J. Math. Anal. Appl. 421 (2015) 842–877

Contents lists available at ScienceDirect

Journal of Mathematical Analysis and Applications

www.elsevier.com/locate/jmaa

Existence of solutions and optimal control for a model of tissue invasion by solid tumours ☆

Anderson L.A. de Araujo [a,*], Paulo M.D. de Magalhães [b]

[a] *Departamento de Matemática, Universidade Federal de Viçosa, MG, Brazil*
[b] *Departamento de Matemática, Universidade Federal de Ouro Preto, MG, Brazil*

ARTICLE INFO

Article history:
Received 19 August 2013
Available online 25 July 2014
Submitted by B. Kaltenbacher

Keywords:
Fixed point theorem
Optimal control
Tumour invasion of tissue

ABSTRACT

In this paper we study the distributed optimal control problem for the two-dimensional mathematical model of cancer invasion. Existence of optimal state-control and stability is proved and an optimality system is derived.

1. Introduction

In this paper we will study the following system of equations

$$\begin{cases} \partial_t n - D_n \Delta n = -\chi \nabla (n \nabla f), \\ \partial_t f = -\alpha m f, \\ \partial_t m - D_m \Delta m = \mu n - \lambda m + u, \\ \partial_t c - D_c \Delta c = \beta f - \gamma n - \sigma c. \end{cases} \tag{1.1}$$

This model, with $u \equiv 0$, was proposed by Anderson [2]. Here the system holds in $Q = \Omega \times (0, T)$, Ω a spatial domain in $\mathbb{R}^2$, u is the control variable, D_n, D_m, D_c, χ, α, μ, λ, β, γ and σ are positive constants. The system (1.1) is supplemented with the following boundary conditions

$$\begin{aligned} (D_n \nabla n - \chi n \nabla f) \cdot \eta = 0 \quad &\text{on } S = \partial\Omega \times (0, T), \\ D_m \nabla m.\eta = D_c \nabla c.\eta = 0 \quad &\text{on } S, \end{aligned} \tag{1.2}$$

where η is the unit normal vector on $\partial\Omega$ and initial conditions

☆ The first author was supported in part by FAPESP, Brazil, grant 2013/22328-8.
* Corresponding author.
E-mail addresses: anderson.araujo@ufv.br (A.L.A. de Araujo), pmdm@iceb.ufop.br (P.M.D. de Magalhães).

http://dx.doi.org/10.1016/j.jmaa.2014.07.038
0022-247X/

$$n(0) = n_0, \qquad m(0) = m_0, \qquad f(0) = f_0, \qquad c(0) = c_0 \quad \text{on } \Omega. \tag{1.3}$$

This model belongs to the wide class of chemotaxis models. There exists a vast literature concerning mathematical analysis of different reaction–diffusion–taxis models, with a generic mathematical models given by

$$\begin{cases} \partial_t n - D_n \Delta n = -\nabla \cdot \big(\chi(f) n \nabla f\big) + F_1(n, f, m), \\ \partial_t f = F_2(f, m), \\ \partial_t m - D_m \Delta m = F_3(n, f, m). \end{cases} \tag{1.4}$$

The reaction–diffusion–taxis models have been applied to describe the cancer invasion, angiogenesis, etc., see for example [2,4,6,7] and references therein.

The study of optimal control for chemotaxis equations is present in the literature. For example, Ryu and Yagi [22] studied the optimal control problem for the Keller–Segel equations to describe the aggregation process of the cellular slime molds by chemical attraction (see also Ryu [21]):

$$\text{Minimize } J(u)$$

with the cost functional $J(u)$ of the form

$$J(u) := \int_0^T \big\| y(u) - y_d \big\|^2_{H^1(\Omega)} dt + \gamma \int_0^T \|u\|^2_{H^\epsilon(\Omega)} dx dt, \quad u \in L^2\big(0, T; H^\epsilon(\Omega)\big),$$

where $y = y(u)$ is governed by the Keller–Segel equations

$$\begin{cases} \partial_t y = a\Delta y - b\nabla(y\nabla\rho) & \text{in } \Omega \times (0, T], \\ \partial_t \rho = d\Delta\rho + fy - g\rho + u & \text{in } \Omega \times (0, T], \\ \dfrac{\partial y}{\partial \eta} = \dfrac{\partial \rho}{\partial \eta} = 0 & \text{on } \partial\Omega \times (0, T], \\ y(x, 0) = y_0(x), \quad \rho(x, 0) = \rho_0(x) & \text{in } \Omega. \end{cases} \tag{1.5}$$

Here, Ω is a bounded region in $\mathbb{R}^2$ of class C^3, where a, b, d, f and g are assigned positive values, γ is a given nonnegative constant, $u \geq 0$ is a control function in a bounded subset and ϵ is a fixed exponent such that $0 < \epsilon < 1/2$.

Aggregation of cellular slime mold is known as a model of self organization by cell interaction mediated by the chemical substance cAMP. The authors are concerned with the question of whether one can control the aggregation of cells by cAMP. For simplicity they consider a distributed, optimal control problem in the region Ω with the cost functional $J(u)$ above. The existence of an optimal control and the necessary first-order condition satisfied by the optimal control was verified. The results obtained by these authors where the main motivation for our study.

In Vilas et al. [26], only numerical methods were used for the study of systems described by coupled sets of partial and ordinary differential equations of the form:

$$\begin{cases} \partial_t x = \nabla \cdot (k\nabla x) - \nabla \cdot (\mathbf{v}x) + f(x, y, u), \\ \partial_t y = g(x, y, u) \end{cases} \tag{1.6}$$

where $u(t)$ represent the control variables vector. The state variables are split into spatially distributed $x(\xi, t)$ and lumped $y(t)$ variables, $f(x, y, u)$ and $g(x, y, u)$ are two given nonlinear functions which may represent, for instance, chemical reactions.

Mathematical models for cancer chemotherapy treatments have a long history (for a survey of the studies see, for example [12] and [24]). In Bahrami and Kim [3] the authors apply engineering optimal control theory to investigate the drug regimen for reducing an experimental tumor cell population. However, Swan and Vincent [25] were the first to utilize engineering optimal control theory for a chemotherapy problem involving a human tumor. While biomedical research concentrates on the development of new drugs and experimental (in vitro) and clinical (in vivo) procedures to determine their treatment schedules, the analysis of models can assist in testing various treatment strategies searching for optimal ones, see also Swan [24]. In view of the biological motivations and the studies done in [2] and [24], we have opted to place the control u in the third equation give in (1.1).

As a purely mathematical study, we could have chosen to apply one or more controls as in [26], but we decided to apply a single control to measure the difficulty of the problem so that in the future we will be able to study controllability issues associated with system (1.1), that is, prove that in finite time T the solution n satisfies $n(x,T) = 0$. This is a delicate problem when considered from a purely mathematical standpoint as well as a very interesting problem from a biological perspective.

As measure of performance we use the following cost functional

$$J[n,f,m,c;u] := \frac{\alpha_1}{2}\int_0^T\int_\Omega |n-n_d|^2 dxdt + \frac{\alpha_2}{2}\int_0^T\int_\Omega |f-f_d|^2 dxdt + \frac{\alpha_3}{2}\int_0^T\int_\Omega |m-m_d|^2 dxdt + \frac{\alpha_4}{2}\int_0^T\int_\Omega |c-c_d|^2 dxdt + \frac{\alpha_5}{2}\int_0^T\int_\Omega |u|^4 dxdt. \tag{1.7}$$

We consider the optimal control problem formed by state variables (n, f, m, c) and control variable u, where we seek a quintuple $(n, f, m, c; u)$ such that the functional (1.7) is minimized subject to (1.1)–(1.3) where n_d, f_d, m_d and c_d are the desired states and α_i, $i = 1, 2, 3, 4, 5$ are the positive penalty parameters which can be used to change the relative importance of the terms that appear in the definition of the functional.

In the study of the existence of a solution to system (1.1) in comparison to the A. Marciniak-Czochra and M. Ptashnyk [11], a new proof is presented in our paper, that provides more information about the solution n. In our study $n \in L^q(Q)$ for every $q \geq 1$ with fixed regularity of the initial data. Also, being unable to apply the results of A. Marciniak-Czochra and M. Ptashnyk [11] in the system (1.1) due to the lack of logistic growth, i.e., $\mu_n n(1 - n - f)$, we were unable to apply the method of bounded invariant rectangles to the reformulated system and thus not able to prove uniform boundedness of the solution. In this paper we overcome this difficulty by proving an estimate L^q, for the value of q appropriate, under the assumption that initial data are sufficiently small and using the Leray–Schauder fixed point theorem as our main tool.

The model studied by Morales-Rodrigo [20] is very similar to the model presented in our paper, without the control term and oxygen equation, we do not apply the results obtained by the authors regarding existence because we want results of existence that apply for any fixed finite time. Whereas Morales-Rodrigo proved only a local result in Hoelder's spaces, in our study, we needed a more regularly result to the solutions to prove the necessary first-order condition by the optimal control. The studies of Corrias, Perthame and Zaag [9,10] differ from ours in part because they only consider models parabolic-elliptic system and parabolic-degenerate system as well as the Keller–Segel models and almost all models with $\Omega = \mathbb{R}^d$.

Other studies in the literature for the Keller–Segel models with or without optimal control are Lebiedz and Brandt-Pollmann [17], K.R. Fister and M.L. Mccarthy [14], Corrias, Perthame and Zaag [9], Chiu and Yu [8] and the references contained therein.

Our study differs in part from the studies so far reported in the literature, not for the existence and uniqueness of the model but for being one of the first studies that addresses optimal control for a model with haptotaxis flow characterized by the first three equations of (1.1). It is highlighted that not only the existence of an optimal control was proved but also the necessary first-order condition satisfied by the optimal control was verified. This differs even more from the studies previously presented and in this way provides a new contribution to the literature.

We note that obtaining the necessary first-order condition for an optimal control problem is important because it is useful for designing feedback controls and also in the development of more efficient and faster numerical simulations of optimal control algorithms.

For simplicity, we follow the same assumptions of [20] for the first three equations of (1.1), observing that these assumptions agree in part with the Keller–Segel model in Ryu and Yagi [22] and Ryu [21]. However, the authors did not consider the second equation of (1.1) making it different from shape of the coupling equations. The reason to adopt such assumptions is that as we wanted to prove the necessary first-order condition satisfied by the optimal controls. To do this, we needed to prove that the solution operator associated with the system (1.1), besides being well defined, needs to be Fréchet differentiable, which for more general assumptions on F_1, F_2, F_3 in (1.4) makes it much more difficult problem to be studied.

The paper is organized as follows. In Section 2 we present the notations, and recall certain concepts and results that will use. We explicitly state our technical assumptions and our main results concerning existence, regularity and uniqueness of solutions. In Section 3 we introduce a regularized problem related to (1.1)–(1.3) and we prove a result of existence of solutions to regularized problem using Leray–Schauder fixed point theorem. To investigate the existence of regularized model solutions, we change the variables so that we obtain an equivalent system with the first equation expressed in divergent form with a diagonal diffusion matrix, similar as found in [9], and more recently in [11]. Sections 4 and 5 are dedicated to the proof of our main results. In Section 6 we will study a problem of optimal control, considering it for the cost functional (1.7) associated with system (1.1)–(1.3). We prove the existence of optimal control that minimizes this functional. We also find optimal conditions that are needed to be met for each optimal control.

2. Preliminary results and the main result

Let $\Omega \subset \mathbb{R}^N$ $(N = 2)$ be an open and bounded domain with a sufficiently smooth boundary, $\partial\Omega \in C^3$ and $Q = \Omega \times (0,T)$ the space–time cylinder with lateral surface $\sum = \partial\Omega \times (0,T)$. For $t \in (0,T]$, we denote $Q_t = \Omega \times (0,t)$.

Let s be a positive integer, and let $1 \le p < \infty$. The Sobolev space $W_p^s(\Omega)$ is the set of functions defined on Ω with finite norm

$$\|u\|_{W_p^s(\Omega)} = \left(\int_\Omega \sum_{|\alpha|\le s} \left|D^\alpha u(x)\right|^p dx\right)^{1/p}, \tag{2.1}$$

where $\alpha = (\alpha_1,\dots,\alpha_N)$, α_j are nonnegative integers, $|\alpha| = \alpha_1 + \cdots + \alpha_N$, $D_k = \partial/\partial x_k$, $D^\alpha = D^{\alpha_1}\dots D^{\alpha_d}$ (the derivatives in (2.1) are understood in the sense of distributions). In the case $0 < s < 1$, the Sobolev space $W_p^s(\Omega)$ consists of functions $u \in L^p(\Omega)$ such that

$$\|u\|_{W_p^s(\Omega)} = \left(\|u\|^p_{L^p(\Omega)} + \int_\Omega\int_\Omega \frac{|u(x)-u(y)|^p}{|x-y|^{d+ps}}dxdy\right)^{1/p}. \tag{2.2}$$

For a noninteger $s > 1$ we set $s = [s] + \sigma$, where $[s]$ is the integer part of s. Then $W_p^s(\Omega)$ consists of elements $u \in W_p^{[s]}(\Omega)$ such that $D^\alpha u \in W_p^\sigma(\Omega)$ for $|\alpha| = [s]$, with the norm

$$\|u\|_{W_p^s(\Omega)} = \left(\|u\|^p_{W_p^{[s]}(\Omega)} + \sum_{|\alpha|=[s]} \left\|D^\alpha u\right\|^p_{W_p^\sigma(\Omega)}\right)^{1/p}, \tag{2.3}$$

where the norms $\|\cdot\|_{W_p^{[s]}(\Omega)}$ and $\|\cdot\|_{W_p^{\sigma}(\Omega)}$ are defined in (2.1) and (2.2) respectively. When $p = 2$ we denote $W_2^s(\Omega) = H^s(\Omega)$.

For functions depending on spatial and temporal variables we use the following functional spaces, whose ratings and definitions can be found in Ladyzhenskaya [16].

$L^{q,r}(Q)$ is the Banach space of (classes) functions $u(x,t)$ from Q to $\mathbb{R}$ measurable (in the sense of Lebesgue) whose norm is given by

$$\|u\|_{q,r,Q} = \left(\int_0^T \left(\int_\Omega |u(x,t)|^q dx\right)^{r/q} dt\right)^{1/r} \quad (q, r \geq 1).$$

For $q = r$ the notation $L^{q,q}(Q) = L^q(Q)$ is used.

