{6}$$

with the initial conditions

$$u_{i,n}^{\varepsilon}(x,0) = u_{i,0,n}(x) := \sum_{l=1}^{n} c_{i,n,l}(0) e_l(x),$$

where

$$c_{i,n,l}(0) = (u_{i,0}, e_l)_{L^2(\Omega)}, \quad i = 1, \cdots, 4.$$

Now, the above equations can be rewritten as a system of ordinary differential equations in the following form:

$$\begin{aligned}
c_{1,n,m}'(t) &= -D_1 \int_\Omega \nabla u_{1,n}^{\varepsilon} \cdot \nabla e_m \mathrm{d}x - \int_\Omega ((a_1 f_\varepsilon^+(u_{1,n}^{\varepsilon}) + f_\varepsilon^+(u_{2,n}^{\varepsilon}))\nabla u_{1,n}^{\varepsilon} + f_\varepsilon^+(u_{1,n}^{\varepsilon})\nabla u_{2,n}^{\varepsilon}) \cdot \nabla e_m \mathrm{d}x \\
&\quad + \alpha_1 \int_\Omega u_{1,n}^{\varepsilon} e_m \mathrm{d}x - \int_\Omega F_{1,\varepsilon}(u_{1,n}^{\varepsilon}, u_{2,n}^{\varepsilon}, u_{4,n}^{\varepsilon}) e_m \mathrm{d}x, \\
&=: E_1^m \left(t, \{c_{1,n,l}\}_{l=1}^n, \{c_{2,n,l}\}_{l=1}^n, \{c_{4,n,l}\}_{l=1}^n\right), \\
c_{2,n,m}'(t) &= -D_2 \int_\Omega \nabla u_{2,n}^{\varepsilon} \cdot \nabla e_m \mathrm{d}x - \int_\Omega (f_\varepsilon^+(u_{2,n}^{\varepsilon})\nabla u_{1,n}^{\varepsilon} + (f_\varepsilon^+(u_{1,n}^{\varepsilon}) + a_2 f_\varepsilon^+(u_{2,n}^{\varepsilon}))\nabla u_{2,n}^{\varepsilon}) \cdot \nabla e_m \mathrm{d}x \\
&\quad + \int_\Omega (c_2 - \mu) u_{2,n}^{\varepsilon} e_m \mathrm{d}x - \int_\Omega F_{2,\varepsilon}(u_{1,n}^{\varepsilon}, u_{2,n}^{\varepsilon}, u_{4,n}^{\varepsilon}) e_m \mathrm{d}x, \\
&=: E_2^m \left(t, \{c_{1,n,l}\}_{l=1}^n, \{c_{2,n,l}\}_{l=1}^n, \{c_{4,n,l}\}_{l=1}^n\right), \\
c_{3,n,m}'(t) &= -\int_\Omega D_3(u_{3,n}^{\varepsilon})\nabla u_{3,n}^{\varepsilon} \cdot \nabla e_m \mathrm{d}x + \int_\Omega (\alpha_2 - \beta) u_{3,n}^{\varepsilon} e_m \mathrm{d}x - \int_\Omega F_{3,\varepsilon}(u_{3,n}^{\varepsilon}, u_{4,n}^{\varepsilon}) e_m \mathrm{d}x, \\
&=: E_3^m \left(t, \{c_{3,n,l}\}_{l=1}^n, \{c_{4,n,l}\}_{l=1}^n\right), \\
c_{4,n,m}'(t) &= -\int_\Omega D_4(u_{4,n}^{\varepsilon})\nabla u_{4,n}^{\varepsilon} \cdot \nabla e_m \mathrm{d}x - \int_\Omega \gamma u_{4,n}^{\varepsilon} e_m \mathrm{d}x + \int_\Omega v e_m \mathrm{d}x - \int_\Omega F_{4,\varepsilon}(u_{1,n}^{\varepsilon}, u_{4,n}^{\varepsilon}) e_m \mathrm{d}x, \\
&=: E_4^m \left(t, \{c_{1,n,l}\}_{l=1}^n, \{c_{4,n,l}\}_{l=1}^n\right).
\end{aligned} \tag{7}$$

Next, we prove the existence of local solution to the system of ordinary differential equations (7). Then, the components E_i^m, $i = 1, \cdots, 4$, can be bounded as follows:

$$\begin{aligned}
&|E_1^m \left(t, \{c_{1,n,l}\}_{l=1}^n, \{c_{2,n,l}\}_{l=1}^n, \{c_{4,n,l}\}_{l=1}^n\right)| \\
&\le D_1 \left(\int_\Omega \left|\sum_{l=1}^n c_{1,n,l}(t) \nabla e_l(x)\right|^2 \mathrm{d}x\right)^{\frac{1}{2}} \left(\int_\Omega |\nabla e_m|^2 \mathrm{d}x\right)^{\frac{1}{2}} \\
&+ \frac{(a_1+1)}{\varepsilon} \left(\int_\Omega \left|\sum_{l=1}^n c_{1,n,l}(t) \nabla e_l(x)\right|^2 \mathrm{d}x\right)^{\frac{1}{2}} \left(\int_\Omega |\nabla e_m|^2 \mathrm{d}x\right)^{\frac{1}{2}} + \frac{meas(\Omega)}{\varepsilon} \left(\int_\Omega |e_m|^2 \mathrm{d}x\right)^{\frac{1}{2}} \\
&+ \left(\frac{1}{\varepsilon} \left(\int_\Omega \left|\sum_{l=1}^n c_{2,n,l}(t) \nabla e_l(x)\right|^2 \mathrm{d}x\right)^{\frac{1}{2}} + \alpha_1 \left(\int_\Omega \left|\sum_{l=1}^n c_{1,n,l}(t) e_l(x)\right|^2 \mathrm{d}x\right)^{\frac{1}{2}}\right) \left(\int_\Omega |\nabla e_m|^2 \mathrm{d}x\right)^{\frac{1}{2}} \\
&\le c(\varepsilon, R, n),
\end{aligned}$$

where the constant $c > 0$ depends only on ε, R and n. Similarly, we get

$$\begin{aligned}
|E_2^m \left(t, \{c_{1,n,l}\}_{l=1}^n, \{c_{2,n,l}\}_{l=1}^n, \{c_{4,n,l}\}_{l=1}^n\right)| &\le c(\varepsilon, R, n), \\
|E_3^m \left(t, \{c_{3,n,l}\}_{l=1}^n, \{c_{4,n,l}\}_{l=1}^n\right)| &\le c(\varepsilon, R, n), \\
|E_4^m \left(t, \{c_{1,n,l}\}_{l=1}^n, \{c_{4,n,l}\}_{l=1}^n\right)| &\le c(\varepsilon, R, n).
\end{aligned}$$

Therefore, using the standard ODE theory, there exist absolutely continuous functions $\{c_{i,n,l}\}_{l=1}^n$, $i = 1, \cdots, 4$, satisfies (7) and the initial conditions for a.e. $t \in [0, \rho']$ where $\rho' > 0$. This proves that the sequences $\{u_{i,n}^{\varepsilon}\}$, $i = 1, \cdots, 4$ well defined and the approximate solutions to (7) on $T' \in [0, \rho')$. For absolutely continuous coefficients $b_{i,n,l}$, $i = 1, \cdots, 4$, we set $\phi_{i,n}(x,t) = \sum_{l=1}^n b_{i,n,l}(t) e_l(x)$, $i = 1, \cdots, 4$. Then, the approximate solutions satisfy the weak formulation,

$$\begin{aligned}
\int_\Omega \partial_t u_{1,n}^{\varepsilon} \phi_{1,n} \mathrm{d}x &= -D_1 \int_\Omega \nabla u_{1,n}^{\varepsilon} \cdot \nabla \phi_{1,n} \mathrm{d}x - \int_\Omega ((a_1 f_\varepsilon^+(u_{1,n}^{\varepsilon}) + f_\varepsilon^+(u_{2,n}^{\varepsilon}))\nabla u_{1,n}^{\varepsilon} + f_\varepsilon^+(u_{1,n}^{\varepsilon})\nabla u_{2,n}^{\varepsilon}) \cdot \nabla \phi_{1,n} \mathrm{d}x \\
&\quad + \alpha_1 \int_\Omega u_{1,n}^{\varepsilon} \phi_{1,n} \mathrm{d}x - \int_\Omega F_{1,\varepsilon}(u_{1,n}^{\varepsilon}, u_{2,n}^{\varepsilon}, u_{4,n}^{\varepsilon}) \phi_{1,n} \mathrm{d}x,
\end{aligned}$$

$$
\begin{aligned}
\int_\Omega \partial_t u^\varepsilon_{2,n}\phi_{2,n}\mathrm{d}x &= -D_2\int_\Omega \nabla u^\varepsilon_{2,n}\cdot\nabla\phi_{2,n}\mathrm{d}x\\
&\quad-\int_\Omega (f^+_\varepsilon(u^\varepsilon_{2,n})\nabla u^\varepsilon_{1,n}+(f^+_\varepsilon(u^\varepsilon_{1,n})+a_2 f^+_\varepsilon(u^\varepsilon_{2,n}))\nabla u^\varepsilon_{2,n})\cdot\nabla\phi_{2,n}\mathrm{d}x\\
&\quad+\int_\Omega (c_2-\mu)u^\varepsilon_{2,n}\phi_{2,n}\mathrm{d}x-\int_\Omega F_{2,\varepsilon}(u^\varepsilon_{1,n},u^\varepsilon_{2,n},u^\varepsilon_{4,n})\phi_{2,n}\mathrm{d}x,\\
\int_\Omega \partial_t u^\varepsilon_{3,n}\phi_{3,n}\mathrm{d}x &= -\int_\Omega D_3(u^\varepsilon_{3,n})\nabla u^\varepsilon_{3,n}\cdot\nabla\phi_{3,n}\mathrm{d}x+\int_\Omega(\alpha_2-\beta)u^\varepsilon_{3,n}\phi_{3,n}\mathrm{d}x\\
&\quad-\int_\Omega F_{3,\varepsilon}(u^\varepsilon_{3,n},u^\varepsilon_{4,n})\phi_{3,n}\mathrm{d}x,\\
\int_\Omega \partial_t u^\varepsilon_{4,n}\phi_{4,n}\mathrm{d}x &= -\int_\Omega D_4(u^\varepsilon_{4,n})\nabla u^\varepsilon_{4,n}\cdot\nabla\phi_{4,n}\mathrm{d}x-\int_\Omega \gamma u^\varepsilon_{4,n}\phi_{4,n}\mathrm{d}x\\
&\quad+\int_\Omega v\phi_{4,n}\mathrm{d}x-\int_\Omega F_{4,\varepsilon}(u^\varepsilon_{1,n},u^\varepsilon_{4,n})\phi_{4,n}\mathrm{d}x,
\end{aligned}
\tag{8}
$$