$W_q^{2,1}(Q)$ is the Banach space ($q \geq 1$) of functions $u(\cdot,\cdot) \in L^q(Q)$ with generalized derivatives $D_x u, D_x^2 u, D_t u$ on $L^q(Q)$. We Consider in $W_q^{2,1}(Q)$ the norm defined by

$$\|u\|_{W_q^{2,1}(Q)} = \|u\|_{L^q(Q)} + \|D_x u\|_{L^q(Q)} + \left\|D_x^2 u\right\|_{L^q(Q)} + \|D_t u\|_{L^q(Q)}.$$

Given X, Y Banach spaces, we denote by $X \hookrightarrow Y$ the *continuous embedding* of X in Y. Next, we state the following embedding result for Sobolev spaces of type $W_p^{r,s}(Q)$. It is a particular case of Lemma 3.3 in Ladyzhenskaya et al. [16, p. 80], obtained by taking $l = 1$ and $r = s = 0$.

Lemma 2.1. *Let Ω be a domain of $\mathbb{R}^N$ with boundary $\partial\Omega$ (at least satisfying the cone property). Then for any function $u \in W_p^{2,1}(Q)$ we also have $u \in L^q(Q)$, and the following inequality is valid*

$$\|u\|_{L^q(Q)} \leq C\|u\|_{W_p^{2,1}(Q)},$$

provided that: $q = \infty$ if $p > \frac{N+2}{2}$; $q \geq 1$ if $p = \frac{N+2}{2}$ and $q = \frac{p(N+2)}{N+2-2p}$ if $p < \frac{N+2}{2}$. The constant C depends only on T, p, q, N and Ω.

Now, we will formulate one the main theorems of this paper that proves the existence and the uniqueness of solutions for the problem (1.1)–(1.3):

Theorem 2.2. *Let $\Omega \subset \mathbb{R}^2$ be a limited domain, $0 < T < \infty$ fixed, $u \in L^4(Q)$ a nonnegative function, $c_0 \in H^1(\Omega)$, $m_0 \in W_4^{3/2}(\Omega)$, $n_0 \in W_3^{4/3}(\Omega)$ and $f_0 \in H^2(\Omega) \cap W_\infty^1(\Omega)$, with $n_0, f_0, m_0 \geq 0$. Then, there exist $\xi > 0$ such that, if*

$$\|n_0\|_{L^1(\Omega)} < \xi,$$

there exist functions (f, n, m, c) satisfying:

(i) $f \in L^\infty(0, T; W_{4/3}^2(\Omega))$, $f_t \in L^2(Q)$, $f(0) = f_0$;
(ii) $n \in L^\infty(0, T; H^1(\Omega)) \cap L^q(Q)$ *for every* $q \geq 1$, $n_t \in L^2(Q)$, $n(0) = n_0$;
(iii) $m \in W_4^{2,1}(Q)$, $m(0) = m_0$;
(iv) $c \in W_2^{2,1}(Q)$, $c(0) = c_0$

such that

$$\int_0^T \int_\Omega \partial_t n \varphi dx ds + D_n \int_0^T \int_\Omega \nabla n \nabla \varphi dx ds = \chi \int_0^T \int_\Omega n \nabla f \nabla \varphi dx ds, \tag{2.4}$$

for all $\varphi \in L^2(0,T;H^1(\Omega))$.

$$\partial_t f = -\alpha m f \quad q.t.p. \text{ in } Q, \tag{2.5}$$

$$\partial_t m - D_m \Delta m = \mu n - \lambda m + u \quad q.t.p. \text{ in } Q, \tag{2.6}$$

$$\partial_t c - D_c \Delta c = \beta f - \gamma n - \sigma c \quad q.t.p. \text{ in } Q, \tag{2.7}$$

$$(D_n \nabla n - \chi n \nabla f) \cdot \eta = \nabla m \cdot \eta = \nabla c \cdot \eta = 0 \quad q.t.p. \text{ on } \partial\Omega \times (0,T). \tag{2.8}$$

Furthermore, $f \geq 0$, $n \geq 0$ *and* $m \geq 0$.

Remark 2.3. $\xi = \xi(T)$ goes to zero when T tends to infinity.

Remark 2.4. This solution is called a weak solution the problem (1.1)–(1.3) because of Eq. (2.4). Throughout this paper we will refer to the solution of any system as the solution given by (2.4)–(2.8).

Remark 2.5. The conditions $m_0 \in W_4^{3/2}(\Omega)$ and $u \in L^4(Q)$ can be replaced by the conditions $m_0 \in W_q^{2-2/q}(\Omega)$ and $u \in L^q(Q)$, with $q > 2$. It is important that the embedding $W_q^{2-2/q}(\Omega) \hookrightarrow C^1(\overline{\Omega})$ is compact ($n = 2$).

Remark 2.6. The result of Theorem 2.2 is still true if only $f_0 \in H^2(\Omega)$. The condition $f_0 \in H^2(\Omega) \cap W_\infty^1(\Omega)$ is a sufficient condition for the control problem to have a solution.

We also have the following result:

Theorem 2.7. *Let* (n_i, f_i, m_i, c_i) *be the corresponding solutions of the problem (1.1)–(1.3), founded in Theorem 2.2. Suppose further that the other conditions of Theorem 2.2 are satisfied. Then*

$$\begin{aligned}
&\|n_1 - n_2\|_{L^2(0,T;H^1(\Omega))} + \|m_1 - m_2\|_{W_2^{2,1}(Q)} + \|c_1 - c_2\|_{W_2^{2,1}(Q)} + \|f_1 - f_2\|_{L^2(0,T;W_4^1(\Omega))} \\
&\quad \leq C\|u_1 - u_2\|_{L^4(Q)},
\end{aligned}$$

where C *is a positive constant that depends on the constants of the problem and the initial data.*

In the sequel, C denotes a generic positive constant which may change from line to line.

Corollary 2.8. *If we consider the assumptions of Theorem 2.2. Then the problem (1.1)–(1.3) has a unique solution.*

3. Regularized problem

In this section we introduce a regularized problem related to (1.1)–(1.3) and will prove a result of existence of solutions applying the Leray–Schauder fixed point theorem in a form stated in Friedman [15, p. 189, Theorem 3].

Theorem 3.1 *(Leray–Schauder). Given the mapping* T *from* $X \times [a,b]$ *to* X*, where* $a, b \in \mathbb{R}$ *and* X *is a Banach space. Assume that:*

(a) *For any fixed* k, $T(x,k)$ *is a compact transformation, i.e., it is continuous and maps bounded sets into relatively compacts sets.*

(b) *For x in bounded sets of X, $T(x,k)$ is uniformly continuous in k, i.e., for any bounded set $X_0 \subset X$ and for any $\epsilon > 0$ there exists a $\delta > 0$ such that if $x \in X_0$, $|k_1 - k_2| < \delta$, $a \leq k_1, k_2 \leq b$, then $\|T(x,k_1) - T(x,k_2)\| < \epsilon$.*

(c) *There exists a (finite) constant R such that every possible solution x of $x - T(x,k) = 0$ ($x \in X$, $k \in [a,b]$) satisfies: $\|x\| \leq R$.*

(d) *The equation $x - T(x,a) = 0$ has a unique solution in X.*

Then there exists a solution of the equation $x - T(x,b) = 0$.

Now, we recall certain results that will be helpful in the introduction of such a regularized problem. Recall that there is an extension operator $\mathrm{Ext}(\cdot)$ taking any function w in the space

$$W_2^{2,1}(Q) = \{w \in L^2(Q)/D_x w,\ D_x^2 w \in L^2(Q),\ w_t \in L^2(Q)\}$$

and extending it to a function $\mathrm{Ext}(w) \in W_2^{2,1}(\mathbb{R}^{N+1})$ with compact support satisfying:

$$\|\mathrm{Ext}(w)\|_{W_2^{2,1}(\mathbb{R}^{N+1})} \leq C_{ext}\|w\|_{W_2^{2,1}(Q)}$$

with C_{ext} independent of w (see, Mikhailov [19, p. 157]).

For $\delta \in (0,1)$, let $\rho_\delta \in C_0^\infty(\mathbb{R}^{N+1})$ be a family of symmetric positive mollifier functions with compact support converging to the Dirac delta function, and denote by $*$ the convolution operation. Then, given a function $m \in W_2^{2,1}(Q)$, we define a regularization $\rho_\delta(m) \in C_0^\infty(\mathbb{R}^{N+1})$ of m by

$$\rho_\delta(m) = \rho_\delta * \mathrm{Ext}(m). \tag{3.1}$$

Now, we are in a position to define the following family of regularized problems. For $\delta \in (0,1)$, we consider the system

$$\begin{cases} \partial_t n_\delta - D_n \Delta n_\delta = -\chi \nabla(n_\delta \nabla f_\delta) & \text{in } Q, \\ \partial_t f_\delta = -\alpha \rho_\delta(m_\delta) f_\delta & \text{in } Q, \\ \partial_t m_\delta - D_m \Delta m_\delta = \mu n_\delta - \lambda m_\delta + u & \text{in } Q, \\ \partial_t c_\delta - D_c \Delta c_\delta = \beta f_\delta - \gamma n_\delta - \sigma c_\delta & \text{in } Q, \\ n_\delta(0) = n_0^\delta, \quad f_\delta(0) = f_0^\delta, & \text{in } \Omega, \\ m_\delta(0) = m_0^\delta, \quad c_\delta(0) = c_0^\delta & \text{in } \Omega, \\ (D_n \nabla n_\delta - \chi n_\delta \nabla f_\delta)\eta = D_m \nabla m_\delta.\eta = D_c \nabla c_\delta.\eta = 0 & \text{on } S. \end{cases} \tag{3.2}$$

Remark 3.2. The central idea of the study is to solve the regularized problem (3.2), to prove the existence of solutions, obtain estimates uniform in relation to parameter δ, use arguments of reflexivity and compactness to pass the limit in the regularized problem and obtain a solution of the problem (1.1)–(1.3).

Consider the following result for the regularized problem:

Proposition 3.3. *Let $\Omega \subset \mathbb{R}^2$ be a limited domain, $0 < T < \infty$ fixed, $u \in L^4(Q)$ a nonnegative function, for each $\delta \in (0,1)$, $n_0^\delta \in W_3^{4/3}(\Omega)$; $m_0^\delta \in W_4^{3/2}(\Omega)$, $c_0^\delta \in C^1(\overline{\Omega})$ and $f_0^\delta \in C^2(\overline{\Omega})$, with $n_0^\delta, f_0^\delta, m_0^\delta \geq 0$. Then, there are functions $(f^\delta, n^\delta, m^\delta, c^\delta)$ satisfying (3.2) and*

(i) *$f^\delta \in L^\infty(0,T; W_4^2(\Omega))$, $f_t^\delta \in L^2(Q)$, $f^\delta(0) = f_0^\delta$, $f^\delta \geq 0$;*
(ii) *$n^\delta \in L^3(0,T; W_3^2(\Omega))$, $n_t^\delta \in L^3(Q)$, $n^\delta(0) = n_0^\delta$, $n^\delta \geq 0$;*
(iii) *$m^\delta \in W_4^{2,1}(Q)$, $m^\delta(0) = m_0^\delta$, $m^\delta \geq 0$;*
(iv) *$c^\delta \in W_2^{2,1}(Q)$, $c^\delta(0) = c_0^\delta$.*

3.1. Preparatory results

To simplify the notation, in this sections we will omit the superscript δ of the variables n_δ, m_δ, f_δ and c_δ.

To prove Proposition 3.3 we will apply the Leray–Schauder Fixed point theorem. For this, we take $q \geq 4$ and consider the family of operators $L : [0,1] \times L^q(Q) \to L^q(Q)$ defined by, $L(l,\phi) = n$, where n is the only solution the first equation of the decoupled system

$$\begin{cases} \partial_t n - D_n \Delta n = -l\chi \nabla(n\nabla f) & \text{in } Q, \\ \partial_t f = -\alpha \rho_\delta(m) f & \text{in } Q, \\ \partial_t m - D_m \Delta m = l\mu\phi - \lambda m + u & \text{in } Q, \\ \partial_t c - D_c \Delta c = \beta f - \gamma n - \sigma c & \text{in } Q, \\ n(0) = n_0, \quad f(0) = f_0, \quad m(0) = m_0, \quad c(0) = c_0 & \text{in } \Omega, \\ (D_n \nabla n - l\chi n \nabla f)\eta = D_m \nabla m.\eta = D_c \nabla c.\eta = 0 & \text{on } S. \end{cases} \tag{3.3}$$

As $\phi \in L^q(Q)$, particularly $\phi \in L^4(Q)$, by linear theory of parabolic PDE's there is a unique $m \in W_4^{2,1}(Q)$ solving the equation

$$\begin{cases} \partial_t m - D_m \Delta m = l\mu\phi - \lambda m + u & \text{in } Q, \\ m(0) = m_0 & \text{in } \Omega, \\ D_m \nabla m.\eta = 0 & \text{on } S \end{cases} \tag{3.4}$$

and

$$\|m\|_{W_4^{2,1}(Q)} \leq C\big(\|m_0\|_{W_4^{3/2}(\Omega)} + \|\phi\|_{L^4(Q)} + \|u\|_{L^4(Q)}\big), \tag{3.5}$$

in particular $m \in W_2^{2,1}(Q)$, for more details see Ladyzenskaja [16, Theorem 9.1, p. 341] which applies to Dirichlet conditions, modified properly by observing the end of Section 9 on Chapter 4 to Neumann condition.

It follows from second equation of (3.3) that

$$f(t,x) = f_0(x) \exp\left(-\alpha \int_0^t \rho_\delta(m)(s,x)ds\right). \tag{3.6}$$

By (3.1), it follows that $|\nabla \rho_\delta(m)| \in L^\infty(Q)$ and $\Delta \rho_\delta(m) \in L^\infty(Q)$ and therefore, $|\nabla f| \in L^\infty(Q)$ and $\Delta f \in L^\infty(Q)$.

Now, consider the linear equation:

$$\begin{cases} \partial_t n - D_n \Delta n = -l\chi \nabla n \nabla f - l\chi n \Delta f & \text{in } Q, \\ n(0) = n_0 & \text{in } \Omega, \\ (D_n \nabla n - l\chi n \nabla f)\eta = 0 & \text{on } S. \end{cases} \tag{3.7}$$

As $n_0 \in W_3^{4/3}(\Omega)$, it follows from [16] that there is only one

$$n \in W_3^{2,1}(Q) \tag{3.8}$$

solution of (3.7). By Lemma 2.1 we conclude that

$$n \in L^\infty(Q). \tag{3.9}$$

From the last results we conclude that, $n(\cdot,t)\in H^1(\Omega), \nabla f(\cdot,t)\in L^\infty(\Omega)$ and

$$\nabla\big(n(\cdot,t)\nabla f(\cdot,t)\big) = \nabla n(\cdot,t)\nabla f(\cdot,t) + n(\cdot,t)\Delta f(\cdot,t),$$

see Brezis [5, Proposition 9.4]. Therefore, $\nabla(n(\cdot,t)\nabla f(\cdot,t))\in L^2(\Omega)$, that is, $n(\cdot,t)\nabla f(\cdot,t)\in H^1(\Omega)$.

From the above arguments, we conclude that $n\in W_3^{2,1}(Q)$ is the only solution of the equation

$$\begin{cases} \partial_t n - D_n\Delta n = -l\chi\nabla(n\nabla f) & \text{in } Q,\\ n(0)=n_0 & \text{in } \Omega,\\ (D_n\nabla n - l\chi n\nabla f)\eta = 0 & \text{on } S. \end{cases} \tag{3.10}$$

The continuity of embedding $W_3^{2,1}(Q)$ in $L^q(Q)$, follows from the operator L being well defined.

As $\chi\Delta f\in L^\infty(Q)$, it follows from Eq. (3.7) and the maximum principle that

$$n\geq 0. \tag{3.11}$$

Lemma 3.4. *The mapping $L:[0,1]\times L^q(Q)\to L^q(Q)$ has the following properties:*

(i) *$L(l,\cdot): L^q(Q)\to L^q(Q)$ is compact for every $l\in[0,1]$, i.e., it is continuous and maps bounded sets into relatively compacts sets.*

(ii) *For every $\epsilon>0$ and every bounded set $A\subset L^q(Q)$ there exists $\delta>0$ such that*

$$\big\|L(l_1,w)-L(l_2,w)\big\|_{L^q(Q)}<\epsilon,$$

whenever $w\in A$ and $|l_1-l_2|<\delta$.

Proof. *Proof of* (i): Let $\phi_1,\phi_2\in L^q(Q)$, consider $L(l,\phi_1)=n_1$ and $L(l,\phi_2)=n_2$ and furthermore, $\phi=\phi_1-\phi_2$, $n=n_1-n_2$, $f=f_1-f_2$, $m=m_1-m_2$ and $c=c_1-c_2$.

We have n_1 and n_2 as solutions of (3.10), where even $n=n_1-n_2$ satisfies the equation

$$\begin{cases} \partial_t n - D_n\Delta n = -l\chi\big(\nabla(n_1\nabla f_1)-\nabla(n_2\nabla f_2)\big) & \text{in } Q,\\ n(0)=0 & \text{in } \Omega,\\ \big(D_n\nabla n - \chi(n_1\nabla f_1 - n_2\nabla f_2)\big)\eta = 0 & \text{on } S. \end{cases} \tag{3.12}$$

Testing the first equation (3.12) by $|n|^{q-2}n$ and integrating in Ω, using the Hoelder inequality and (3.6), we conclude that

$$\begin{aligned} &\frac{1}{q}\frac{d}{dt}\int_\Omega \big|n(t)\big|^q dx + D_n(q-1)\int_\Omega \big|n(t)\big|^{q-2}\big|\nabla n(t)\big|^2 dx\\ &= (q-1)l\chi\int_\Omega \nabla f_1\nabla n|n|^{q-1}dx - (q-1)l\chi\int_\Omega n_2\nabla f\nabla n|n|^{q-2}dx\\ &\leq \frac{D_n(q-1)}{2}\int_\Omega |n|^{q-2}|\nabla n|^2dx + C\|\nabla f_1\|^2_{L^\infty(Q)}\int_\Omega |n|^q dx\\ &\quad + C\|n_2\|^q_{L^\infty(Q)}\|\nabla f\|^q_{L^\infty(Q)} + \frac{q-2}{q}\int_\Omega |n|^q dx\\ &= \frac{D_n(q-1)}{2}\int_\Omega |n|^{q-2}|\nabla n|^2dx \end{aligned}$$

$$+ C\|n_2\|^q_{L^\infty(Q)}\|\nabla f\|^q_{L^\infty(Q)} + \left[C\|\nabla f_1\|^2_{L^\infty(Q)} + \frac{q-2}{q}\right]\int_\Omega |n|^q dx. \tag{3.13}$$

Using Gronwall's inequality we obtain

$$\int_\Omega \left|n(t)\right|^q dx \le TC\|n_2\|^q_{L^\infty(Q)}\|\nabla f\|^q_{L^\infty(Q)} \exp\left(t\left[C\|\nabla f_1\|^2_{L^\infty(Q)} + \frac{q-2}{q}\right]\right). \tag{3.14}$$

From (3.6), we have

$$\begin{aligned}\left|\nabla f(x,t)\right| \le \alpha^2 f_0(x)\int_0^t \left|\rho_\delta(m_1)\right|ds \int_0^t \left|\rho_\delta(m_1)-\rho_\delta(m_2)\right|ds \\ + \alpha\int_0^t \left|\nabla\rho_\delta(m_1)-\nabla\rho_\delta(m_2)\right|ds + \alpha\left|\nabla f_0(x)\right|\int_0^t \left|\rho_\delta(m_1)-\rho_\delta(m_2)\right|ds.\end{aligned} \tag{3.15}$$

By the assumptions about ρ_δ, $\mathrm{Ext}(\cdot)$ and using the fact that $m = m_1 - m_2$ satisfies the equation

$$\begin{cases} \partial_t m - D_m\Delta m = l\mu\phi - \lambda m & \text{in } Q, \\ m(0) = 0 & \text{in } \Omega, \\ D_m\nabla m.\eta = 0 & \text{on } S, \end{cases} \tag{3.16}$$

we conclude by (3.15) that

$$\|\nabla f\|^q_{L^\infty(Q)} \le C\big(\|f_0\|_{L^\infty}, \|\nabla f_0\|_{L^\infty}, T, \delta, \|\phi_1\|_{L^q(Q)}\big)\|\phi\|_{L^q(Q)}. \tag{3.17}$$

By (3.14) and (3.17) we have that

$$\int_\Omega \left|n(t)\right|^q dx \le C\|\phi\|^q_{L^q(Q)}, \tag{3.18}$$

for each $0 \le t \le T$. Therefore,

$$\left\|L(l,\phi_1) - L(l,\phi_2)\right\|_{L^q(Q)} \le C\|\phi_1 - \phi_2\|_{L^q(Q)},$$

which proves the continuity of $L(l,\cdot)$.

To prove the compactness of $L(l,\cdot)$, we note that $L(l,\cdot)$ can be written as the composition of the solution operator from $L^q(Q) \to W^{2,1}_q(Q)$ with the inclusion operator $W^{2,1}_q(Q) \hookrightarrow L^q(Q)$, that is compact by Simon [23]. This proves item (i).

Proof of item (ii) is analogously to (3.13) with $\phi \in A$, $\phi_1 = l_1\phi$, $\phi_2 = l_2\phi$, $L(l_1,\phi) = n_1$ and $L(l_2,\phi) = n_2$. Using (3.15) and (3.17) we conclude that

$$\left\|L(l_1,\phi) - L(l_2,\phi)\right\|_{L^q(Q)} \le C\big(\|\phi\|_{L^q(Q)}\big)|l_1 - l_2| \le C(R)|l_1 - l_2|,$$

where $\|\phi\|_{L^q(Q)} \le R$ for all $\phi \in A$. For $\epsilon > 0$, we take $\delta = \frac{\epsilon}{C(R)} > 0$, then

$$|l_1 - l_2| < \delta$$

implies

$$\left\|L(l_1,\phi)-L(l_2,\phi)\right\|_{L^q(Q)}<\epsilon,$$

for each $\phi \in A$. □

Lemma 3.5. *Suppose that the assumptions from Proposition 3.3 are satisfied. Then there exists a number $\rho > 0$, such that any fixed point $n \in L^q(Q)$ of $L(l,\cdot)$ for any $l \in [0,1]$, i.e., $L(l,n) = n$ for some $l \in [0,1]$, that satisfies*

$$\|n\|_{L^q(Q)} < \rho. \tag{3.19}$$

Proof. Let n a solution of $L(l,n) = n$. Again by the maximum principle we have from Eq. (3.4), with $\phi = n$, and hypotheses about u, that

$$m \geq 0. \tag{3.20}$$

Replacing $s = \frac{n}{\psi(f)}$, where $\psi(f)$ is a function such that, for any $f \geq 0$, we have

$$D_n\psi'(f) = l\chi\psi(f)$$

and

$$\psi(0) = 1.$$

We can consider

$$\psi(f) = \exp\left(\frac{l\chi}{D_n}f\right).$$

We note that $\psi(f) \geq 1$, for all $f \geq 0$. We can write the system (3.3) as

$$\begin{cases} \psi(f)\partial_t s - D_n\nabla\cdot\big(\psi(f)\nabla s\big) = l\dfrac{\alpha\chi}{D_n}sf\rho_\delta(m)\psi(f) & \text{in } Q,\\ \partial_t f = -\alpha\rho_\delta(m)f & \text{in } Q,\\ \partial_t m - D_m\Delta m = l\mu s\psi(f) - \lambda m + u & \text{in } Q,\\ \partial_t c - D_c\Delta c = \beta v - \gamma s\psi(f) - \sigma c & \text{in } Q,\\ s(0) = s_0 = \dfrac{n_0}{\psi(f_0)}, \quad f(0) = f_0, & \text{in } \Omega,\\ m(0) = m_0, \quad c(0) = c_0 & \text{in } \Omega,\\ D_n\psi(f)\nabla s.\eta = D_m\nabla m.\eta = D_c\nabla c.\eta = 0 & \text{on } S. \end{cases} \tag{3.21}$$

We have shown that the solutions s, v and m are nonnegative. Integrating the first equation of (3.21) on Ω, we conclude that

$$\partial_t\int_\Omega \psi\big(f(t)\big)s(t)dx = 0.$$

Integrating with respect to variable t, and using that

$$f \leq \sup_{x\in\Omega} f_0(x), \qquad 1 \leq \psi(f) \leq C_0, \tag{3.22}$$

we have

$$\int_\Omega s(t)dx \leq \int_\Omega \psi(f)s(t)dx = \int_\Omega \psi(f_0)s_0 dx, \quad \forall t \in [0,T]. \tag{3.23}$$

Testing the first equation of (3.21) by qs^{q-1}, to $q \geq 4$, we get

$$\int_\Omega q\psi(f)\partial_t s s^{q-1}dx = D_n q\int_\Omega \nabla\cdot\big(\psi(f)\nabla s\big)s^{q-1}dx + l\frac{\alpha\chi}{D_n}q\int_\Omega f\rho_\delta(m)s^q\psi(f)dx.$$

Therefore,

$$\partial_t\int_\Omega \psi(f)s^q dx + l\frac{\alpha\chi}{D_n}\int_\Omega f\rho_\delta(m)s^q\psi(f)dx = -D_n q\int_\Omega (q-1)\psi(f)|\nabla s|^2 s^{q-2}dx + l\frac{\alpha\chi}{D_n}q\int_\Omega f\rho_\delta(m)s^q\psi(f)dx.$$

Using the identity

$$\big|\nabla\big(s^{\frac{q}{2}}\big)\big|^2 = \frac{q^2}{4}s^{q-2}|\nabla s|^2,$$

we obtain that

$$\partial_t\int_\Omega \psi(f)s^q dx + \frac{4(q-1)D_n}{q}\int_\Omega \psi(f)\big|\nabla\big(s^{\frac{q}{2}}\big)\big|^2 dx + l\frac{\alpha\chi}{D_n}\int_\Omega f\rho_\delta(m)s^q\psi(f)dx = l\frac{\alpha\chi}{D_n}q\int_\Omega f\rho_\delta(m)s^q\psi(f)dx.$$

Thus,

$$\begin{aligned}
&\partial_t\int_\Omega \psi(f)s^q dx + \frac{4(q-1)D_n}{q}\int_\Omega \psi(f)\big|\nabla\big(s^{\frac{q}{2}}\big)\big|^2 dx \\
&= l\frac{\alpha\chi}{D_n}\int_\Omega f\rho_\delta(m)\psi(f)s^q(q-1)dx \leq \frac{\alpha\chi}{D_n}(q-1)\sup_{x\in\Omega} f_0(x)C_0\int_\Omega \rho_\delta(m)s^q dx \\
&\leq \frac{\alpha\chi}{D_n}(q-1)\sup_{x\in\Omega} f_0(x)C_0\left(\frac{q^q}{q+1}\int_\Omega \big|\rho_\delta(m)\big|^{q+1}dx + \frac{1}{q+1}\int_\Omega |s|^{q+1}dx\right).
\end{aligned} \tag{3.24}$$

By the interpolation inequality, see Brezis [5, p. 93, Remark 2], with $p \leq r \leq z$, we have

$$\|u\|_{L^r} \leq \|u\|_{L^p}^{\alpha}\|u\|_{L^z}^{1-\alpha}, \qquad \frac{1}{r} = \frac{\alpha}{p} + \frac{1-\alpha}{z}, \quad 0 \leq \alpha \leq 1.$$

Choosing $p = 1$, $r \geq q+1$ and $\alpha = \frac{1}{q+1}$ we obtain

$$\|s\|_{L^{q+1}(\Omega)} \leq C(\Omega)\|s\|_{L^1(\Omega)}^{\frac{1}{q+1}}\|s\|_{L^z}^{\frac{q}{q+1}} = C(\Omega)\|s\|_{L^1(\Omega)}^{\frac{1}{q+1}}\big\|s^{\frac{q}{2}}\big\|_{L^{\frac{2z}{q}}}^{\frac{2}{q+1}}.$$

Consequently,

$$\begin{aligned}
\int_\Omega s^{q+1}dx &\leq C(\Omega,q)\|s\|_{L^1(\Omega)}\big\|s^{\frac{q}{2}}\big\|_{L^{\frac{2z}{q}}}^2 \leq C(\Omega,q)\|s\|_{L^1(\Omega)}\big\|s^{\frac{q}{2}}\big\|_{H^1(\Omega)}^2 \\
&= C(\Omega,q)\|s\|_{L^1(\Omega)}\big(\big\|s^{\frac{q}{2}}\big\|_{L^2(\Omega)}^2 + \big\|\nabla s^{\frac{q}{2}}\big\|_{L^2(\Omega)}^2\big) = C(\Omega,q)\|s\|_{L^1(\Omega)}\big(\|s\|_{L^q(\Omega)}^q + \big\|\nabla s^{\frac{q}{2}}\big\|_{L^2(\Omega)}^2\big).
\end{aligned}$$