Set $\phi_{i,n}=u^\varepsilon_{i,n}$, $i=1,\cdots,4$ respectively, in the above eqs. (8), using Holder's inequality, Young's inequality, assumptions of the theorem and then summing the equations, we get

$$
\begin{aligned}
&\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega\left(|u^\varepsilon_{1,n}|^2+|u^\varepsilon_{2,n}|^2+|u^\varepsilon_{3,n}|^2+|u^\varepsilon_{4,n}|^2\right)\mathrm{d}x\\
&+\int_\Omega(D_1|\nabla u^\varepsilon_{1,n}|^2+D_2|\nabla u^\varepsilon_{2,n}|^2+\delta_3|\nabla u^\varepsilon_{3,n}|^2+\delta_4|\nabla u^\varepsilon_{4,n}|^2)\mathrm{d}x\le\\
&c\left(\int_\Omega |u^\varepsilon_{1,n}|^2+|u^\varepsilon_{2,n}|^2+|u^\varepsilon_{3,n}|^2+|u^\varepsilon_{4,n}|^2\right)\mathrm{d}x,
\end{aligned}
\tag{9}
$$

for some positive constant c independent of n. Using Gronwall's inequality, we obtain

$$
\int_\Omega\left(|u^\varepsilon_{1,n}|^2+|u^\varepsilon_{2,n}|^2+|u^\varepsilon_{3,n}|^2+|u^\varepsilon_{4,n}|^2\right)\mathrm{d}x\le c. \tag{10}
$$

Use (10) into (9), we conclude that

$$
\|u^\varepsilon_{i,n}\|_{L^\infty(0,T';L^2(\Omega))}+\|u^\varepsilon_{i,n}\|_{L^2(0,T';H^1(\Omega))}\le c,\quad i=1,2,3,4, \tag{11}
$$

and

$$
\left.\begin{aligned}
&\|F_{1,\varepsilon}(u^\varepsilon_{1,n},u^\varepsilon_{2,n},u^\varepsilon_{4,n})u^\varepsilon_{1,n}\|_{L^1(Q_T)}\\
&\|F_{2,\varepsilon}(u^\varepsilon_{1,n},u^\varepsilon_{2,n},u^\varepsilon_{3,n})u^\varepsilon_{2,n}\|_{L^1(Q_T)}\\
&\|F_{3,\varepsilon}(u^\varepsilon_{3,n},u^\varepsilon_{4,n})u^\varepsilon_{3,n}\|_{L^1(Q_T)}\\
&\|F_{4,\varepsilon}(u^\varepsilon_{1,n},u^\varepsilon_{4,n})u^\varepsilon_{4,n}\|_{L^1(Q_T)}
\end{aligned}\right\}\le c, \tag{12}
$$

where constant c is positive depends on the given data and is independent of n. Moreover, to prove that $(\partial_t u^\varepsilon_{1,n},\partial_t u^\varepsilon_{2,n},\partial_t u^\varepsilon_{3,n},\partial_t u^\varepsilon_{4,n})$ are bounded in $L^2(0,T';(H^1(\Omega))^*)$, choosing $\phi_{i,n}=\phi_i\in L^2(0,T';H^1(\Omega))$, $i=1,2,3$, respectively, in (8) and using the boundedness, we get

$$
\left|\int_0^{T'}\langle\partial_t u^\varepsilon_{i,n},\phi_{i,n}\rangle\mathrm{d}t\right|\le c\,\|\phi_i\|_{L^2(0,T';H^1(\Omega))}, \tag{13}
$$

where $c>0$ is a constant independent of n. To prove the global existence, we use the similar approach as in [29,49] and the above estimates.

Using the previous results and compactness arguments, the sequences have convergent subsequences (also denoted by $\{u^\varepsilon_{i,n}\}$, $i=1,\cdots,4$). Then, there exist limit functions $\{u^\varepsilon_{i,n}\}$, $i=1,\cdots,4$. Therefore as $n\to\infty$, we have,

$$
\begin{aligned}
u^\varepsilon_{i,n}&\rightharpoonup u^\varepsilon_i \quad \text{weakly } * \text{ in } L^\infty(0,T;L^2(\Omega)),\\
u^\varepsilon_{i,n}&\rightharpoonup u^\varepsilon_i \quad \text{weakly in } L^2(0,T;H^1(\Omega)),\quad i=1,2,3,4,\\
\nabla u^\varepsilon_{i,n}&\rightharpoonup \nabla u^\varepsilon_i \quad \text{weakly in } L^2(Q_T),\quad i=1,2,\\
D_i(u^\varepsilon_{i,n})\nabla u^\varepsilon_{i,n}&\rightharpoonup \xi_i \quad \text{weakly in } L^2(Q_T),\quad i=3,4,\\
f^+_\varepsilon(u^\varepsilon_{i,n})&\to f^+_\varepsilon(u^\varepsilon_i) \quad \text{a.e. in } Q_T,\quad i=1,2,\\
\partial_t u^\varepsilon_{i,n}&\rightharpoonup \partial_t u^\varepsilon_i \quad \text{weakly in } L^2(0,T;(H^1(\Omega))^*),\quad i=1,2,3,4.
\end{aligned}
$$

Next, we prove $D_i(u_i^\varepsilon)\nabla u_i^\varepsilon = \xi_i$, $i = 3, 4$. Multiply the third equation of (4) by $u_{3,n}^\varepsilon$, then integrate with Q_T and as $n \to \infty$, we get

$$\frac{1}{2}\int_\Omega |u_3^\varepsilon(x,T)|^2 \mathrm{d}x + \int_{Q_T} \xi_3 \nabla u_3^\varepsilon \mathrm{d}x\,\mathrm{d}t = \alpha_2 \int_{Q_T} |u_3^\varepsilon|^2 \mathrm{d}x\,\mathrm{d}t - \beta \int_{Q_T} |u_3^\varepsilon|^2 \mathrm{d}x\,\mathrm{d}t$$
$$- \int_{Q_T} F_{3,\varepsilon}(u_3^\varepsilon, u_4^\varepsilon) u_3^\varepsilon \mathrm{d}x\,\mathrm{d}t + \frac{1}{2}\int_\Omega |u_{3,0}(x)|^2 \mathrm{d}x. \tag{14}$$

Assume the following monotonicity condition holds true. Then

$$\int_\Omega \left(D_3(u_{3,n}^\varepsilon)\nabla u_{3,n}^\varepsilon - D_3(u_n^\varepsilon)\nabla u_n^\varepsilon\right)(\nabla u_{3,n}^\varepsilon - \nabla u_n^\varepsilon)\mathrm{d}x \geq 0.$$

Next, multiply the third equation of (4) by $u_{3,n}^\varepsilon$, and integrating with Ω, we have

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega |u_{3,n}^\varepsilon|^2 \mathrm{d}x + \int_\Omega D_3(u_{3,n}^\varepsilon)\nabla u_{3,n}^\varepsilon \cdot \nabla u_{3,n}^\varepsilon \mathrm{d}x = \alpha_2 \int_\Omega |u_{3,n}^\varepsilon|^2 \mathrm{d}x - \beta \int_\Omega |u_{3,n}^\varepsilon|^2 \mathrm{d}x$$
$$- \int_\Omega F_{3,\varepsilon}(u_{3,n}^\varepsilon, u_{4,n}^\varepsilon) u_{3,n}^\varepsilon \mathrm{d}x,$$

Using the above monotonicity condition, we get

$$-\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega |u_{3,n}^\varepsilon|^2 \mathrm{d}x - \int_\Omega D_3(u_{3,n}^\varepsilon)\nabla u_{3,n}^\varepsilon \cdot \nabla u_n^\varepsilon \mathrm{d}x - \int_\Omega D_3(u_n^\varepsilon)\nabla u_n^\varepsilon\,(\nabla u_{3,n}^\varepsilon - \nabla u_n^\varepsilon)\mathrm{d}x$$
$$+ \alpha_2 \int_\Omega |u_{3,n}^\varepsilon|^2 \mathrm{d}x - \beta \int_\Omega |u_{3,n}^\varepsilon|^2 \mathrm{d}x - \int_\Omega F_{3,\varepsilon}(u_{3,n}^\varepsilon, u_{4,n}^\varepsilon) u_{3,n}^\varepsilon \mathrm{d}x \geq 0.$$

Integrating over $(0,T)$, taking limit as $n \to \infty$ and comparing the resulting equation with (14), we get

$$\int_{Q_T} (\xi_3 - D_3(u^\varepsilon)\nabla u^\varepsilon)(\nabla u_3^\varepsilon - \nabla u^\varepsilon)\,\mathrm{d}x\,\mathrm{d}t \geq 0.$$

We set $u^\varepsilon := u_3^\varepsilon - \eta_1 \phi$ for any $\eta_1 > 0$ and $\phi \in L^2(0,T;H^1(\Omega))$ in previous inequality and obtain

$$\int_{Q_T} (\xi_3 - (D_3(u_3^\varepsilon - \eta_1\phi))(\nabla u_3^\varepsilon - \eta_1 \nabla\phi))\nabla\phi\,\mathrm{d}x\,\mathrm{d}t \geq 0.$$