From this last inequality and (3.23), it follows that

$$\int_\Omega s^{q+1}dx \le C(\Omega,q)\big\|\psi(f_0)s_0\big\|_{L^1(\Omega)}\big(\|s\|^q_{L^q(\Omega)} + \big\|\nabla s^{\frac{q}{2}}\big\|^2_{L^2(\Omega)}\big).$$

Thus, we conclude

$$\|s\|^q_{L^q(\Omega)} + \big\|\nabla s^{\frac{q}{2}}\big\|^2_{L^2(\Omega)} \ge \frac{1}{C(\Omega,q)\|\psi(f_0)s_0\|_{L^1(\Omega)}}\int_\Omega s^{q+1}dx. \tag{3.25}$$

From (3.24), (3.25) and using that $\psi(f)\ge 1$, we obtain

$$\begin{aligned}
&\partial_t\int_\Omega \psi(f)s^q dx + \frac{4(q-1)D_n}{q}\frac{1}{C(\Omega,q)\|\psi(f_0)s_0\|_{L^1(\Omega)}}\int_\Omega s^{q+1}dx \\
&\quad\le \frac{\alpha\chi}{D_n}(q-1)\sup_{x\in\Omega} f_0(x)C_0\bigg(\frac{q^q}{q+1}\int_\Omega \big|\rho_\delta(m)\big|^{q+1}dx + \frac{1}{q+1}\int_\Omega |s|^{q+1}dx\bigg) \\
&\qquad + \frac{4(q-1)D_n}{q}\int_\Omega s^q dx.
\end{aligned} \tag{3.26}$$

Integrating in $(0,t)$, with $t\le T$, using that $s_0\in W_3^{4/3}(\Omega)\hookrightarrow L^q(\Omega)$ and the latter inequality we obtain

$$\begin{aligned}
&\int_\Omega \psi\big(f(t)\big)s(t)^q dx + \frac{4(q-1)D_n}{q}\frac{1}{C(\Omega,q)\|\psi(f_0)s_0\|_{L^1(\Omega)}}\int_0^t\int_\Omega s^{q+1}dxds \\
&\quad\le \frac{\alpha\chi}{D_n}(q-1)\sup_{x\in\Omega} f_0(x)C_0\bigg(\frac{q^q}{q+1}\int_0^t\int_\Omega \big|\rho_\delta(m)\big|^{q+1}dxds + \frac{1}{q+1}\int_0^t\int_\Omega |s|^{q+1}dxds\bigg) \\
&\qquad + \frac{4(q-1)D_n}{q}\int_0^t\int_\Omega s^q dxds + \int_\Omega \psi(f_0)s_0^q dx \\
&\quad\le \frac{\alpha\chi}{D_n}(q-1)\sup_{x\in\Omega} f_0(x)C_0\frac{q^q}{q+1}\int_0^t\int_\Omega \big|\rho_\delta(m)\big|^{q+1}dxds \\
&\qquad + \frac{\alpha\chi}{D_n}(q-1)\sup_{x\in\Omega} f_0(x)C_0\frac{1}{q+1}\int_0^t\int_\Omega |s|^{q+1}dxds + \frac{4(q-1)D_n}{q}\frac{q}{q+1}\int_0^t\int_\Omega s^{q+1}dxds \\
&\qquad + \frac{4(q-1)D_n}{q}\frac{1}{q+1}T|\Omega| + \int_\Omega \psi(f_0)s_0^q dx.
\end{aligned} \tag{3.27}$$

From where we conclude that

$$\begin{aligned}
&\int_\Omega \psi\big(f(t)\big)s(t)^q dx + \frac{q-1}{q+1}\bigg[\frac{4D_n}{C(\Omega,q)\|\psi(f_0)s_0\|_{L^1(\Omega)}} - \frac{\alpha\chi}{D_n}\sup_{x\in\Omega} f_0(x)C_0 - 4D_n\bigg]\int_0^t\int_\Omega s^{q+1}dxds \\
&\quad\le \frac{\alpha\chi}{D_n}(q-1)\sup_{x\in\Omega} f_0(x)C_0\frac{q^q}{q+1}\int_0^t\int_\Omega \big|\rho_\delta(m)\big|^{q+1}dxds + \frac{4(q-1)D_n}{q}\frac{1}{q+1}T|\Omega|
\end{aligned}$$

$$+\int_\Omega \psi(f_0)s_0^q dx. \tag{3.28}$$

From properties of the convolution, from the properties of the operator extension and from the second equation of (3.21), we have

$$\begin{aligned}\int_0^t\int_\Omega \left|\rho_\delta * \mathrm{Ext}(m)(s)\right|^{q+1}dxds &= \left\|\rho_\delta * \mathrm{Ext}(m)\right\|^{q+1}_{L^{q+1}(Q_t)} \\ &\le \|\rho_\delta\|^{q+1}_{L^1(\mathbb{R}^3)}\left\|\mathrm{Ext}(m)\right\|^{q+1}_{L^{q+1}(\mathbb{R}^3)} \\ &= \left\|\mathrm{Ext}(m)\right\|^{q+1}_{L^{q+1}(\mathbb{R}^3)} \le C\left\|\mathrm{Ext}(m)\right\|^{q+1}_{W_2^{2,1}(\mathbb{R}^3)} \\ &\le C_{ext}\|m\|^{q+1}_{W_2^{2,1}(Q)} \le C_{ext}\|s\|^{q+1}_{L^2(Q)} + C. \end{aligned}\tag{3.29}$$

By Young's inequality, we obtain

$$\|s\|^{q+1}_{L^2(Q)} \le \left(T|\Omega|\right)^{\frac{q-1}{2}}\|s\|^{q+1}_{L^{q+1}(Q)} = \left(T|\Omega|\right)^{\frac{q-1}{2}}\int_0^T\int_\Omega s^{q+1}dxds. \tag{3.30}$$

From (3.28), (3.29) and (3.30) we obtain

$$\begin{aligned}&\int_\Omega \psi\big(f(t)\big)s(t)^q dx + \frac{q-1}{q+1}\left[\frac{4D_n}{C(\Omega,q)\|n_0\|_{L^1(\Omega)}} - \frac{\alpha\chi}{D_n}\sup_{x\in\Omega} f_0(x)C_0 - 4D_n\right]\int_0^t\int_\Omega s^{q+1}dxds \\ &\le \frac{q-1}{q+1}\frac{\alpha\chi}{D_n}\sup_{x\in\Omega} f_0(x)C_0q^qC_{ext}\left(T|\Omega|\right)^{\frac{q-1}{2}}\int_0^T\int_\Omega s^{q+1}dxds + C\frac{\alpha\chi}{D_n}(q-1)\sup_{x\in\Omega} f_0(x)C_0\frac{q^q}{q+1} \\ &+ \frac{4(q-1)D_n}{q}\frac{1}{q+1}T|\Omega| + \int_\Omega \psi(f_0)s_0^q dx, \end{aligned}\tag{3.31}$$

for all $t \in [0,T]$.

In particular, we conclude that

$$\begin{aligned}&\frac{q-1}{q+1}\left[\frac{4D_n}{C(\Omega,q)\|n_0\|_{L^1(\Omega)}} - \frac{\alpha\chi}{D_n}\sup_{x\in\Omega} f_0(x)C_0\left\{1+q^qC_{ext}\left(T|\Omega|\right)^{\frac{q-1}{2}}\right\} - 4D_n\right]\int_0^T\int_\Omega s^{q+1}dxds \\ &\le C\frac{\alpha\chi}{D_n}(q-1)\sup_{x\in\Omega} f_0(x)C_0\frac{q^q}{q+1} + \frac{4(q-1)D_n}{q}\frac{1}{q+1}T|\Omega| + \int_\Omega \psi(f_0)s_0^q dx. \end{aligned}\tag{3.32}$$

Assuming that

$$\frac{4D_n}{C(\Omega,q)\|n_0\|_{L^1(\Omega)}} - \frac{\alpha\chi}{D_n}\sup_{x\in\Omega} f_0(x)C_0\left\{1+q^qC_{ext}\left(T|\Omega|\right)^{\frac{q-1}{2}}\right\} - 4D_n > 0, \tag{3.33}$$

or equivalently,

$$\|n_0\|_{L^1(\Omega)} < \xi = \frac{4D_n}{C(\Omega,q)\left\{\frac{\alpha\chi}{D_n}\sup_{x\in\Omega} f_0(x)C_0\left\{1+q^qC_{ext}(T|\Omega|)^{\frac{q-1}{2}}\right\}+4D_n\right\}}, \tag{3.34}$$

then from (3.32) and (3.34), there is a positive constant C independent of $\delta > 0$ and l, such that

$$\|s\|_{L^{q+1}(Q)} \leq C. \tag{3.35}$$

From (3.32) and (3.35) there is a positive constant C independent of δ and l, such that

$$\int_{\Omega} s(t)^q dx \leq C. \tag{3.36}$$

Therefore,

$$\int_{\Omega} n(t)^q dx \leq C, \tag{3.37}$$

where C is a constant independent of $\delta > 0$ and of l, thus proving (3.19). □

3.2. Proof of Proposition 3.3

From Lemma 3.5, we know the existence of a number $\rho > 0$ which satisfies the property stated in (3.19). For $l = 0$, the problem $L(0, n) = n$ has a unique solution, because, (n, f, m, c) is a solution of the system

$$\begin{cases} \partial_t n - D_n \Delta n = 0 & \text{in } Q, \\ \partial_t f = -\alpha \rho_\delta(m) f & \text{in } Q, \\ \partial_t m - D_m \Delta m = -\lambda m + u & \text{in } Q, \\ \partial_t c - D_c \Delta c = \beta f - \gamma n - \sigma c & \text{in } Q, \\ n(0) = n_0, \quad f(0) = f_0, \quad m(0) = m_0, \quad c(0) = c_0 & \text{in } \Omega, \\ D_n \nabla n \eta = D_m \nabla m.\eta = D_c \nabla c.\eta = 0 & \text{on } S. \end{cases} \tag{3.38}$$

By Leray–Schauder's fixed point theorem, the equation $L(1, n) = n$ has a unique solution. In other words, problem (3.2) has at least one solution.

By Leray–Schauder's fixed point theorem and (3.38), there exist s, m, f and c that are solutions of

$$\begin{cases} \psi(f)\partial_t s - D_n \nabla \cdot \big(\psi(f) \nabla s\big) = \dfrac{\alpha\chi}{D_n} s f \rho_\delta(m) \psi(f) & \text{in } Q, \\ \partial_t f = -\alpha \rho_\delta(m) f & \text{in } Q, \\ \partial_t m - D_m \Delta m = \mu s \psi(f) - \lambda m + u & \text{in } Q, \\ \partial_t c - D_c \Delta c = \beta f - \gamma s \psi(f) - \sigma c & \text{in } Q, \\ s(0) = s_0 = \dfrac{n_0}{\psi(f_0)}, \quad f(0) = f_0, \quad m(0) = m_0, \quad c(0) = c_0 & \text{in } \Omega, \\ D_n \psi(f) \nabla s.\eta = D_m \nabla m.\eta = D_c \nabla c.\eta = 0 & \text{on } S. \end{cases} \tag{3.39}$$

As $f, n \in L^2(Q)$, by linear parabolic PDE's theory (see Ladyzenskaja [16, Theorem 9.1, p. 341]) there is a unique $c \in W_2^{2,1}(Q)$ that solves the equation

$$\begin{cases} \partial_t c - D_c \Delta c = \beta f - \gamma s \psi(f) - \sigma c & \text{in } Q, \\ c(0) = c_0 & \text{in } \Omega, \\ D_c \nabla c.\eta = 0 & \text{on } S. \end{cases} \tag{3.40}$$

Particularly,

$$\|c\|_{W_2^{2,1}(Q)} \leq C\big(\|c_0\|_{H^1(\Omega)} + \|f\|_{L^q(Q)} + \|n\|_{L^q(Q)}\big). \tag{3.41}$$

By (3.6), (3.8), (3.40), (3.6), (3.11), (3.20) and making the replacement $s\psi(f) = n$ in (3.39), Proposition 3.3 is proved.

4. Proof of Theorem 2.2

In Proposition 3.3 let $n_0^\delta = n_0$, $m_0^\delta = m_0$, $c_0^\delta \in C^1(\overline{\Omega})$ and $f_0^\delta \in C^2(\overline{\Omega})$ such that c_0^δ converges to c_0 in $H^1(\Omega)$ and f_0^δ converges to f_0 in $H^2(\Omega)$.

Testing the first equation (3.39) by $\partial_t s$ and integrating on Ω, we obtain

$$\int_\Omega \psi(f)(\partial_t s)^2 dx + D_n \int_\Omega \psi(f)\nabla s \nabla \partial_t s dx = \frac{\alpha\chi}{D_n}\int_\Omega f\rho_\delta(m)s\partial_t s\psi(f)dx.$$

Consequently

$$\int_\Omega \psi(f)(\partial_t s)^2 dx + D_n \int_\Omega \psi(f)\frac{1}{2}\frac{d}{dt}|\nabla s|^2 dx = \frac{\alpha\chi}{D_n}\int_\Omega f\rho_\delta(m)s\partial_t s\psi(f)dx.$$

Therefore,

$$\begin{aligned}
&\int_\Omega \psi(f)(\partial_t s)^2 dx + D_n\frac{1}{2}\frac{d}{dt}\int_\Omega \big(\psi(f)|\nabla s|^2\big)dx \\
&\quad= \frac{\alpha\chi}{D_n}\int_\Omega f\rho_\delta(m)s\partial_t s\psi(f)dx - \frac{\alpha\chi}{D_n}q\int_\Omega f\rho_\delta(m)|\nabla s|^2\psi(f)dx \\
&\quad\le \frac{\alpha\chi}{D_n}\sup_{x\in\Omega} f_0(x)C_0\int_\Omega \big|\rho_\delta(m)\big||\partial_t s||s|dx.
\end{aligned} \tag{4.1}$$

Using $\frac{1}{4}+\frac{1}{2}+\frac{1}{4}=1$, we have from Gagliardo–Nirenberg's inequality (see Brezis [5, p. 314]) and Young's inequality that

$$\begin{aligned}
\int_\Omega \big|\rho_\delta(m)\big||\partial_t s||s|dx &\le \big\|s(t)\big\|_{L^4(\Omega)}\big\|s_t(t)\big\|_{L^2(\Omega)}\big\|\rho_\delta(m)(t)\big\|_{L^4(\Omega)} \\
&\le C\big\|s(t)\big\|_{L^4(\Omega)}\big\|s_t(t)\big\|_{L^2(\Omega)}\big\|\rho_\delta(m)(t)\big\|^{\frac{1}{2}}_{H^1(\Omega)}\big\|\rho_\delta(m)(t)\big\|^{\frac{1}{2}}_{L^2(\Omega)} \\
&\le \epsilon\big\|s_t(t)\big\|^2_{L^2(\Omega)} + C(\epsilon)\big\|s(t)\big\|^2_{L^4(\Omega)}\big\|\rho_\delta(m)(t)\big\|^2_{H^1(\Omega)} \\
&\le \epsilon\big\|s_t(t)\big\|^2_{L^2(\Omega)} + C(\epsilon)C\big\|\rho_\delta(m)(t)\big\|^2_{H^1(\Omega)}.
\end{aligned} \tag{4.2}$$

Note that

$$\begin{aligned}
\big\|\rho_\delta(m)(t)\big\|^2_{H^1(\Omega)} &= \int_\Omega \big|\rho_\delta(m)(t)\big|^2 dx + \int_\Omega \big|\nabla\rho_\delta(m)(t)\big|^2 dx \\
&= \int_\Omega \big|\rho_\delta * \mathrm{Ext}(m)(t)\big|^2 dx + \int_\Omega \big|\nabla\rho_\delta * \mathrm{Ext}(m)(t)\big|^2 dx.
\end{aligned} \tag{4.3}$$

Integrating (4.1) on interval $(0,t)$ and using (4.2) and (4.3), we obtain

$$\int_0^t \int_\Omega \psi(f)(\partial_t s)^2 dx + D_n \frac{1}{2} \int_\Omega \big(\psi(f)|\nabla s|^2\big) dx$$
$$\le D_n \frac{1}{2} \int_\Omega \big(\psi(f_0)|\nabla s_0|^2\big) dx + \epsilon \int_0^t \big\|s_t(s)\big\|^2_{L^2(\Omega)} ds + C \int_0^t \int_\Omega \big|\rho_\delta * \mathrm{Ext}(m)(s)\big|^2 dx ds$$
$$+ C \int_0^t \int_\Omega \big|\nabla \rho_\delta * \mathrm{Ext}(m)(s)\big|^2 dx ds. \tag{4.4}$$

Now,

$$\begin{aligned}\int_0^t \int_\Omega \big|\rho_\delta * \mathrm{Ext}(m)(s)\big|^2 dx ds &= \big\|\rho_\delta * \mathrm{Ext}(m)\big\|^2_{L^2(Q_t)} \\ &\le \|\rho_\delta\|^2_{L^1(\mathbb{R}^3)} \big\|\mathrm{Ext}(m)\big\|^2_{L^2(\mathbb{R}^3)} \\ &= \big\|\mathrm{Ext}(m)\big\|^2_{L^2(\mathbb{R}^3)} \le \big\|\mathrm{Ext}(m)\big\|^2_{W_2^{2,1}(\mathbb{R}^3)} \\ &\le C\big\|\mathrm{Ext}(m)\big\|^2_{W_2^{2,1}(Q)} \le C\|n\|^2_{L^q(Q)} + C \le C. \end{aligned} \tag{4.5}$$

Analogously,

$$\int_0^t \int_\Omega \big|\rho_\delta * \nabla \mathrm{Ext}(m)(s)\big|^2 dx ds \le C\big\|\mathrm{Ext}(m)\big\|^2_{W_2^{2,1}(Q)} \le C\|n\|^2_{L^q(Q)} + C \le C. \tag{4.6}$$

As $\psi(f) \ge 1$, it follows from (4.4), (4.5) and (4.6) that

$$\int_0^t \int_\Omega (\partial_t s)^2 dx + \int_\Omega |\nabla s|^2 dx \le C, \tag{4.7}$$

where C is a uniform constant in $\delta > 0$.

We will now analyze the equation

$$f_t = -\alpha \rho_\delta(m) f, \qquad f(x,0) = f_0(x),$$

whose solution is

$$f(x,t) = f_0(x) \exp\left(-\alpha \int_0^t \rho_\delta(m) ds\right). \tag{4.8}$$

Computing the i-th partial derivative of (4.8) we obtain

$$f_{x_i} = -\alpha f_0 \int_0^t \rho_\delta * \mathrm{Ext}(m)_{x_i} ds \exp\left(-\alpha \int_0^t \rho_\delta(m) ds\right) + \partial_{x_i} f_0 \exp\left(-\alpha \int_0^t \rho_\delta(m) ds\right). \tag{4.9}$$

Therefore,

$$\nabla f(x,t) = -\alpha f_0 \int_0^t \rho_\delta * \nabla \operatorname{Ext}(m) ds \exp\left(-\alpha \int_0^t \rho_\delta(m) ds\right) + \nabla f_0 \exp\left(-\alpha \int_0^t \rho_\delta(m) ds\right). \tag{4.10}$$

Similarly,

$$\begin{aligned} f_{x_i x_j} &= -\alpha f_0 \int_0^t \rho_\delta * \operatorname{Ext}(m)_{x_i x_j} ds f(x,t) \\ &\quad + \left(-\alpha \int_0^t \rho_\delta * \operatorname{Ext}(m)_{x_i} ds\right)\left(-\alpha \int_0^t \rho_\delta * \operatorname{Ext}(m)_{x_j} ds\right) \\ &\quad + 2\partial_{x_i} f_0 \left(-\alpha \int_0^t \rho_\delta * \operatorname{Ext}(m)_{x_j} ds\right) \exp\left(-\alpha \int_0^t \rho_\delta(m) ds\right) \\ &\quad + \partial_{x_i x_j} f_0 \exp\left(-\alpha \int_0^t \rho_\delta(m) ds\right). \end{aligned} \tag{4.11}$$

From (4.10) and (4.11) we conclude that

$$\left|\nabla f(x,t)\right| \le \alpha\Big(\sup_{x\in\Omega} f_0\Big) \int_0^t \left|\rho_\delta * \nabla \operatorname{Ext}(m)\right| ds + |\nabla f_0| \tag{4.12}$$

and

$$\begin{aligned} |f_{x_i x_j}| &\le \alpha\Big(\sup_{x\in\Omega} f_0\Big) \int_0^t \left|\rho_\delta * \operatorname{Ext}(m)_{x_i x_j}\right| ds + \left(\alpha \int_0^t \left|\rho_\delta * \operatorname{Ext}(m)_{x_i}\right| ds\right)\left(\alpha \int_0^t \left|\rho_\delta * \operatorname{Ext}(m)_{x_j}\right| ds\right) \\ &\quad + 2|\partial_{x_i} f_0| \left(\alpha \int_0^t \left|\rho_\delta * \operatorname{Ext}(m)_{x_j}\right| ds\right) + |\partial_{x_i x_j} f_0|. \end{aligned} \tag{4.13}$$

By Jensen's inequality (see Evans [13]), we conclude from (4.12) that

$$\left|\nabla f(x,t)\right|^2 \le 4\alpha^2 T \Big(\sup_{x\in\Omega} f_0\Big)^2 \int_0^t \left|\rho_\delta * \nabla \operatorname{Ext}(m)\right|^2 ds + 4|\nabla f_0|^2. \tag{4.14}$$

Integrating (4.14) on Ω, we conclude that

$$\begin{aligned} \int_\Omega \left|\nabla f(x,t)\right|^2 dx &\le 4\alpha^2 T \Big(\sup_{x\in\Omega} f_0\Big)^2 \int_0^t \int_\Omega \left|\rho_\delta * \nabla \operatorname{Ext}(m)\right|^2 dx ds + 4 \int_\Omega |\nabla f_0|^2 dx \\ &\le 4\alpha^2 T \Big(\sup_{x\in\Omega} f_0\Big)^2 \|\nabla m\|^2_{L^2(Q)} + 4 \int_\Omega |\nabla f_0|^2 dx \\ &\le 4\alpha^2 T \Big(\sup_{x\in\Omega} f_0\Big)^2 \|n\|^2_{L^q(Q)} + 4 \int_\Omega |\nabla f_0|^2 dx \end{aligned}$$

$$\leq 4\alpha^2 T\Big(\sup_{x\in\Omega} f_0\Big)^2 C + 4\int_\Omega |\nabla f_0|^2 dx, \tag{4.15}$$

where C does not depend on $\delta > 0$.

Again, by Jensen's inequality we conclude from (4.13) that

$$\begin{aligned}|f_{x_ix_j}|^{4/3} \leq{}& C^3\alpha^4\Big(\sup_{x\in\Omega} f_0\Big)^4 T^2 + \frac{2}{3}\int_0^t \big|\rho_\delta * \operatorname{Ext}(m)_{x_ix_j}\big|^2 ds \\ &+ C\alpha^{8/3}T^{2/3}\int_0^t \big|\rho_\delta * \nabla \operatorname{Ext}(m)\big|^{8/3} ds \\ &+ \frac{C^3 2^4\alpha^4}{3}|\partial_{x_i} f_0|^4 + \frac{2}{3}T\int_0^t \big|\rho_\delta * \operatorname{Ext}(m)_{x_j}\big|^2 ds + \frac{2}{3}|\partial_{x_ix_j} f_0|^2 + C. \end{aligned} \tag{4.16}$$

Integrating (4.16) on Ω, we obtain

$$\begin{aligned}\int_\Omega |f_{x_ix_j}|^{4/3} dx \leq{}& C^3\alpha^4\Big(\sup_{x\in\Omega} f_0\Big)^4 T^2|\Omega| + \frac{2}{3}\int_0^t\int_\Omega \big|\rho_\delta * \operatorname{Ext}(m)_{x_ix_j}\big|^2 dxds \\ &+ C\alpha^{8/3}T^{2/3}\int_0^t\int_\Omega \big|\rho_\delta * \nabla \operatorname{Ext}(m)\big|^{8/3} dxds \\ &+ \frac{C^3 2^4\alpha^4}{3}\int_\Omega |\partial_{x_i} f_0|^4 dx + \frac{2}{3}T\int_0^t\int_\Omega \big|\rho_\delta * \operatorname{Ext}(m)_{x_j}\big|^2 dxds \\ &+ \frac{2}{3}\int_\Omega |\partial_{x_ix_j} f_0|^2 dx + C|\Omega|. \end{aligned} \tag{4.17}$$

We will analyze the term $\int_0^t\int_\Omega |\rho_\delta * \nabla \operatorname{Ext}(m)|^{8/3} dxds$. As $\rho_\delta * \nabla \operatorname{Ext}(m)(t) \in L^4(\Omega)\cap W_2^2(\Omega)$, it follows from Gagliardo–Nirenberg inequality (see Brezis [5, p. 314]) that

$$\big\|\nabla\big(\rho_\delta * \operatorname{Ext}(m)\big)(t)\big\|_{L^{8/3}(\Omega)} \leq C\big\|\rho_\delta * \operatorname{Ext}(m)(t)\big\|_{H^2(\Omega)}^{1/2}\big\|\rho_\delta * \operatorname{Ext}(m)(t)\big\|_{L^4(\Omega)}^{1/2}.$$

Therefore,

$$\begin{aligned}&\int_0^t \big\|\nabla\big(\rho_\delta * \operatorname{Ext}(m)\big)(s)\big\|_{L^{8/3}(\Omega)}^{8/3} ds \\ &\leq C\int_0^t \big\|\rho_\delta * \operatorname{Ext}(m)(t)\big\|_{H^2(\Omega)}^{4/3}\big\|\rho_\delta * \operatorname{Ext}(m)(t)\big\|_{L^4(\Omega)}^{4/3} ds \\ &\leq \int_0^t \frac{2}{3}C\big\|\rho_\delta * \operatorname{Ext}(m)(t)\big\|_{H^2(\Omega)}^2 + \frac{1}{3}\big\|\rho_\delta * \operatorname{Ext}(m)(t)\big\|_{L^4(\Omega)}^4 ds \\ &\leq C\big\|\operatorname{Ext}(m)\big\|_{W_2^{2,1}(\mathbb{R}^3)}^2 + \frac{1}{3}\big\|\operatorname{Ext}(m)\big\|_{L^4(Q)}^4 \leq C\|m\|_{W_2^{2,1}(Q)}^2 + \frac{1}{3}C\big\|\operatorname{Ext}(m)\big\|_{W_2^{2,1}(Q)}^4\end{aligned}$$

$$\leq C\|m\|^2_{W_2^{2,1}(Q)} + \frac{1}{3}C\|m\|^4_{W_2^{2,1}(Q)} \leq C\|n\|^2_{L^q(Q)} + \frac{1}{3}C\|n\|^4_{L^q(Q)} + C \leq C, \tag{4.18}$$

where C is independent of $\delta > 0$. Analogous estimates are obtained for the remaining terms on the right side of (4.17). Thus, we conclude from (4.17) that

$$\big\|D^2 f(t)\big\|^{4/3}_{L^{4/3}(\Omega)} \leq C\Big(1 + \Big(\sup_{x\in\Omega} f_0\Big)^4 + \|\nabla f_0\|^4_{L^4(\Omega)} + \big\|D^2 f_0\big\|^2_{L^2(\Omega)}\Big), \tag{4.19}$$

where C is independent of $\delta > 0$.

By (4.8), (4.15) and (4.19) we conclude that $f_\delta \in L^\infty(0,T;W^2_{4/3}(\Omega))$.