As $\eta_1 \to 0$ and by the dominated convergence theorem, we have

$$\int_{Q_T} (\xi_3 - (D_3(u_3^\varepsilon)\nabla u_3^\varepsilon))\,\nabla\phi\,\mathrm{d}x\,\mathrm{d}t \geq 0,$$

for any $\phi \in L^2(0,T;H^1(\Omega))$. This proves that $D_3(u_3^\varepsilon)\nabla u_3^\varepsilon = \xi_3$. Similarily, it is easy to prove that $D_4(u_4^\varepsilon)\nabla u_4^\varepsilon = \xi_4$. □

Lemma 1. *If $u_{i,0} \in L^2(\Omega)$, $v \in L^2(Q_T)$ are nonnegative, then u_i^ε, $i = 1, \cdots, 4$, is nonnegative.*

Proof. We consider $u_i^{-\varepsilon} = \sup(-u_i^\varepsilon, 0)$, $i = 1, \cdots, 4$. Multiplying (4), respectively, by $u_i^{-\varepsilon}$ and integrating with Ω, we get

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \left(|u_1^{-\varepsilon}|^2 + |u_2^{-\varepsilon}|^2 + |u_3^{-\varepsilon}|^2 + |u_4^{-\varepsilon}|^2\right)\mathrm{d}x \leq 0,$$

where we have used the nonnegativity of the right-hand side and initial conditions. □

Proof of theorem 1. Choosing, $\phi_i = u_i^\varepsilon$, $i = 1, \cdots, 4$, respectively, in (5) and using the hypothesis, we obtain

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \left(|u_1^\varepsilon|^2 + |u_2^\varepsilon|^2 + |u_3^\varepsilon|^2 + |u_4^\varepsilon|^2\right)\mathrm{d}x + \int_\Omega (D_1|\nabla u_1^\varepsilon|^2 + D_2|\nabla u_2^\varepsilon| + \delta_3|\nabla u_3^\varepsilon| + \delta_4|\nabla u_4^\varepsilon|^2) \leq$$
$$c\left(\int_\Omega |u_1^\varepsilon|^2 + |u_2^\varepsilon|^2 + |u_3^\varepsilon|^2 + |u_4^\varepsilon|^2\right)\mathrm{d}x. \tag{15}$$

Then, the application of Gronwall's inequality proves that

$$\int_\Omega \left(|u_1^\varepsilon|^2 + |u_2^\varepsilon|^2 + |u_3^\varepsilon|^2 + |u_4^\varepsilon|^2\right) \mathrm{d}x \le c. \tag{16}$$

From (15) and (16), we prove that

$$\|(u_1^\varepsilon, u_2^\varepsilon, u_3^\varepsilon, u_4^\varepsilon)\|_{L^\infty(0,T;L^2(\Omega))} + \|(u_1^\varepsilon, u_2^\varepsilon, u_3^\varepsilon, u_4^\varepsilon)\|_{L^2(0,T;H^1(\Omega))} \le c, \tag{17}$$

and

$$\left.\begin{array}{l} \|F_{1,\varepsilon}(u_1^\varepsilon, u_2^\varepsilon, u_4^\varepsilon)u_1^\varepsilon\|_{L^1(Q_T)} \\ \|F_{2,\varepsilon}(u_1^\varepsilon, u_2^\varepsilon, u_3^\varepsilon)u_2^\varepsilon\|_{L^1(Q_T)} \\ \|F_{3,\varepsilon}(u_3^\varepsilon, u_4^\varepsilon)u_3^\varepsilon\|_{L^1(Q_T)} \\ \|F_{4,\varepsilon}(u_1^\varepsilon, u_4^\varepsilon)u_4^\varepsilon\|_{L^1(Q_T)} \end{array}\right\} \le c. \tag{18}$$

Moreover, one can show that

$$\|(\partial_t u_1^\varepsilon, \partial_t u_2^\varepsilon, \partial_t u_3^\varepsilon, \partial_t u_4^\varepsilon)\|_{L^2(0,T;(W^{1,\infty}(\Omega))^*)} \le c, \tag{19}$$

where $c > 0$ is a constant depending only on the given data and is independent of ε. Now, we show that $D_i(u_i^\varepsilon) \in L^2(0,T;H^1(\Omega))$, $i = 3,4$. To prove this, we take $\mathcal{D}_i(r) = \int_0^r D_i(s)\mathrm{d}s$. Now, we multiply third and fourth equation of (4), by $\mathcal{D}_3(u_3^\varepsilon)$ and $\mathcal{D}_4(u_4^\varepsilon)$, respectively, and integrating over Q_T and using boundedness of solutions, we obtain

$$\int_{Q_T} |\nabla \mathcal{D}_3(u_3^\varepsilon)|^2 + |\nabla \mathcal{D}_4(u_4^\varepsilon)|^2 \mathrm{d}x \le c,$$

where $c > 0$ is a constant independent of ε.

From the above results and compactness arguments, there exist limit functions (u_1, u_2, u_3, u_4) such that as $\varepsilon \to 0$, we obtain

$$\begin{aligned} u_i^\varepsilon &\rightharpoonup u_i \quad \text{weakly } * \text{ in } L^\infty(0,T;L^2(\Omega)), \\ u_i^\varepsilon &\rightharpoonup u_i \quad \text{weakly in } L^2(0,T;H^1(\Omega)), \quad i = 1,2,3,4, \\ \nabla u_i^\varepsilon &\rightharpoonup \nabla u_i \quad \text{weakly in } L^2(Q_T), \quad i = 1,2, \\ D_i(u_i^\varepsilon)\nabla u_i^\varepsilon &\rightharpoonup \xi_i \quad \text{weakly in } L^2(Q_T), \quad i = 3,4, \\ f_\varepsilon(u_i^\varepsilon) &\to u_i \quad \text{a.e. in } Q_T, \quad i = 1,2, \\ \partial_t u_i^\varepsilon &\rightharpoonup \partial_t u_i \quad \text{weakly in } L^2(0,T;(W^{1,\infty}(\Omega))^*), \quad i = 1,2,3,4. \end{aligned}$$

Similarily, we use the same method as in theorem 2 to prove $D_i(u_i)\nabla u_i = \xi_i$, $i = 3,4$. Finally, we apply Young's and Holder's inequality to get

$$\begin{aligned} \|f_\varepsilon(u_i^\varepsilon) - u_i\|_{L^2(Q_T)} &\le \sqrt{2}\|u_i^\varepsilon - u_i\|_{L^2(Q_T)} + \sqrt{2}\left\|\frac{\varepsilon u_i^\varepsilon u_i}{1+\varepsilon u_i^\varepsilon}\right\|_{L^2(Q_T)} \\ &\le \sqrt{2}\|u_i^\varepsilon - u_i\|_{L^2(Q_T)} + \sqrt{2}\left\|\frac{\varepsilon u_i^\varepsilon u_i}{(1+\varepsilon u_i^\varepsilon)^{2/3}(\varepsilon u_i^\varepsilon)^{1-2/3}}\right\|_{L^2(Q_T)} \\ &\le \sqrt{2}\|u_i^\varepsilon - u_i\|_{L^2(Q_T)} + \sqrt{2}\varepsilon^{2/3}\left\|(u_i^\varepsilon)^{2/3}u_i\right\|_{L^2(Q_T)} \\ &\le \sqrt{2}\|u_i^\varepsilon - u_i\|_{L^2(Q_T)} + \sqrt{2}\varepsilon^{2/3}\|u_i^\varepsilon\|^{2/3}_{L^\infty(0,T;L^2(\Omega))}\|u_i\|_{L^2(0,T;L^6(\Omega))}. \end{aligned} \tag{20}$$

By the Sobolev embedding $(H^1(\Omega) \subset L^6(\Omega))$ we deduce from (20) that $f_\varepsilon(u_i^\varepsilon) \to u_i$, $i = 1,2,3,4$ a.e. in Q_T and strongly in $L^r(Q_T)$ for all $r \in [1,2]$. Therefore, we prove that there exists a weak solution (u_1, u_2, u_3, u_4) to the system (2) in the sense of definition 1. □

4 Existence of optimal control

In this section, we study the existence of optimal solution of the optimal control problem. Then, we derive the adjoint problem and the optimality conditions for the optimal control. The goal is to minimize the functional (1) subject to state equations with respect to input rate v. Introducing the reduced cost functional as follows:

$$J(v) := \hat{J}(u_1, v). \tag{21}$$

Theorem 3. *Suppose* (u_1, u_2, u_3, u_4) *are the weak solutions of the system* (2), *then there exists an optimal solution* v^* *of the optimal control problem* (21).

Proof. The main goal of this theorem is to prove that there exists an optimal control v^* such that $J(v^*) = \inf_v J(v)$. Since the functional J is bounded, there exists a minimizing sequence (v_n) such that $J(v_n) \to \inf J(v)$ and

$$\inf_v J(v) \leq J(v_n) \leq \inf_v J(v) + \frac{1}{n},,$$

for $n \geq 1$. Since the sequence (v_n) is bounded, we extract a subsequence denoted by (v_n) such that $v_n \rightharpoonup v^*$ in $L^2(Q_T)$. Furthermore, replacing (u_1, u_2, u_3, u_4, v) in (2) by $(u_{1,n}, u_{2,n}, u_{3,n}, u_{4,n}, v_n)$ and passing the limits theorem 1, we have that $(u_1^*, u_2^*, u_3^*, u_4^*, v^*)$ satisfies (2). Further, using the lower-semicontinuity on L^2- norm, we get,

$$J(v^*) \leq \lim_{n\to\infty} \inf J(v_n) = \min_v J(v).$$

Finally, we get $v^* := v$ is an optimal solution of (21). □

4.1 Optimality conditions and adjoint problem

Define the Lagrangian function as follows:

$$\begin{aligned}
&L\left(u_1, u_2, u_3, u_4, p_1, p_2, p_3, p_4, v\right) = \\
&\frac{A}{2}\int_{Q_T} |u_1 - u_{1Q}|^2 \mathrm{d}x\, \mathrm{d}t + \frac{B}{2}\int_{\Omega} |u_1(T) - u_{1T}|^2 \mathrm{d}x + \frac{C}{2}\int_{Q_T} |v - v_d|^2 \mathrm{d}x\, \mathrm{d}t \\
&-\int_{Q_T} \partial_t p_1 u_1 \mathrm{d}x\, \mathrm{d}t - D_1 \int_{Q_T} \Delta p_1 u_1 + \int_{Q_T} ((a_1 u_1 + u_2)\nabla u_1 + u_1 \nabla u_2)\cdot \nabla p_1 \mathrm{d}x\, \mathrm{d}t \\
&-\int_{\Gamma_T} ((a_1 u_1 + u_2)\nabla u_1 + u_1 \nabla u_2) p_1 \mathrm{d}y\, \mathrm{d}t - \int_{Q_T} \alpha_1 u_1 (1 - b u_1) p_1 \mathrm{d}x\, \mathrm{d}t \\
&+\int_{Q_T} c_1 u_2 u_1 p_1 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} K_T u_4 u_1 p_1 \mathrm{d}x\, \mathrm{d}t \\
&-\int_{Q_T} \partial_t p_2 u_2 \mathrm{d}x\, \mathrm{d}t - D_2 \int_{Q_T} \Delta p_2 u_2 + \int_{Q_T} (u_2 \nabla u_1 + (u_1 + a_2 u_2)\nabla u_2)\cdot \nabla p_2 \mathrm{d}x\, \mathrm{d}t \\
&-\int_{\Gamma_T} (u_2 \nabla u_1 + (u_1 + a_2 u_2)\nabla u_2) p_2 \mathrm{d}y\, \mathrm{d}t - \int_{Q_T} c_2 u_2 (1 - d u_2) p_2 \mathrm{d}x\, \mathrm{d}t \\
&+\int_{Q_T} \mu u_2 p_2 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} \rho u_1 u_2 p_2 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} K_N (1-\nu) u_4 u_2 p_2 \mathrm{d}x\, \mathrm{d}t \\
&-\int_{Q_T} \partial_t p_3 u_3 \mathrm{d}x\, \mathrm{d}t - \int_{Q_T} \nabla\cdot (D_3(u_3)\nabla p_3) u_3 \mathrm{d}x\, \mathrm{d}t \\
&+\int_{\Gamma_T} u_3 (D_3(u_3))\nabla p_3 \mathrm{d}y\, \mathrm{d}t - \int_{\Gamma_T} (D_3(u_3)\nabla u_3) p_3 \mathrm{d}y\, \mathrm{d}t - \int_{Q_T} \alpha_2 u_3 p_3 \mathrm{d}x\, \mathrm{d}t \\
&+\int_{Q_T} \beta u_3 p_3 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} K_C (1-\nu) u_4 u_3 p_3 \mathrm{d}x\, \mathrm{d}t - \int_{Q_T} \partial_t p_4 u_4 \mathrm{d}x\, \mathrm{d}t \\
&-\int_{Q_T} \nabla\cdot (D_4(u_4)\nabla p_4) u_4 \mathrm{d}x\, \mathrm{d}t + \int_{\Gamma_T} u_4 (D_4(u_4))\nabla p_4 \mathrm{d}y\, \mathrm{d}t - \int_{\Gamma_T} (D_4(u_4)\nabla u_4) p_4 \mathrm{d}y\, \mathrm{d}t \\
&+\int_{Q_T} \gamma u_4 p_4 \mathrm{d}x\, \mathrm{d}t - \int_{Q_T} v p_4 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} k_T u_1 u_4 p_4 \mathrm{d}x\, \mathrm{d}t.
\end{aligned}$$

Theorem 4. *If* $(u_1^*, u_2^*, u_3^*, u_4^*)$ *and* v^* *is an optimal solution of the system* (2) *and optimal control of* (1) *respectively, then there exists the adjoint solution* (p_1, p_2, p_3, p_4) *of the following system:*

$$\begin{aligned}
&-\partial_t p_1 - D_1 \Delta p_1 + (a_1 \nabla u_1 + \nabla u_2) \cdot \nabla p_1 + \nabla u_2 \cdot \nabla p_2 - \alpha_1(1-2bu_1)p_1 + c_1 u_2 p_1 + K_T u_4 p_1 \\
&+ \rho u_2 p_2 + k_T u_4 p_4 - A(u_1 - u_{1Q}) = 0, \quad \textit{in } Q_T, \\
&-\partial_t p_2 - D_2 \Delta p_2 + (\nabla u_1 + a_2 \nabla u_2) \cdot \nabla p_2 + \nabla u_1 \cdot \nabla p_1 - c_2(1-2du_2)p_2 + \mu p_2 + \rho u_1 p_2 \\
&+ K_N(1-\nu)u_4 p_2 + c_1 u_1 p_1 = 0, \quad \textit{in } Q_T, \\
&-\partial_t p_3 - \nabla \cdot (D_3(u_3)\nabla p_3) + D_3'(u_3)\nabla u_3 \cdot \nabla p_3 + \beta p_3 - \alpha_2 p_3 + K_C(1-\nu)u_4 p_3 = 0, \quad \textit{in } Q_T, \\
&-\partial_t p_4 - \nabla \cdot (D_4(u_4)\nabla p_4) + D_4'(u_4)\nabla u_4 \cdot \nabla p_4 + \gamma p_4 + k_T u_1 p_4 + K_T u_1 p_1 \\
&+ K_N(1-\nu)u_2 p_2 + K_C(1-\nu)u_3 p_3 = 0, \quad \textit{in } Q_T,
\end{aligned}$$

subject to boundary and final conditions

$$\begin{aligned}
&\frac{\partial p_1}{\partial \eta} = 0 \quad \textit{on } \Sigma_T \quad \textit{and} \quad p_1(T) = B\left(u_1(x,T) - u_{1T}(x)\right), \quad \textit{on } \Omega, \\
&\frac{\partial p_i}{\partial \eta} = 0 \quad \textit{on } \Sigma_T \quad \textit{and} \quad p_i(T) = 0, \quad \textit{on } \Omega, \quad i = 2,3,4.
\end{aligned}$$

Furthermore, the optimality condition is given by

$$v^* = v_d - \frac{p_4}{C} \quad \textit{in } Q_T, \quad \textit{provided } C \neq 0.$$

Proof. Using the Karush-Kuhn-Tucker (KKT) conditions, we obtain the optimality system by equating the partial derivatives of $L(u_1, u_2, u_3, u_4, p_1, p_2, p_3, p_4, v)$ with respect to u_1, u_2, u_3 and u_4 to zero. Now, we get

$$\begin{aligned}
\left(\frac{\partial L}{\partial u_1}, \delta u_1\right) &= \int_{Q_T} \{-\partial_t p_1 - D_1 \Delta p_1 + (a_1 \nabla u_1 + a_2 \nabla u_2) \cdot \nabla p_1 + \nabla u_2 \cdot \nabla p_2 - \alpha_1(1-2bu_1)p_1 + c_1 u_2 p_1 \\
&\quad + K_T u_4 p_1 + \rho u_2 p_2 + k_T u_4 p_4 - A(u_1 - u_{1Q})\}\delta u_1 \mathrm{d}x\,\mathrm{d}t, \\
\left(\frac{\partial L}{\partial u_2}, \delta u_2\right) &= \int_{Q_T} \{-\partial_t p_2 - D_2 \Delta p_2 + (a_3 \nabla u_1 + a_4 \nabla u_2) \cdot \nabla p_2 + \nabla u_1 \cdot \nabla p_1 - c_2(1-2du_2)p_2 + \mu p_2 \\
&\quad + \rho u_1 p_2 + K_N(1-\nu)u_4 p_2 + c_1 u_1 p_1\}\delta u_2 \mathrm{d}x\,\mathrm{d}t, \\
\left(\frac{\partial L}{\partial u_3}, \delta u_3\right) &= \int_{Q_T} \{-\partial_t p_3 - \nabla \cdot (D_3(u_3)\nabla p_3) + D_3'(u_3)\nabla u_3 \cdot \nabla p_3 + \beta p_3 - \alpha_2 p_3 \\
&\quad + K_C(1-\nu)u_4 p_3\}\delta u_3 \mathrm{d}x\,\mathrm{d}t, \\
\left(\frac{\partial L}{\partial u_4}, \delta u_4\right) &= \int_{Q_T} \{-\partial_t p_4 - \nabla \cdot (D_4(u_4)\nabla p_4) + D_4'(u_4)\nabla u_4 \cdot \nabla p_4 + \gamma p_4 + k_T u_1 p_4 + K_T u_1 p_1 \\
&\quad + K_N(1-\nu)u_2 p_2 + K_C(1-\nu)u_3 p_3\}\delta u_4 \mathrm{d}x\,\mathrm{d}t,
\end{aligned} \tag{22}$$

with

$$\begin{aligned}
&\frac{\partial p_1}{\partial \eta} = 0 \quad \text{and} \quad p_1(T) = B\left(u_1(x,T) - u_{1T}(x)\right), \\
&\frac{\partial p_2}{\partial \eta} = 0 \quad \text{and} \quad p_2(T) = 0, \\
&\frac{\partial p_3}{\partial \eta} = 0 \quad \text{and} \quad p_3(T) = 0, \\
&\frac{\partial p_4}{\partial \eta} = 0 \quad \text{and} \quad p_4(T) = 0.
\end{aligned} \tag{23}$$

From (22)-(23), we get,

$$
\begin{aligned}
&-\partial_t p_1 - D_1 \Delta p_1 + (a_1 \nabla u_1 + a_2 \nabla u_2)\cdot \nabla p_1 + \nabla u_2 \cdot \nabla p_2 - \alpha_1(1-2bu_1)p_1\\
&+ c_1 u_2 p_1 + K_T u_4 p_1 + \rho u_2 p_2 + k_T u_4 p_4 - A(u_1 - u_{1Q}) = 0, \quad \text{in } Q_T,\\
&-\partial_t p_2 - D_2 \Delta p_2 + (a_3 \nabla u_1 + a_4 \nabla u_2)\cdot \nabla p_2 + \nabla u_1 \cdot \nabla p_1 - c_2(1-2du_2)p_2\\
&+ \mu p_2 + \rho u_1 p_2 + K_N(1-\nu)u_4 p_2 + c_1 u_1 p_1 = 0, \quad \text{in } Q_T,\\
&-\partial_t p_3 - \nabla\cdot(D_3(u_3)\nabla p_3) + D_3'(u_3)\nabla u_3 \cdot \nabla p_3 + \beta p_3 - \alpha_2 p_3 + K_C(1-\nu)u_4 p_3 = 0, \quad \text{in } Q_T,\\
&-\partial_t p_4 - \nabla\cdot(D_4(u_4)\nabla p_4) + D_4'(u_4)\nabla u_4 \cdot \nabla p_4 + \gamma p_4 + k_T u_1 p_4 + K_T u_1 p_1\\
&+ K_N(1-\nu)u_2 p_2 + K_C(1-\nu)u_3 p_3 = 0, \quad \text{in } Q_T,
\end{aligned}
\tag{24}
$$

with following boundary conditions:

$$
\frac{\partial p_1}{\partial \eta} = \frac{\partial p_2}{\partial \eta} = \frac{\partial p_3}{\partial \eta} = \frac{\partial p_4}{\partial \eta} = 0 \quad \text{on } \Sigma_T. \tag{25}
$$

The above system (24) and (25) is the required dual problem for the given control problem 3 with PDE constraints (2).