Therefore, $f_\delta \in \{u \in L^\infty(0,T;W^2_{4/3}(\Omega)); u_t \in L^2(0,T;L^2(\Omega))\}$. As $W^2_{4/3}(\Omega) \hookrightarrow C^0(\overline{\Omega}) \hookrightarrow L^2(\Omega)$, with the first embedding compact (because $n = 2$). It follows from Simon [23, Corollary 4], passing to a subsequence if necessary, that

$$f_\delta \to f \quad \text{in } C\big([0,T];C^0(\overline{\Omega})\big), \tag{4.20}$$

particularly,

$$\psi(f_\delta) \to \psi(f) \quad \text{in } C\big([0,T];C^0(\overline{\Omega})\big). \tag{4.21}$$

From (3.5) and (3.37) we have

$$m_\delta \quad \text{is bounded in } W_4^{2,1}(Q). \tag{4.22}$$

From (3.37) and (3.41) we have

$$c_\delta \quad \text{is bounded in } W_2^{2,1}(Q). \tag{4.23}$$

From (4.5) we have

$$\partial_t s_\delta \quad \text{is bounded in } L^2(Q) \tag{4.24}$$

and

$$s_\delta \quad \text{is bounded in } L^\infty\big(0,T;H^1(\Omega)\big). \tag{4.25}$$

From compactness of the embedding of $W_q^{2,1}(Q)$ in $L^2(Q)$, $q \geq 2$, we can obtain a subsequence such that

$$m_\delta \rightharpoonup m \quad \text{weakly in } W_4^{2,1}(Q), \tag{4.26}$$

$$m_\delta \to m \quad \text{strongly in } L^2(Q) \tag{4.27}$$

and

$$m_\delta \to m \quad \text{a.e. on } Q. \tag{4.28}$$

Therefore,

$$\rho_\delta(m_\delta) \to m \quad \text{strongly in } L^2(Q) \tag{4.29}$$

and

$$\rho_\delta(m_\delta) \to m \quad \text{a.e. on } Q. \tag{4.30}$$

Consequently, passing to a subsequence if necessary,

$$\int_0^t \rho_\delta(m_\delta)ds \to \int_0^t mds \quad \text{strongly in } L^2(Q) \tag{4.31}$$

and

$$\int_0^t \rho_\delta(m_\delta)ds \to \int_0^t mds \quad \text{a.e. on } Q. \tag{4.32}$$

From continuity,

$$f_\delta(x,t) = f_0^\delta \exp\left(-\alpha \int_0^t \rho_\delta(m_\delta)ds\right) \to f_0 \exp\left(-\alpha \int_0^t mds\right) \quad \text{a.e. in } Q. \tag{4.33}$$

By uniqueness of limits (4.20) and (4.33) we have

$$f(x,t) = f_0 \exp\left(-\alpha \int_0^t mds\right) \quad \text{on } Q, \tag{4.34}$$

and therefore, by the assumptions with respect to f_0, we obtain

$$f \geq 0, \tag{4.35}$$

and

$$f_t = -\alpha m f \quad \text{on } Q. \tag{4.36}$$

From (4.34) we have

$$\nabla f(x,t) = \nabla f_0 \exp\left(-\alpha \int_0^t m(x,s)ds\right) - f_0\alpha \int_0^t \nabla m(x,s)ds \exp\left(-\alpha \int_0^t mds\right). \tag{4.37}$$

By hypothesis we have $f_0 \in W^1_\infty(\Omega)$ and from continuity of the embedding $W^2_4(\Omega) \hookrightarrow C^1(\overline{\Omega})$, see Adams [1], we have

$$W^{2,1}_4(\Omega) \hookrightarrow L^4\big(0,T;W^2_4(\Omega)\big) \hookrightarrow L^4\big(0,T;C^1(\overline{\Omega})\big) \tag{4.38}$$

is continuous, and by (3.5) with $\phi = n$ and (3.37) we conclude that

$$\big\|\nabla f(t)\big\|_{L^\infty(\Omega)} \leq \|\nabla f_0\|_{L^\infty(\Omega)} + \|f_0\|_{L^\infty(\Omega)}\alpha \int_0^T \big\|\nabla m(s)\big\|_{L^\infty(\Omega)}ds \leq C. \tag{4.39}$$

By (4.36), (3.5) and (3.36) we conclude that

$$\|f_t\|_{L^2(Q)} \leq \alpha \|f\|_{L^\infty(Q)} \|m\|_{L^2(Q)} \leq C. \tag{4.40}$$

By compactness of embedding of $W = \{u, u \in L^\infty(0,T;H^1(\Omega)); u_t \in L^2(Q)\}$ in $C([0,T];L^2(\Omega))$, it follows from (4.24) and (4.25), passing to a subsequence if necessary, that

$$\partial_t s_\delta \rightharpoonup \partial_t s \quad \text{weakly in } L^2(Q), \tag{4.41}$$

$$\nabla s_\delta \rightharpoonup \nabla s \quad \text{weakly in } L^2(Q), \tag{4.42}$$

$$s_\delta \to s \quad \text{strongly in } C\big([0,T];L^2(\Omega)\big) \tag{4.43}$$

and

$$s_\delta \to s \quad \text{a.e. on } Q. \tag{4.44}$$

From (4.23), passing to a subsequence if necessary, we have

$$c_\delta \rightharpoonup c \quad \text{weakly in } W_2^{2,1}(Q). \tag{4.45}$$

Now, multiplying the first equation of (3.39) by $\varphi \in L^2(0,T;H^1(\Omega))$, integrating on Q_t and using integration by parts, we obtain

$$\int_0^t \int_\Omega \psi(f_\delta)\partial_t s_\delta \varphi dxds + D_n \int_0^t \int_\Omega \psi(f_\delta)\nabla s_\delta \nabla \varphi dxds = \frac{\alpha\chi}{D_n} \int_0^t \int_\Omega s_\delta f_\delta \rho_\delta(m_\delta)\psi(f_\delta)\varphi dxds, \tag{4.46}$$

for every $t \in [0,T]$.

From (4.20), (4.21), (4.30) and (4.44) we obtain

$$s_\delta f_\delta \rho_\delta(m_\delta)\psi(f_\delta) \to sfm\psi(f) \quad \text{a.e. on } Q. \tag{4.47}$$

Moreover, it follows from (3.22), (3.36) and the Gagliardo–Nirenberg inequality that

$$\begin{aligned}
&\int_0^T \int_\Omega \left|s_\delta f_\delta \rho_\delta(m_\delta)\psi(f_\delta)\right|^2 dxds \\
&\quad \leq C \int_0^T \int_\Omega \left|s_\delta \rho_\delta(m_\delta)\right|^2 dxds \leq C \int_0^T \left\|s_\delta(s)\right\|^2_{L^4(\Omega)} \left\|\rho_\delta(m_\delta)(s)\right\|^2_{L^4(\Omega)} ds \leq C \int_0^T \left\|\rho_\delta(m_\delta)(s)\right\|^2_{L^4(\Omega)} ds \\
&\quad \leq C \int_0^T \left\|\rho_\delta(m_\delta)(s)\right\|_{H^1(\Omega)} \left\|\rho_\delta(m_\delta)(s)\right\|_{L^2(\Omega)} ds \\
&\quad \leq \frac{C}{2} \int_0^T \left\|\rho_\delta(m_\delta)(s)\right\|^2_{H^1(\Omega)} ds + \frac{C}{2} \int_0^T \left\|\rho_\delta(m_\delta)(s)\right\|^2_{L^2(\Omega)} ds \leq C,
\end{aligned} \tag{4.48}$$

where C is a constant independent of $\delta > 0$. It follows from Lions [18, Lemma 1.3] that

$$s_\delta f_\delta \rho_\delta(m_\delta)\psi(f_\delta) \rightharpoonup sfm\psi(f) \quad \text{weakly in } L^2(Q). \tag{4.49}$$

Taking the limit when $\delta \to 0^+$ and (4.46), it follows from (4.21), (4.41), (4.42) and (4.49) that

$$\int_0^t \int_\Omega \psi(f)\partial_t s\varphi dxds + D_n \int_0^t \int_\Omega \psi(f)\nabla s\nabla\varphi dxds = \frac{\alpha\chi}{D_n} \int_0^t \int_\Omega sfm\psi(f)\varphi dxds, \tag{4.50}$$

for every $t \in [0,T]$ and for all $\varphi \in L^2(0,T;H^1(\Omega))$.

From estimates (4.22) and (4.23), we can obtain subsequences, that will continue denoting by (m_δ) and (c_δ), such that passing the limit in the equations

$$\begin{cases} \partial_t m_\delta - D_m\Delta m_\delta = \mu s_\delta\psi(f_\delta) - \lambda m_\delta + u & \text{in } Q, \\ m_\delta(0) = m_0^\delta & \text{in } \Omega, \\ D_m\nabla m_\delta.\eta = 0 & \text{on } S, \end{cases} \tag{4.51}$$

and

$$\begin{cases} \partial_t c_\delta - D_c\Delta c_\delta = \beta f_\delta - \gamma s_\delta\psi(f_\delta) - \sigma c_\delta & \text{in } Q, \\ c_\delta(0) = c_0^\delta & \text{in } \Omega, \\ D_c\nabla c_\delta.\eta = 0 & \text{on } S, \end{cases} \tag{4.52}$$

we obtain

$$\begin{cases} \partial_t m - D_m\Delta m = \mu s\psi(f) - \lambda m + u & \text{in } Q, \\ m(0) = m_0 & \text{in } \Omega, \\ D_m\nabla m.\eta = 0 & \text{on } S \end{cases} \tag{4.53}$$

and

$$\begin{cases} \partial_t c - D_c\Delta c = \beta f - \gamma s\psi(f) - \sigma c & \text{in } Q, \\ c(0) = c_0 & \text{in } \Omega, \\ D_c\nabla c.\eta = 0 & \text{on } S. \end{cases} \tag{4.54}$$

By (3.11), (3.20), (4.35) and the convergences (4.20), (4.28) and (4.44) and the fact that $n_\delta = \psi(f_\delta)s_\delta$, we conclude by limit that

$$n \geq 0, \qquad f \geq 0 \quad \text{and} \quad m \geq 0. \tag{4.55}$$

Computing the change of variable $n = \psi(f)s$ in (4.50) and differentiating we have

$$n_t = -\alpha\frac{\chi}{D_n}\psi(f)mfs + \psi(f)s_t.$$

We conclude that

$$|n_t|^2 \leq 2\left(\alpha\frac{\chi}{D_n}C\right)^4 \|f\|^4_{L^\infty(Q)}|m|^4 + 2|s|^4 + C|s_t|^2.$$

Integrating in Q, and using (3.5), (3.36) and (4.7) we obtain

$$\int_Q |n_t|^2 dxdt \leq 2\left(\alpha\frac{\chi}{D_n}C\right)^4 \|f\|^4_{L^\infty(Q)} \int_Q |m|^4 dxdt + 2\int_Q |s|^4 dxdt + C\int_Q |s_t|^2 dxdt \leq C. \tag{4.56}$$

It follows from (3.37) that

$$\|n\|_{L^q(Q)} \leq C, \tag{4.57}$$

for all $q \geq 1$.

Therefore from (4.40), (4.53), (4.54), (4.55), (4.56) and (4.57) we conclude the proof of Theorem 2.2.

5. Proof of Theorem 2.7

We assume that there exist two solutions of (1.1)–(1.3) denoted by (n_1, f_1, m_1, c_1) and (n_2, f_2, m_2, c_2). The differences $n = n_1 - n_2$, $f = f_1 - f_2$, $m = m_1 - m_2$, $c = c_1 - c_2$ and $u = u_1 - u_2$ satisfy

$$\begin{gathered}\int_0^\tau \int_\Omega (\partial_t n \phi_1 + D_n \nabla n \nabla \phi_1) dx dt = \int_0^\tau \int_\Omega \chi n_1 \nabla f \nabla \phi_1 dx dt + \chi \int_0^\tau \int_\Omega n \nabla f_2 \nabla \phi_1 dx dt, \\ \partial_t f + \alpha m_1 f + \alpha f_2 m = 0, \qquad \partial_t m - D_m \Delta m = \mu n - \lambda m + u, \\ \partial_t c - D_c \Delta c = \beta f - \gamma n - \sigma c, \qquad n(0) = f(0) = m(0) = c(0) = 0, \quad \text{on } \Omega\end{gathered} \tag{5.1}$$

for any $\tau \in [0, T]$ and for all $\phi_1 \in L^2(0, T; H^1(\Omega))$. Using n as test function in (5.1), we obtain, for any $\tau \in [0, T]$

$$\frac{1}{2} \int_\Omega |n(\tau)|^2 dx + D_n \int_0^\tau \int_\Omega |\nabla n|^2 dx ds = \int_0^\tau \int_\Omega \chi n_1 \nabla f \nabla n dx ds + \chi \int_0^\tau \int_\Omega n \nabla f_2 \nabla n dx ds, \tag{5.2}$$

by Theorem 2.2(i), Gronwall and Gagliardo–Nirenberg inequalities, we estimate

$$\begin{aligned}&\chi \int_0^\tau \int_\Omega n \nabla f_2 \nabla n dx ds \\ &\leq \chi \int_0^\tau \|n(s)\|_{L^4(\Omega)} \|\nabla f_2(s)\|_{L^4(\Omega)} \|\nabla n(s)\|_{L^2(\Omega)} ds \leq C \int_0^\tau \|n(s)\|_{L^4(\Omega)} \|\nabla n(s)\|_{L^2(\Omega)} ds \\ &\leq C \int_0^\tau \|\nabla n(s)\|_{L^2(\Omega)}^{3/2} \|n(s)\|_{L^2(\Omega)}^{1/2} ds \leq \frac{\epsilon}{2} \int_0^\tau \|\nabla n(s)\|_{L^2(\Omega)}^2 ds + C(\epsilon) \int_0^\tau \|n(s)\|_{L^2(\Omega)}^2 ds.\end{aligned} \tag{5.3}$$

By (3.37), Theorem 2.2(i) and Gronwall inequality we estimate

$$\begin{aligned}\int_0^\tau \int_\Omega \chi n_1 \nabla f \nabla n dx ds &\leq \int_0^\tau \chi \|n_1\|_{L^4(\Omega)} \|\nabla f\|_{L^4(\Omega)} \|\nabla n\|_{L^2(\Omega)} ds \\ &\leq C \int_0^\tau \|\nabla f(s)\|_{L^4(\Omega)}^2 ds + \frac{D_n}{2} \int_0^\tau \|\nabla n(s)\|_{L^2(\Omega)}^2 ds.\end{aligned} \tag{5.4}$$

Differentiating the equation for f with respect to x_i, $1 \leq i \leq 2$, and using $|f_{x_i}|^2 f_{x_i}$ as a test function, we obtain for $\eta \in [0, t]$, with $t \leq T$,

$$\int_0^\eta \int_\Omega (\partial_t f_{x_i} + \alpha \partial_{x_i} m_1 f + m_1 f_{x_i} + \alpha \partial_{x_i} f_2 m + f_2 m_{x_i}) |f_{x_i}|^2 f_{x_i} dx ds = 0. \tag{5.5}$$

We have

$$\begin{aligned}\int_0^\eta\int_\Omega \partial_t|f_{x_i}|^4 dxds &\le C\int_0^\eta\int_\Omega \big(|\partial_{x_i}m_1||f||f_{x_i}|^3 + |\partial_{x_i}f_2||m||f_{x_i}|^3 + |f_2||m_{x_i}||f_{x_i}|^3\big)dxds \\ &\le C\int_0^\eta\int_\Omega\left(\epsilon|m_{x_i}|^4 + \frac{3}{\epsilon}|f_{x_i}|^4\right)dxds + \epsilon\|m\|^4_{L^4(0,\eta;L^8(\Omega))}\|\partial_{x_i}f_2\|^4_{L^\infty(0,\eta;L^8(\Omega))} \\ &\quad + \epsilon\|\partial_{x_i}m_1\|^4_{L^4(0,\eta;L^8(\Omega))}\|f\|^4_{L^\infty(0,\eta;L^8(\Omega))}. \end{aligned} \tag{5.6}$$

For the Sobolev embedding theorem (with $n = 2$), the third equation in (5.1) and (3.5) yield

$$\|m\|^4_{L^4(0,\eta;L^8(\Omega))} \le C\|m\|^4_{L^8(Q_\eta)} \le C\|m\|^4_{W_4^{2,1}(Q_\eta)} \le C\big(\|n\|^4_{L^4(Q_\eta)} + \|u\|^4_{L^2(Q_\eta)}\big).$$

Since,

$$f_i(x,t) = f_0(x)\exp\left(-\alpha\int_0^t m_i(x,s)ds\right), \quad i = 1,2.$$

By the mean value theorem we have

$$f = f_0(x)\exp\left(-\lambda\alpha\int_0^t m_1(x,s)ds - (1-\lambda)\alpha\int_0^t m_2(x,s)ds\right)\times\left[-\alpha\int_0^t mds\right],$$

for $0 \le \lambda \le 1$. Therefore,

$$|f_1 - f_2| \le \alpha\big|f_0(x)\big|\left[\int_0^t |m_1 - m_2|ds\right].$$

We conclude that

$$\big\|f(t)\big\|^4_{L^8(\Omega)} \le \alpha^4 T^{7/2}\|f_0\|^4_{L^\infty(\Omega)}\|m\|^4_{L^8(Q_t)}. \tag{5.7}$$

The Sobolev embedding theorem (with $n = 2$), (3.5) and (5.7) yield

$$\big\|f(t)\big\|^4_{L^8(\Omega)} \le \alpha^4 T^{7/2}\|f_0\|^4_{L^\infty(\Omega)}C\big(\|n\|^4_{L^4(Q_\eta)} + \|u\|^4_{L^4(Q_\eta)}\big). \tag{5.8}$$

Thus, using

$$\|\nabla f_2\|^4_{L^\infty(0,\eta;L^8(\Omega))} \le C, \qquad \|\nabla m_1\|^4_{L^4(0,\eta;L^8(\Omega))} \le C\big(\|n_1\|_{L^4(Q)}, \|u_1\|_{L^4(Q)}\big)$$

and (5.6) we obtain

$$\int_\Omega \big|f_{x_i}(\eta)\big|^4 dx \le C\int_0^\eta\int_\Omega\left(\epsilon|m_{x_i}|^4 + \frac{3}{\epsilon}|f_{x_i}|^4\right)dxds + \epsilon C\big(\|n\|^4_{L^4(Q_\eta)} + \|u\|^4_{L^4(Q_\eta)}\big). \tag{5.9}$$

Hence

$$\int_\Omega \left|\nabla f(\eta)\right|^4 dx \le C\int_0^\eta \int_\Omega \left(\epsilon|\nabla m|^4 + \frac{3}{\epsilon}|\nabla f|^4\right) dxds + \epsilon 2C\left(\|n\|^4_{L^4(Q_\eta)} + \|u\|^4_{L^4(Q_\eta)}\right). \tag{5.10}$$

On the other hand, by Gagliardo–Nirenberg inequality and (3.37)

$$\begin{aligned}\int_0^\eta \int_\Omega |\nabla m|^4 dxds &= \|\nabla m\|^4_{L^4(Q_\eta)} \le \|m\|^4_{W_4^{2,1}(Q_\eta)} \le C\left(\|n\|^4_{L^4(Q_\eta)} + \|u\|^4_{L^4(Q_\eta)}\right)\\ &\le C\left(\sup_{0\le s\le\eta}\left\|n(s)\right\|^2_{L^2(\Omega)} \int_0^\eta \left\|\nabla n(s)\right\|^2_{L^2(\Omega)} ds + \|u\|^4_{L^4(Q_\eta)}\right)\\ &\le C\left(\left(\sup_{0\le s\le\eta}\left\|n(s)\right\|^2_{L^2(\Omega)}\right)^2 + T\|\nabla n\|^4_{L^2(Q_\eta)} + \|u\|^4_{L^4(Q_\eta)}\right).\end{aligned} \tag{5.11}$$

By (5.10), (5.11) and Gagliardo–Nirenberg inequality we have

$$\begin{aligned}\int_\Omega \left|\nabla f(\eta)\right|^4 dx &\le \epsilon C\left(\left(\sup_{0\le s\le\eta}\left\|n(s)\right\|^2_{L^2(\Omega)}\right)^2 + T\|\nabla n\|^4_{L^2(Q_\eta)}\right)\\ &\quad + C\int_0^\eta \int_\Omega \left(\frac{3}{\epsilon}|\nabla f|^4\right) dxds + \epsilon C\|u\|^4_{L^4(Q_\eta)}.\end{aligned} \tag{5.12}$$

By the Gronwall's inequality we conclude that

$$\left\|\nabla f(\eta)\right\|^4_{L^4(\Omega)} \le \epsilon C\left(\left(\sup_{0\le s\le\eta}\left\|n(s)\right\|^2_{L^2(\Omega)}\right)^2 + T\|\nabla n\|^4_{L^2(Q_\eta)}\right) + \epsilon C\|u\|^4_{L^4(Q_\eta)}. \tag{5.13}$$

Therefore,

$$\left\|\nabla f(\eta)\right\|^2_{L^4(\Omega)} \le \epsilon^{1/2} C\left(\sup_{0\le s\le\eta}\left\|n(s)\right\|^2_{L^2(\Omega)} + T^{1/2}\|\nabla n\|^2_{L^2(Q_\eta)} + \|u\|^2_{L^4(Q_\eta)}\right).$$

Integrating from 0 to τ, with $\tau \le T$ we have

$$\int_0^\tau \left\|\nabla f(\eta)\right\|^2_{L^4(\Omega)} d\eta \le \epsilon^{1/2} TC\left(\sup_{0\le s\le\tau}\left\|n(s)\right\|^2_{L^2(\Omega)} + T^{1/2}\|\nabla n\|^2_{L^2(Q_\tau)} + \|u\|^2_{L^4(Q_\tau)}\right). \tag{5.14}$$

By (5.2), (5.3), (5.4) and (5.14)

$$\begin{aligned}&\frac{1}{2}\int_\Omega \left|n(\tau)\right|^2 dx + D_n \int_0^\tau \int_\Omega |\nabla n|^2 dxds\\ &\le \epsilon^{1/2} TC\left(\sup_{0\le s\le\tau}\left\|n(s)\right\|^2_{L^2(\Omega)} + T^{1/2}\|\nabla n\|^2_{L^2(Q_\tau)} + \|u\|^2_{L^4(Q_\tau)}\right)\\ &\quad + \frac{D_n}{2}\int_0^\tau \left\|\nabla n(s)\right\|^2_{L^2(\Omega)} ds + \frac{\epsilon}{2}\int_0^\tau \left\|\nabla n(s)\right\|^2_{L^2(\Omega)} ds + C(\epsilon)\int_0^\tau \left\|n(s)\right\|^2_{L^2(\Omega)} ds.\end{aligned} \tag{5.15}$$

Grouping the corresponding terms we conclude that

$$\frac{1}{2}\int\limits_{\Omega}|n(\tau)|^2dx + \left(\frac{D_n}{2} - \frac{\epsilon}{2} - \epsilon^{1/2}T^{3/2}C\right)\int\limits_0^\tau\int\limits_\Omega |\nabla n|^2 dxds$$
$$\leq \epsilon^{1/2}TC\Big(\sup_{0\leq s\leq\tau}\|n(s)\|^2_{L^2(\Omega)} + \|u\|^2_{L^4(Q_\tau)}\Big) + C(\epsilon)\int\limits_0^\tau \|n(s)\|^2_{L^2(\Omega)}ds. \tag{5.16}$$

To $\epsilon > 0$ small enough, such that, $\frac{D_n}{2} - \frac{\epsilon}{2} - \epsilon^{1/2}T^{3/2}C > 0$ and considering the supreme of 0 to t, with $t \leq T$ and using that $\tau \leq t$ we conclude that

$$\left(\frac{1}{2} - \epsilon^{1/2}TC\right)\sup_{0\leq s\leq t}\|n(s)\|^2_{L^2(\Omega)} + \left(\frac{D_n}{2} - \frac{\epsilon}{2} - \epsilon^{1/2}T^{3/2}C\right)\int\limits_0^t\int\limits_\Omega |\nabla n|^2 dxds$$
$$\leq \epsilon^{1/2}TC\|u\|^2_{L^4(Q_t)} + C(\epsilon)\int\limits_0^t \|n(s)\|^2_{L^2(\Omega)}ds. \tag{5.17}$$

By the Gronwall's inequality in (5.17) we obtain

$$\|n(t)\|^2_{L^2(\Omega)} + \int\limits_0^t\int\limits_\Omega |\nabla n|^2 dxds \leq C\|u\|^2_{L^4(Q_t)}. \tag{5.18}$$

As $u_1 - u_2 \in L^4(Q) \subset L^2(Q)$, it follows from regularity for linear parabolic differential equations, see Ladyzenskaja [16, Theorem 9.1, p. 341], we conclude from the last two equations of (5.1) that

$$\|m_1 - m_2\|^2_{W_2^{2,1}(Q)} \leq C\|u_1 - u_2\|^2_{L^2(Q)} \tag{5.19}$$

and

$$\|c_1 - c_2\|^2_{W_2^{2,1}(Q)} \leq C\big(\|f_1 - f_2\|^2_{L^2(Q)} + \|n_1 - n_2\|^2_{L^2(Q)}\big). \tag{5.20}$$

By (5.8), (5.14), (5.18), (5.19) and (5.20) we obtain

$$\|n_1 - n_2\|^2_{L^2(0,T;H^1(\Omega))} + \|m_1 - m_2\|^2_{W_2^{2,1}(Q)} + \|c_1 - c_2\|^2_{W_2^{2,1}(Q)} + \|f_1 - f_2\|^2_{L^2(0,T;W_4^1(\Omega))}$$
$$\leq C\|u_1 - u_2\|^2_{L^4(Q)}, \tag{5.21}$$

where C is a positive constant that depends on the constants of the problem and the initial data.

6. The optimal control problem

6.1. The solution operator of (1.1)–(1.3)

In this section we will study the operator $F : L^4(Q) \to L^2(0,T;H^1(\Omega)) \times L^2(0,T;W_4^1(\Omega)) \times W_2^{2,1}(Q) \times W_2^{2,1}(Q)$, which maps the source term $u \in L^4(Q)$ of (1.1) into the corresponding solution $(n, f, m, c) \in V \times W \times W_2^{2,1}(Q) \times W_2^{2,1}(Q)$, where $V = \{n \in L^2(0,T;H^1(\Omega)); n_t \in L^2(Q)\}$ and $W = \{f \in L^2(0,T;W_4^1(\Omega)); f_t \in L^2(Q)\}$. We will prove that F is Fréchet differentiable. From Theorem 2.2, F maps $L^4(Q)$ into $L^2(0,T;H^1(\Omega)) \times L^2(0,T;W_4^1(\Omega)) \times W_2^{2,1}(Q) \times W_2^{2,1}(Q)$. Furthermore in Theorem 2.7 it was proved that F is Lipschitz continuous. Suppose $u \in L^4(Q)$ and consider a perturbation $\delta u \in L^4(Q)$.

Theorem 6.1. *Let u, $u+\delta u \in L^4(Q)$ with $F(u)$, $F(u+\delta u)$ being the corresponding solutions of (1.1)–(1.3) respectively. Then*

$$\big\|F(u+\delta u) - F(u) - F'(u)\delta u\big\|_{L^2(0,T;H^1(\Omega))\times L^2(0,T;W_4^1(\Omega))\times (W_2^{2,1}(Q))^2} \le C\|\delta u\|^2_{L^4(Q)}, \tag{6.1}$$

where $F'(u) : L^4(Q) \to L^2(0,T;H^1(\Omega)) \times L^2(0,T;W_4^1(\Omega)) \times W_2^{2,1}(Q) \times W_2^{2,1}(Q)$ is a linear operator, and $(n^*, f^*, m^*, c^*) = F'(u)\delta u$ is the solution of the problem

$$\begin{gathered}
\partial_t n^* - D_n \Delta n^* = -\chi \nabla\big[n^*\nabla f + n\nabla f^*\big] \quad \text{in } Q,\\
\partial_t f^* = -\alpha\big(m^* f + m f^*\big) \quad \text{in } Q,\\
\partial_t m^* - D_m \Delta m^* = \mu n^* - \lambda m^* + \delta u \quad \text{in } Q,\\
\partial_t c^* - D_c \Delta c^* = \beta f^* - \gamma n^* - \sigma c^* \quad \text{in } Q,\\
\big(D_n \nabla n^* - \chi\big(n^*\nabla f + n\nabla f^*\big)\big)\eta = \frac{\partial m^*}{\partial \eta} = \frac{\partial c^*}{\partial \eta} = 0 \quad \text{on } S,\\
n^*(0) = f^*(0) = m^*(0) = c^*(0) = 0 \quad \text{in } \Omega,
\end{gathered} \tag{6.2}$$

where n, f and m are the first three components of $F(u)$.

Proof. By Theorem 2.7

$$\begin{aligned}
&\|n_\delta - n\|_{L^2(0,T;H^1(\Omega))} + \|f_\delta - f\|_{L^2(0,T;W_4^1(\Omega))} + \|m_\delta - m\|_{W_2^{2,1}(Q)} + \|c_\delta - c\|_{W_2^{2,1}(Q)}\\
&\quad \le C\|\delta u\|_{L^4(Q)},
\end{aligned} \tag{6.3}$$

where C is a positive constant that depends on the constants of the problem and the initial data.