Further, to find the optimality conditions, we calculate the gradient of the functional $J(v)$:

$$
\left(\frac{\partial L}{\partial v}, \delta v\right) = \int_{Q_T} \{C(v - v_d) + p_4\}\delta v \mathrm{d}x\, \mathrm{d}t \quad \text{and } \nabla J(v) = \frac{\partial L}{\partial v}.
$$

Furthermore, the optimality condition is then

$$
v^* = v_d - \frac{p_4}{C} \quad \text{in } Q_T.
$$

□

4.2 Existence of a weak solution for the adjoint problem

In this subsection, we prove the existence of solution for the system (24)-(25). Before that we give the definition of weak solution of system as follows:

Definition 2. *A weak solution of the system* (24) *is a 4-tuple* (p_1, p_2, p_3, p_4) *such that*

$$
\begin{aligned}
&p_i \in L^2(0,T; H^1(\Omega)) \cap L^\infty(0,T; L^2(\Omega)) \cap C([0,T], L^2(\Omega)),\\
&\partial_t p_i \in L^2(0,T; (W^{1,\infty}(\Omega))^*), \quad i = 1,2,3,4,
\end{aligned}
$$

and satisfying the following weak formulation:

$$
\begin{aligned}
&-\int_0^T \langle \partial_t p_1, \psi_1\rangle \mathrm{d}t + D_1 \int_{Q_T} \nabla p_1 \cdot \nabla \phi_1 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} (a_1 \nabla u_1 + a_2 \nabla u_2)\nabla p_1 \psi_1 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} \nabla u_2 \cdot \nabla p_2 \psi_1 \mathrm{d}x\, \mathrm{d}t\\
&+ \int_{Q_T} \rho u_2 p_2 \psi_1 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} k_T u_4 p_4 \psi_1 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} (-\alpha_1(1-2bu_1) + c_1 u_2 + K_T u_4) p_1 \psi_1 \mathrm{d}x\, \mathrm{d}t\\
&- A \int_{Q_T} (u_1 - u_{1Q})\psi_1 \mathrm{d}x\, \mathrm{d}t = 0,\\
&-\int_0^T \langle \partial_t p_2, \psi_2\rangle \mathrm{d}t + D_2 \int_{Q_T} \nabla p_2 \cdot \nabla \phi_2 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} (a_3 \nabla u_1 + a_4 \nabla u_2)\nabla p_2 \psi_2 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} \nabla u_1 \cdot \nabla p_1 \psi_2 \mathrm{d}x\, \mathrm{d}t\\
&+ \int_{Q_T} c_1 u_1 p_1 \psi_2 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} (-c_2(1-2du_2) + \mu + \rho u_1 + K_N(1-\nu)u_4) p_2 \psi_2 \mathrm{d}x\, \mathrm{d}t = 0,\\
&-\int_0^T \langle \partial_t p_3, \psi_3\rangle \mathrm{d}t + \int_{Q_T} D_3(u_3)\nabla p_3 \nabla \psi_3 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} D_3'(u_3)\nabla u_3 \nabla p_3 \psi_3 \mathrm{d}x\, \mathrm{d}t\\
&+ \int_{Q_T} (\beta - \alpha_2 + K_C(1-\nu)u_4) p_3 \psi_3 \mathrm{d}x\, \mathrm{d}t = 0,\\
&-\int_0^T \langle \partial_t p_4, \psi_4\rangle \mathrm{d}t + \int_{Q_T} D_4(u_4)\nabla p_4 \nabla \psi_4 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} D_4'(u_4)\nabla u_4 \nabla p_4 \psi_4 \mathrm{d}x\, \mathrm{d}t\\
&+ \int_{Q_T} (K_T u_1 p_1 + K_N(1-\nu)u_2 p_2 + K_C(1-\nu)u_3 p_3)\psi_4 \mathrm{d}x\, \mathrm{d}t + \int_{Q_T} (\gamma + k_T u_1) p_4 \psi_4 \mathrm{d}x\, \mathrm{d}t = 0,
\end{aligned}
$$

$\forall$, $\psi_i \in L^2(0,T; W^{1,\infty}(\Omega))$, $i = 1$ *to* 4.

Theorem 5. *If the hypotheses of theorem* 1 *are true and* (u_1, u_2, u_3, u_4) *is a weak solution of the system* (2)*, then there exists a weak solution to the system* (24)-(25)*.*

The proof of the above theorem is based on the Faedo-Galerkin method. Then, to show the existence of solution to the adjoint system (24) with (25), we consider the regularized system. First, we prove the existence of solutions of the regularization system. Then, we show the existence of solutions of adjoint problem by taking the parameter $\varepsilon \to 0$. Therefore, proceeding as in theorem 1, we prove the existence solution interval $(0, T]$ for the Faedo-Galerkin solution and also the global existence of the Faedo-Galerkin weak solution, so we excluded the details of the proof.

5 Numerical experiments

In this section, we perform a series of numerical computations to understand the impact of control terms in the tumor invasion system. Here, all numerical computations are performed in the unit square domain $\Omega = [0,1] \times [0,1]$ and $T > 0$. We used Freefem++ [50] for finite element scheme and UMFPACK [51,52] to solve the resulting algebraic system. All computations are carried out using Intel (R) Core (TM) i7-7700 CPU with 3.60 GHz and 8 GB RAM. We considered the following parameter values for the proposed control problem in all our computations as in [48]. However, without loss of generality, we assumed diffusion and cross-diffusion coefficients according to the theoretical results in sect. 2:

$$\begin{aligned}
&D_1 = 10^{-8}, \quad D_2 = 10^{-7}, \quad D_3 = 10^{-6}, \quad D_4 = 10^{-6}, \quad K_C = 0.6, \quad a_1 = 1.2,\\
&\alpha_1 = 4.31 \times 10^{-1}, \quad b = 1.02 \times 10^{-14}, \quad c_1 = 3.41 \times 10^{-10}, \quad k_T = 3.2 \times 10^{-9},\\
&K_T = 0.8, \quad a_2 = 1.2, \quad c_2 = 4.12 \times 10^{-2}, \quad \mu = 4.12 \times 10^{-2}, \quad d = 1.02 \times 10^{-14},\\
&\rho = 2.00 \times 10^{-11}, \quad K_N = 0.6, \quad \nu = 0.8, \quad \alpha_2 = 2.4 \times 10^{-2}, \quad \beta = 1.2 \times 10^{-2},\\
&A = 0.1, \quad B = 0.1, \quad C = 0.1.
\end{aligned}$$

We assumed the no-flux Neumann boundary conditions for all unknowns with the following initial conditions:

$$\begin{aligned}
u_1(x,0) &= 1.01 \exp\left(\frac{-r^2}{\epsilon_1}\right), \qquad u_2(x,0) = 0.01\left(1 - u_1(x,0)\right),\\
u_3(x,0) &= 1 - 0.99 \exp\left(\frac{-r^2}{\epsilon_1}\right), \qquad u_4(x,0) = 0.95 \exp\left(\frac{-r^2}{\epsilon_2}\right),\\
u_{1Q} &= 1.01 \exp\left(\frac{-r^2}{\epsilon_1}\right), \qquad v_d = 0.9 \exp\left(\frac{-r^2}{\epsilon_1}\right),
\end{aligned}$$

where $r^2 = (x - 0.5)^2 + (y - 0.5)^2$, $\epsilon_1 = 0.005$ and $\epsilon_2 = 0.075$. Further, for simplicity, we assume $D_3(u_3) = D_3$ and $D_4(u_4) = D_4$ in numerical computations. The above initial conditions for each unknown u_1, u_2, u_3 and u_4 are depicted in fig. 1. Here, we briefly mention the numerical procedure algorithm to solve the state and costate system of proposed control problem.

Algorithm

---

1. Fix the δt, tol, Ω.
2. Pick up an initial guess of the control v_h^0.
3. Initialize the state $u_{j,0}$ and adjoint state $p_{j,N}$. Set the final time T.
   For $n = 1, 2, \ldots, N$ do
4. With the known control v^n, solve the state equation forward time for the state variables.
5. With known state variable, solve the adjoint equation backward in time for the adjoint variables.
6. Update the optimal control $v_h^{n+1} = v_h^n - \frac{1}{C}(C(v^n - v_d) + p_4^n)$.
7. Calculate the $tol = \|v_h^{n+1,m} - v_h^{n+1,m-1}\|_2$. Iterate until the tol is less than prescribed value.

End

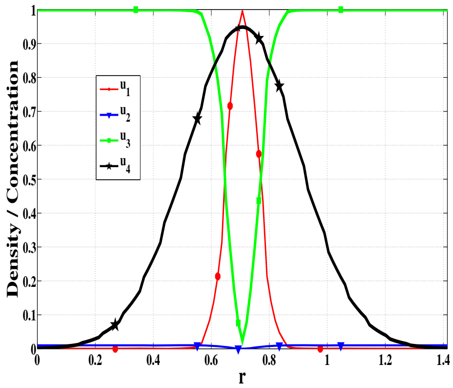

Fig. 1. Assumed initial conditions of unknowns u_1, u_2, u_3 and u_4 of the proposed control problem.

In this algorithm, we first fix the values of $\delta_t = 0.1$, $tol = 10^{-3}$, $\Omega = [0,1] \times [0,1]$ and $T = 5$. We discretize the unit square domain using triangular elements with characteristic element length 120×120 and a uniform mesh size $h = 0.0117851$. We used 14641 degrees of freedom for each unknown in all computations. First, we fix an initial guess the control variable $v_h^0 = 0$. Further, we initialize the state unknowns $u_{j,0}$, $j = 1,2,3,4$ and the adjoint unknowns $p_{j,N}$, $j = 1,2,3,4$. For known control v, we solve the state equation forward in time, Further, an iteration of fixed point type is proposed to handle the nonlinear terms of the system as in [7,8]. In addition, we iterate until the residual is less than the prescribed threshold value (10^{-6}) or the given maximal number of iterations is reached. All our computations are completed within 3 or 4 iterations. For known state variable, solve the adjoint equation backward in time. Now, we update the optimal control and calculate the tol. We iterate until the tol is reached less than prescribed value 10^{-3}. In this proposed algorithm, iterations are completed within 3 iterations for all our simulations.

5.1 Observations on effects of optimal control without cross-diffusion

The computationally obtained numerical results of the cancer cell density, immune cell density, circulating lymphocyte density and the chemotherapeutic drug concentration without cross-diffusion effect at various dimensionless time $T = 1,3,5$ are depicted in figs. 2 and 3. Simulations are performed for the above parameter values with and without control variable in the proposed cancer invasion system. In these figures, solid line represents the density/concentration without control variable. Similarly, dashed line represents the density/concentration with control variable.

In fig. 2, columns (i) and (ii), respectively, represent the evolution of density of cancer cells and immune cells at $T = 1,3$ and 5. Similarly, in fig. 3, columns (i) and (ii), respectively, represent the evolution of density of circulating lymphocyte and concentration of drug at $T = 1,3$ and 5. In all these figures, effect of control is compared with absence of control variable in the proposed system. First, we observed that there is no huge morphological change in the density of cancer cells from the initial density at time $T = 1,3$ and 5. It occurred due to the absence of the cross diffusion terms. Figure 2 (column (i)) clearly indicates that the introduction of a control variable in the chemotherapy treatment results in reduction of density of cancer cells at $T = 3$ and 5. It means that density of cancer cells (u_1) decreases gradually than without control for increased in treatment duration. For example, see the time instance at $T = 3$ and 5 in fig. 2 (column (i)). The density of immune cells remain same in all time instances, see fig. 2 (column (ii)) with/without control terms. The population of immune cells not increased may be the impact of treatment side effects.

Further, in simulations, we observed that density of lymphocyte remain same from the initial density, see fig. 3 (column (i)). It means that density of lymphocyte level rebound to normal level after recover from the infection. Lymphocyte counts indicates that are either too low or too high density may signify patient have an infection or mild illness. Finally, we have seen very important observation in drug concentration with control variable.

Chemotherapy drugs are reducing the production of cancer cells with and without control variable in the system, see fig. 3 (column (ii)). However, presence of control variable increases the amount of drug when there is large density of cancer cells, see fig. 3 (column (ii)) at $T = 3$ and 5. The concentration of drugs gradually decreases to zero, when the control term did not involve in the system. We noticed that level of drug to be taken is reduced drastically in the absence of control variable even there is large density of cancer cells, see fig. 3 (column (ii)) solid lines.

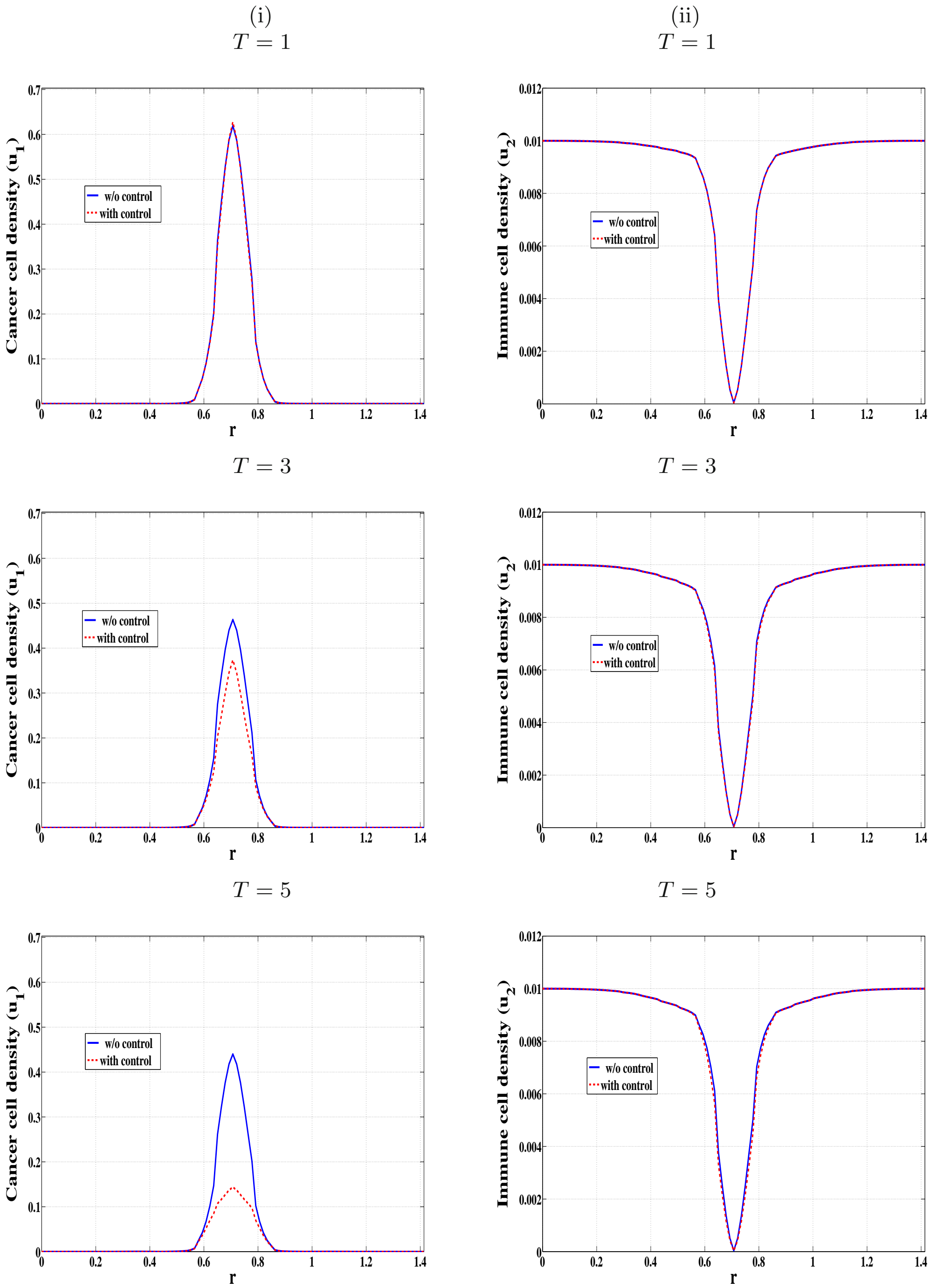

Fig. 2. Sequence of images in columns (i) and (ii), shows the evolution of u_1 and u_2, respectively, at different instances $T = 1, 3, 5$ along the line $y = x$. Solid lines: density without optimal control. Dashed lines: density with optimal control. All other parameters of the model (2) are fixed as in sect. 5.

5.2 Observations on effects of optimal control with cross-diffusion

In this section, observations of the dynamical behavior of cancer cells in the presence of immune cells, circulating lymphocyte and the chemotherapeutic drug concentration with cross-diffusion effect is given by the numerical simulations of the proposed control model. Further, all the computations results are depicted in figs. 4 and 5 at dimensionless time $T = 1, 3, 5$. The initial conditions and all the parameter values of the model are assumed as in the previous section. In order to observe the cross diffusion effect, simulations are performed with and without control variable as in the previous section. Similarly, in figures, solid line represents the density/concentration without control variable and dashed line represents the density/concentration with control variable.

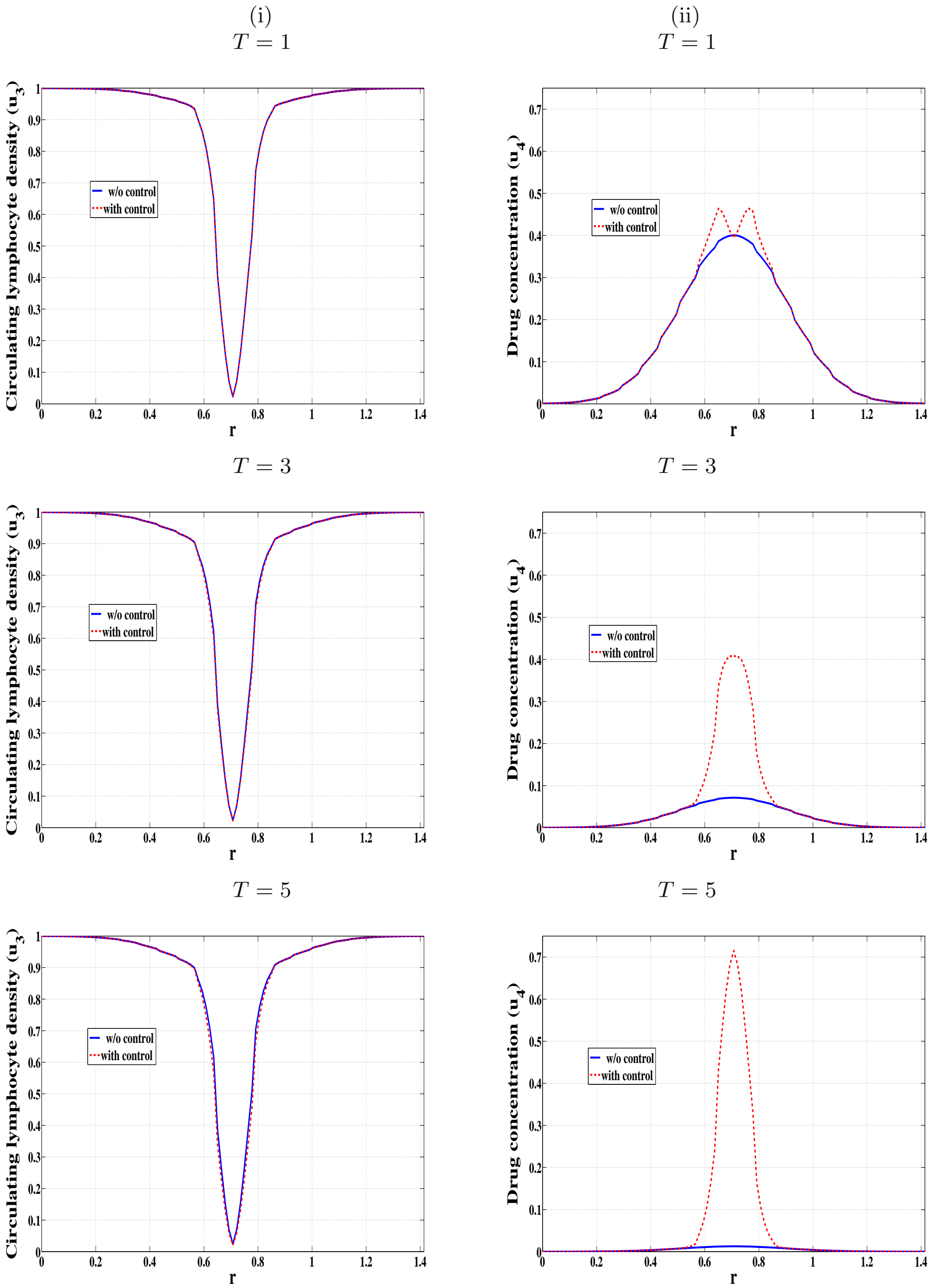

Fig. 3. Sequence of images in columns (i) and (ii), shows the evolution of u_3 and u_4, respectively, at different instances $T = 1, 3, 5$ along the line $y = x$. Solid lines: density/concentration without optimal control. Dashed lines: density/concentration with optimal control. All other parameters of the model (2) are fixed as in sect. 5.

In fig. 4, columns (i) and (ii), respectively, represent the evolution of density of cancer cells and immune cells at $T = 1, 3$ and 5 with cross-diffusion effect. Similarly, in fig. 5, columns (i) and (ii), respectively, represent the evolution of density of circulating lymphocyte and concentration of drug at $T = 1, 3$ and 5 with cross-diffusion effect. Now, we discuss the effect of cross-diffusion with and without control variables in the system. It is observed that in both the cases, density of cancer cells resulted in appreciable decreases from initial density in population due to the cross-diffusion effect, see fig. 4 (column (i)) at $T = 1, 3$ and 5. However, all the strategies are effectively restrain invasion of cancer cells, they cannot totally eliminate a large tumor during the course of treatment. Eventhough density of cancer cells is less, control variable in the chemotherapy treatment reduce the cancer cells population than in the case without control, see fig. 4 (column (i)) at $T = 1, 3$ and 5.

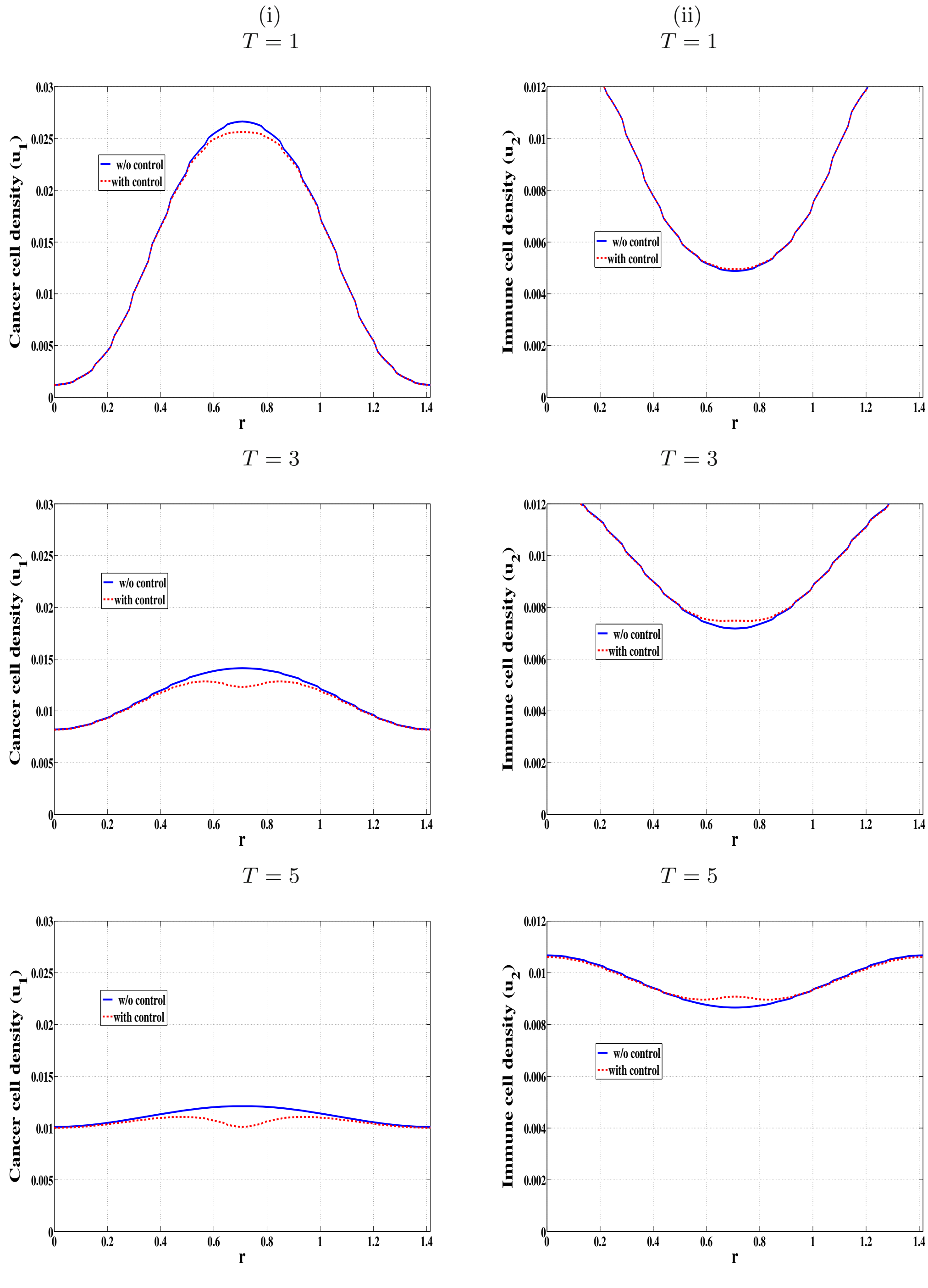

Fig. 4. Sequence of images in columns (i) and (ii), shows the evolution of u_1 and u_2, respectively, at different instances $T = 1, 3, 5$ along the line $y = x$. Solid lines: density without optimal control. Dashed lines: density with optimal control. All other parameters of the model (2) are fixed as in sect. 5.

Furthermore, the density of immune cells increases when time T increases, see fig. 4 (column (ii)) due to the cross-diffusion effect. Eventually, it decreases the population cancer cells, see fig. 4 (columns (i) and (ii)). In particular, the density of cancer cells decrease whenever there is increase in the population of immune cells. Increase in the immune cells can help to fight against cancer cells to destroy them. It delineates that, the influence of control with cross-diffusion plays a vital role in the decreasing the cancer cells and increasing the growth of the immune cells.

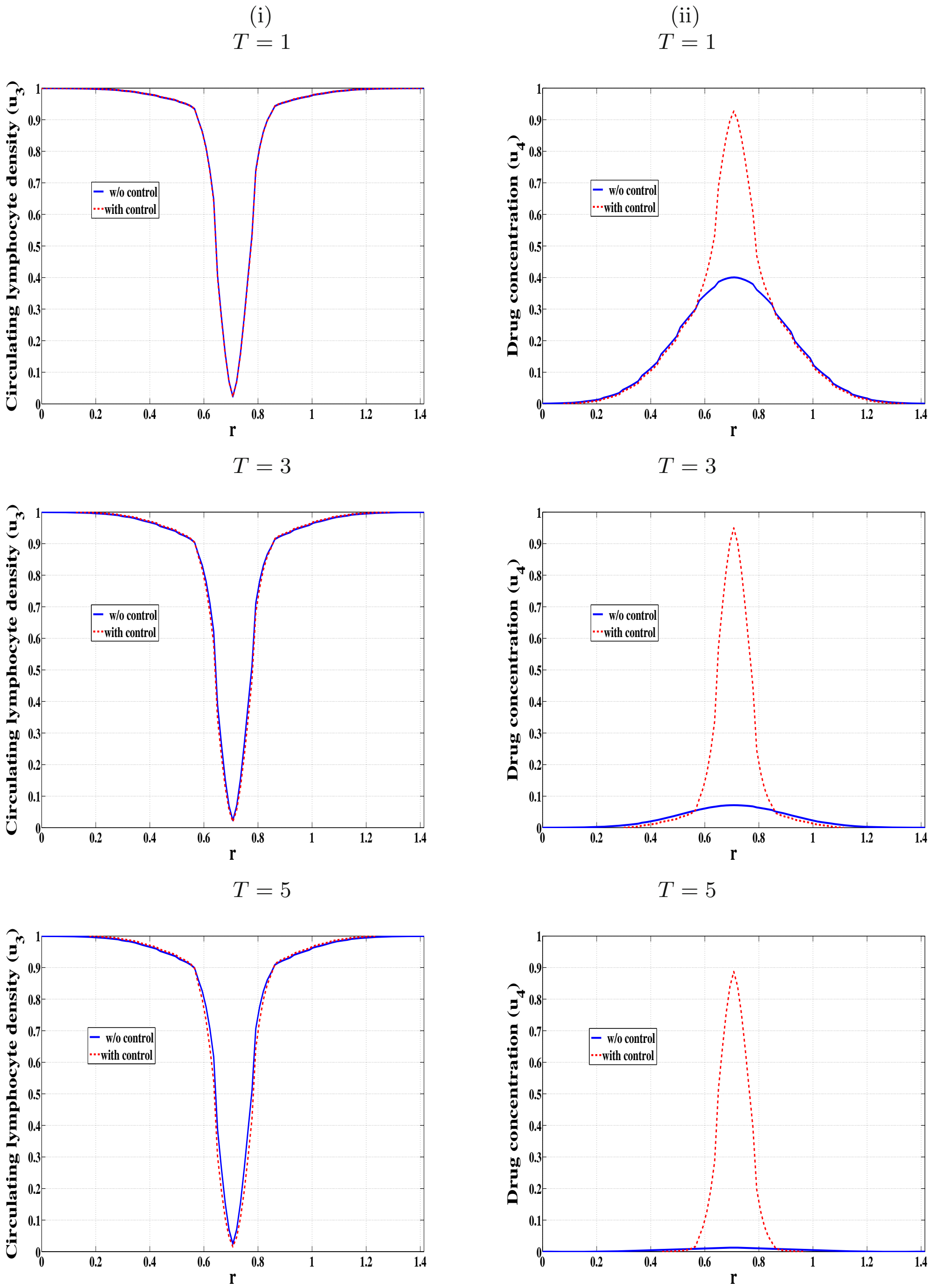

Fig. 5. Sequence of images in columns (i) and (ii), shows the evolution of u_3 and u_4, respectively, at different instances $T = 1, 3, 5$ along the line $y = x$. Solid lines: density/concentration without optimal control. Dashed lines: density/concentration with optimal control. All other parameters of the model (2) are fixed as in sect. 5.

Finally, similar morphological changes also observed in density of circulating lymphocyte and chemotherapy drug concentration as in the previous section, see fig. 5 (columns (i) and (ii)) at $T = 1, 3$ and 5. We observed that the concentration of chemotherapeutic drugs remains maximum level (v_d) at every instance in the case of control. But the concentration of drugs gradually decreases to zero when there is no control term in the treatment. The influence of control plays a vital role in the decreasing the cancer cells and increasing the growth of the immune cells. It is clear that the presence of control function in the system, minimize the density of cancer cells compared with the case without control function.

6 Conclusion

We investigated a distributed optimal control problem constrained by the system of PDEs. The model considered here represents the tumor invasion with cross-diffusion effects. Further, the control parameter of the problem considered in drug concentration is used to minimize the growth of the tumor and side effects of drugs. The existence of a weak solution of the state system established using the Faedo-Galerkin approximation method. Moreover, we derived the first-order necessary optimality conditions and also proved the existence of optimal control and the existence of a weak solution of the adjoint system. Numerical simulations of the above proposed model was performed using finite element scheme in two dimensional domains. Computations are used to understand the effect of cross-diffusion for the considered model. We observed that density of cancer cells minimized with control function and cross-diffusion effect. Furthermore, concentration of chemotherapeutic drug varies in both the case without control and with control under the physical limitations on control. Finally, numerical results suggested that the cross-diffusion with control function is more effective to minimize the invasion of tumor cells. However, all these effects may not be enough to eliminate the entire cancer cells from the body.

The authors would like to thank the anonymous referee for the comments and suggestions which improved the quality of this article. The first and second authors are thankful to the Ministry of Human Resources Development (MHRD) and National Institute of Technology Goa, India for awarding Junior Research Fellowship.

References

1. A.R.A. Anderson, Math. Med. Biol. **22**, 163 (2005).
2. A.R.A. Anderson, M.A.J. Chaplain, E.L. Newman, R.J.C. Steele, A.M. Thompson, Comput. Math. Methods Med. **2**, 129 (2000).
3. R.P. Araujo, D.L.S. McElwain, Bull. Math. Biol. **66**, 1039 (2004).
4. N. Bellomo, N. Li, P.K. Maini, Math. Models Methods Appl. Sci. **18**, 593 (2008).
5. M.A.J. Chaplain, M. Lachowicz, Z. Szymańska, Math. Models Methods Appl. Sci. **21**, 719 (2011).
6. H. Enderling, M.A.J. Chaplain, Curr. Pharm. Des. **20**, 4934 (2014).
7. S. Ganesan, L. Shangerganesh, Commun. Nonlinear. Sci. Numer. Simul. **46**, 135 (2017).
8. S. Ganesan, L. Shangerganesh, Comput. Math. Appl. **73**, 2603 (2017).
9. R.A. Gatenby, E.T. Gawlinski, Cancer Res. **56**, 5745 (1996).
10. S. Eikenberry, C. Thalhauser, Y. Kuang, PLoS Comput. Biol. **5**, e1000362 (2009).
11. H. Chen, M.T. Kuo, Oncotarget **8**, 62742 (2017).
12. H.C. Wei, J.L. Yu, C.Y. Hsu, Comput. Math. Methods Med. **2017**, 2906282 (2017).
13. L.G. de Pillis, W. Gu, A.E. Radunskaya, J. Theor. Biol. **238**, 841 (2006).
14. L.G. de Pillis, A.E. Radunskaya, J. Theor. Med. **3**, 79 (2001).
15. S. Sharma, G. Samanta, Differ. Equ. Dyn. Syst. **24**, 149 (2016).
16. G.I. Bell, Math. Biosci. **16**, 291 (1973).
17. N. Stepanova, Biophysics **24**, 917 (1980).
18. S. Michelson, B. Glicksman, J. Theor. Biol. **128**, 233 (1987).
19. U. Forys, J. Waniewski, P. Zhivkov, J. Biol. Syst. **14**, 13 (2006).
20. A. Ciancio, A. Quartarone, UPB Sci. Bull. Ser. A **75**, 125 (2013).
21. C. Cattani, A. Ciancio, A. de Onofrio, Math. Comput. Model. **52**, 62 (2010).
22. V.A. Kuznetsoz, L.A. Makalkin, M.A. Talor, A.S. Perelson, Bull. Math. Biol. **56**, 295 (1994).
23. L. Pang, Z. Zhao, X. Song, Chaos, Solitons Fractals **87**, 293 (2016).
24. P.M. Glassman, J.P. Balthasar, Cancer Biol. Med. **11**, 20 (2014).
25. G.J. Weiner, Nat. Rev. Cancer **15**, 361 (2015).
26. V. Anaya, M. Bendahmane, M. Sepulveda, Math. Models Methods Appl. Sci. **20**, 731 (2010).
27. P. Hinow, P. Gerlee, L.J. McCawley, V. Quaranta, M. Ciobanu, S. Wang, J.M. Graham, B.P. Ayati, J. Claridge, K.R. Swanson, M. Loveless, Math. Biosci. Eng. **6**, 521 (2009).
28. K.M. Owolabi, K.C. Patidar, A. Shikongo, Commun. Math. Biol. Neurosci. **2018**, 21 (2018).
29. M. Bendahmane, M. Langlais, J. Evol. Equ. **10**, 883 (2010).
30. M. Bendahmane, T. Lepoutre, A. Marrocco, B. Perthame, J. Math. Pures Appl. **92**, 651 (2009).
31. L. Chen, A. Jungel, J. Differ. Equ. **224**, 39 (2006).
32. M. Delgado, M. Montenegro, A. Suarez, J. Differ. Equ. **246**, 2131 (2009).
33. G. Galiano, Comput. Math. Appl. **64**, 1927 (2012).
34. R. Ruiz-Baier, C. Tian, Nonlinear Anal. Real World Appl. **14**, 601 (2013).

35. G. Marinoschi, J. Biol. Dyn. **7**, 88 (2013).
36. A.L.A. de Araujo, P.M.D. de Magalhaes, J. Math. Anal. Appl. **421**, 842 (2015).
37. P. Colli, G. Gilardi, E. Rocca, J. Sprekels, Nonlinearity **30**, 2518 (2017).
38. T. Galochkina, A. Bratus, V.M.P. Garcia, Math. Biosci. **267**, 1 (2015).
39. S. Esmaili, M.R. Eslahchi, J. Optim. Theory Appl. **173**, 1013 (2017).
40. A. Belmiloudi, Int. J. Biomath. **10**, 1750056 (2017).
41. D.A. Knopoff, D.R. Fernandez, G.A. Torres, C.V. Turner, Comput. Math. Appl. **66**, 1104 (2013).
42. U. Ledzewicz, M. Naghnaeian, H. Schattler, J. Math. Biol. **64**, 557 (2012).
43. U. Ledzewicz, H. Schattler, J. Optim. Theory Appl. **153**, 195 (2012).
44. M. Bendahmane, N. Chamakuri, E. Comte, B.E. Ainseba, J. Math. Anal. Appl. **437**, 972 (2016).
45. A.A.I. Quiroga, D. Fernandez, G.A. Torres, C.V. Turner, Appl. Math. Comput. **270**, 358 (2015).
46. S.P. Chakrabarty, F.B. Hanson, Math. Biosci. **219**, 129 (2009).
47. E. Sakine, M.R. Eslahchi, Int. J. Control **92**, 2712 (2018).
48. P. Liu, X. Liu, Chaos, Solitons Fractals **98**, 7 (2017).
49. M. Bendahmane, K.H. Karlsen, Netw. Heterog. Media **1**, 185 (2006).
50. F. Hecht, J. Numer. Math. **20**, 251 (2012).
51. T.A. Davis, ACM Trans. Math. Softw. **30**, 196 (2004).
52. T.A. Davis, ACM Trans. Math. Softw. **30**, 167 (2004).