Defining:

$$\widehat{n} = n_\delta - n - n^*, \qquad \widehat{f} = f_\delta - f - f^*, \qquad \widehat{m} = m_\delta - m - m^*, \qquad \widehat{c} = c_\delta - c - c^*;$$

it is not difficult to verify that $(\widehat{n}, \widehat{f}, \widehat{m}, \widehat{c})$ satisfies the following system:

$$\begin{cases}
\partial_t \widehat{n} - D_n \Delta \widehat{n} = -\chi \nabla(\widehat{n}\nabla f + n\nabla \widehat{f}) + \nabla\big((n_\delta - n).\nabla(f_\delta - f)\big) & \text{in } Q,\\
\partial_t \widehat{f} = -\alpha[\widehat{m} f + m\widehat{f}] - \alpha(m_\delta - m)(f_\delta - f) & \text{in } Q,\\
\partial_t \widehat{m} - D_m \Delta \widehat{m} = \mu \widehat{n} - \lambda \widehat{m} & \text{in } Q,\\
\partial_t \widehat{c} - D_c \Delta \widehat{c} = \beta \widehat{f} - \gamma \widehat{n} - \sigma \widehat{c} & \text{in } Q,\\
\widehat{n}(0) = \widehat{m}(0) = \widehat{f}(0) = \widehat{c}(0) = 0 & \text{in } \Omega,\\
\big(D_n \nabla \widehat{n} - \chi n_\delta \nabla f_\delta + \chi n \nabla f + (n^*\nabla f + n\nabla f^*)\big)\cdot \eta = 0 & \text{on } S,\\
D_m \nabla \widehat{m}.\eta = D_c \nabla \widehat{c}.\eta = 0 & \text{on } S.
\end{cases} \tag{6.4}$$

Remark 6.2. The same method used in the proof of Theorem 2.2 can also be applied to prove the existence of solutions for systems (6.2) and (6.4). But the linear structure and regularity of the coefficients, as well as the existence of solutions to problems (6.2) and (6.4) can be proved by other linear equations methods.

By linear theory for parabolic equations, it follows from the third and fourth equations of (6.4) that

$$\|\widehat{m}\|_{W_4^{2,1}(Q)} \le C\|\widehat{n}\|_{L^4(Q)} \tag{6.5}$$

and

$$\|\widehat{c}\|_{W_2^{2,1}(Q)} \le C\big(\|\widehat{n}\|_{L^2(Q)} + \|\widehat{f}\|_{L^2(Q)}\big). \tag{6.6}$$

Multiplying the first equation of (6.4) by $\widehat{n}$ and integrating on Ω, using integration by parts, Hoelder's inequality, Young's inequality and (4.39) we obtain

$$\begin{aligned}
\frac{1}{2}\int_\Omega \frac{\partial}{\partial t}\big|\widehat{n}(t)\big|^2 dx + \int_\Omega |\nabla\widehat{n}|^2 dx \le{}& \frac{1}{2\epsilon}\big\|\nabla f(t)\big\|^2_{L^\infty(\Omega)} \int_\Omega \big|\widehat{n}(t)\big|^2 dx \\
&+ \frac{3\epsilon}{2}\int_\Omega \big|\nabla\widehat{n}(t)\big|^2 dx + \frac{1}{2\epsilon}\big\|n(t)\big\|^2_{L^4(\Omega)}\|\nabla\widehat{f}\|^2_{L^4(\Omega)} \\
&+ \frac{1}{2\epsilon}\bigg(\int_\Omega |n_\delta - n|^4 dx\bigg)^{1/2}\bigg(\int_\Omega \big|\nabla(f_\delta - f)\big|^4 dx\bigg)^{1/2},
\end{aligned} \tag{6.7}$$

integrating from 0 to t, with $t \le T$ we conclude

$$\begin{aligned}
&\frac{1}{2}\int_\Omega \big|\widehat{n}(t)\big|^2 dx + \bigg(1 - \frac{3\epsilon}{2}\bigg)\int_0^t\int_\Omega |\nabla\widehat{n}|^2 dx \\
&\quad\le \frac{1}{2\epsilon}\|\nabla f\|^2_{L^\infty(Q)}\int_0^t\int_\Omega \big|\widehat{n}(s)\big|^2 dxds + \frac{1}{2\epsilon}\int_0^t \big\|n(s)\big\|^2_{L^4(\Omega)}\big\|\nabla\widehat{f}(s)\big\|^2_{L^4(\Omega)} ds \\
&\qquad+ \frac{1}{4\epsilon}\int_0^t\int_\Omega |n_\delta - n|^4 dxds + \frac{1}{4\epsilon}\int_0^t\int_\Omega \big|\nabla(f_\delta - f)\big|^4 dxds.
\end{aligned} \tag{6.8}$$

Multiplying the second equation of (6.4) by $|\widehat{f}|^2\widehat{f}$ and integrating in Ω, using Hoelder's inequality and Young's inequality we obtain

$$\begin{aligned}
\frac{1}{4}\int_\Omega \frac{\partial}{\partial t}\big|\widehat{f}(t)\big|^4 dx \le{}& \frac{\alpha^4}{4}\|f\|^4_{L^\infty Q}\int_\Omega \big|\widehat{m}(t)\big|^4 dx + \frac{3}{4}\int_\Omega \big|\widehat{f}(t)\big|^4 dx \\
&+ \frac{\alpha^4}{4}\int_\Omega |m_\delta - m|^4|f_\delta - f|^4 dx + \frac{3}{4}\int_\Omega \big|\widehat{f}(t)\big|^4 dx.
\end{aligned} \tag{6.9}$$

Integrating from 0 to t, with $t \le T$ we conclude that

$$\begin{aligned}
\frac{1}{4}\int_\Omega \big|\widehat{f}(t)\big|^4 dx \le{}& \frac{\alpha^4}{4}\|f\|^4_{L^\infty Q}\int_0^t\int_\Omega \big|\widehat{m}(s)\big|^4 dxds + \frac{3}{2}\int_0^t\int_\Omega \big|\widehat{f}(s)\big|^4 dxds \\
&+ \frac{\alpha^8}{8}\int_0^t\int_\Omega |m_\delta - m|^8 dxds + \frac{1}{2}\int_0^t\int_\Omega |f_\delta - f|^8 dxds.
\end{aligned} \tag{6.10}$$

Differentiating the second equation in (6.4) with respect to x_i, for $i = 1, 2$, we conclude

$$\begin{aligned}
(\widehat{f}_{x_i})_t ={}& -\alpha[\widehat{m}_{x_i} f + \widehat{m} f_{x_i} + m_{x_i}\widehat{f} + m\widehat{f}_{x_i}] \\
&- \alpha(m_\delta - m)_{x_i}(f_\delta - f) - \alpha(m_\delta - m)(f_\delta - f)_{x_i}.
\end{aligned} \tag{6.11}$$

Multiplying Eq. (6.11) by $|\widehat{f}_{x_i}|^2\widehat{f}_{x_i}$ and integrating on Ω, using Hoelder's inequality and Young's inequality we obtain

$$\begin{aligned}\frac{1}{4}\int_\Omega \frac{\partial}{\partial t}\left|\widehat{f}_{x_i}(t)\right|^4dx \le{}& \frac{\alpha^4}{4}\|f\|^4_{L^\infty(Q)}\int_\Omega\left|\widehat{m}_{x_i}(t)\right|^4dx+\frac{15}{4}\int_\Omega\left|\widehat{f}_{x_i}(t)\right|^4dx\\ &+\frac{\alpha^4}{4}\left\|\nabla f(t)\right\|^4_{L^\infty(\Omega)}\int_\Omega\left|\widehat{m}(t)\right|^4dx+\frac{\alpha^4}{4}\left\|\nabla m(t)\right\|^4_{L^\infty(\Omega)}\int_\Omega\left|\widehat{f}(t)\right|^4dx\\ &+\frac{\alpha^8}{8}\int_\Omega\left|\nabla(m_\delta-m)(t)\right|^8dx+\frac{1}{8}\int_\Omega|f_\delta-f|^8dx\\ &+\frac{\alpha^4}{4}\|m_\delta-m\|^4_{L^\infty(Q)}\int_\Omega\left|\nabla(f_\delta-f)(t)\right|^4dx. \end{aligned}\tag{6.12}$$

Integrating from 0 to t, with $t\le T$ we conclude

$$\begin{aligned}\frac{1}{4}\int_\Omega\left|\nabla\widehat{f}(t)\right|^4dx \le{}& \frac{\alpha^4}{4}\|f\|^4_{L^\infty(Q)}\int_0^t\int_\Omega\left|\nabla\widehat{m}(s)\right|^4dxds+\frac{15}{4}\int_0^t\int_\Omega\left|\nabla\widehat{f}(s)\right|^4dxds\\ &+\frac{\alpha^4}{4}\|\nabla f\|^4_{L^\infty(Q)}\int_0^t\int_\Omega\left|\widehat{m}(x,s)\right|^4dxds\\ &+\frac{\alpha^4}{4}\int_0^t\left\|\nabla m(s)\right\|^4_{L^\infty(\Omega)}ds\sup_{0\le t\le T}\int_\Omega\left|\widehat{f}(t)\right|^4dx\\ &+\frac{\alpha^8}{8}\int_0^t\int_\Omega\left|\nabla(m_\delta-m)(s)\right|^8dxds+\frac{1}{8}\int_0^t\int_\Omega|f_\delta-f|^8dxds\\ &+\frac{\alpha^4}{4}\|m_\delta-m\|^4_{L^\infty(Q)}\int_0^t\int_\Omega\left|\nabla(f_\delta-f)(s)\right|^4dxds. \end{aligned}\tag{6.13}$$

From (6.8), applying Jensen's inequality, we have

$$\begin{aligned}\left\|\widehat{n}(t)\right\|^4_{L^2(\Omega)} \le{}& \frac{1}{\epsilon^2}T\|\nabla f\|^4_{L^\infty(Q)}\int_0^t\left\|\widehat{n}(s)\right\|^4_{L^2(\Omega)}ds\\ &+\frac{1}{\epsilon^2}T\int_0^t\left\|n(s)\right\|^4_{L^4(\Omega)}\left\|\nabla\widehat{f}(s)\right\|^4_{L^4(\Omega)}ds\\ &+\left(\frac{1}{2\epsilon}\int_0^t\int_\Omega|n_\delta-n|^4dxds+\frac{1}{2\epsilon}\int_0^t\int_\Omega\left|\nabla(f_\delta-f)\right|^4dxds\right)^2. \end{aligned}\tag{6.14}$$

Adding inequalities (6.10), (6.13) and (6.14) and using (3.5), (3.37), (4.38) and (4.39) we obtain

$$\left\|\widehat{n}(t)\right\|^4_{L^2(\Omega)}+\int_\Omega\left|\widehat{f}(t)\right|^4dx+\int_\Omega\left|\nabla\widehat{f}(t)\right|^4dx$$

$$
\begin{aligned}
&\le C\int_0^t\Big(\big\|\widehat{n}(s)\big\|_{L^2(\Omega)}^4+\int_\Omega\big|\widehat{f}(s)\big|^4dx+\int_\Omega\big|\nabla\widehat{f}(s)\big|^4dx\Big)ds\\
&\quad+C\int_0^t\int_\Omega\big|(m_\delta-m)(s)\big|^8dxds+C\int_0^t\int_\Omega|f_\delta-f|^8dxds\\
&\quad+C\Big(\int_0^t\int_\Omega|n_\delta-n|^4dxds+\int_0^t\int_\Omega\big|\nabla(f_\delta-f)\big|^4dxds\Big)^2\\
&\quad+C\int_0^t\int_\Omega\big|\nabla(m_\delta-m)(s)\big|^8dxds\\
&\quad+C\|m_\delta-m\|_{L^\infty(Q)}^4\int_0^t\int_\Omega\big|\nabla(f_\delta-f)(s)\big|^4dxds. \qquad (6.15)
\end{aligned}
$$

Applying Gronwall's lemma to (6.15) we conclude

$$
\begin{aligned}
&\big\|\widehat{n}(t)\big\|_{L^2(\Omega)}^4+\big\|\widehat{f}(t)\big\|_{L^4(\Omega)}^4+\big\|\nabla\widehat{f}(t)\big\|_{L^4(\Omega)}^4\\
&\quad\le C\big(\|m_\delta-m\|_{L^8(Q)}^8+\big\|\nabla(m_\delta-m)\big\|_{L^8(Q)}^8+\|f_\delta-f\|_{L^8(Q)}^8+\big(\|n_\delta-n\|_{L^4(Q)}^4+\big\|\nabla(f_\delta-f)\big\|_{L^4(Q)}^4\big)^2\\
&\qquad+\|m_\delta-m\|_{L^\infty(Q)}^4\big\|\nabla(f_\delta-f)\big\|_{L^4(Q)}^4\big) \qquad (6.16)
\end{aligned}
$$

for all t, $0\le t\le T$. From which we conclude that

$$
\begin{aligned}
&\big\|\widehat{n}(t)\big\|_{L^2(\Omega)}^2+\big\|\widehat{f}(t)\big\|_{L^4(\Omega)}^2+\big\|\nabla\widehat{f}(t)\big\|_{L^4(\Omega)}^2\\
&\quad\le C\big(\|m_\delta-m\|_{L^8(Q)}^4+\big\|\nabla(m_\delta-m)\big\|_{L^8(Q)}^4+\|f_\delta-f\|_{L^8(Q)}^4+\|n_\delta-n\|_{L^4(Q)}^4+\big\|\nabla(f_\delta-f)\big\|_{L^4(Q)}^4\\
&\qquad+\|m_\delta-m\|_{L^\infty(Q)}^2\big\|\nabla(f_\delta-f)\big\|_{L^4(Q)}^2\big), \qquad (6.17)
\end{aligned}
$$

for all t, $0\le t\le T$.

By the Gagliardo–Nirenberg inequality we conclude that

$$
\begin{aligned}
&\big\|\widehat{n}(t)\big\|_{L^2(\Omega)}^2+\big\|\widehat{f}(t)\big\|_{L^4(\Omega)}^2+\big\|\nabla\widehat{f}(t)\big\|_{L^4(\Omega)}^2\\
&\quad\le C\Bigg(\|m_\delta-m\|_{W_4^{2,1}(Q)}^4+\Big(\int_0^T\|f_\delta-f\|_{L^8(\Omega)}^8\Big)^{1/2}+\int_0^T\|n_\delta-n\|_{L^2(\Omega)}^2\big\|\nabla(n_\delta-n)\big\|_{L^2(\Omega)}^2ds\\
&\qquad+\int_0^T\big\|\nabla(f_\delta-f)\big\|_{L^4(\Omega)}^4ds+\|m_\delta-m\|_{W_4^{2,1}(Q)}^2\Big(\int_0^T\big\|\nabla(f_\delta-f)\big\|_{L^4(\Omega)}^4ds\Big)^{1/2}\Bigg), \qquad (6.18)
\end{aligned}
$$

for all t, $0\le t\le T$.

From (5.8) and (5.13) with $f=f_\delta-f$, $n=n_\delta-n$, $u=\delta u$, (5.18) and (6.3) we conclude

$$
\big\|\widehat{n}(t)\big\|_{L^2(\Omega)}^2+\big\|\widehat{f}(t)\big\|_{L^4(\Omega)}^2+\big\|\nabla\widehat{f}(t)\big\|_{L^4(\Omega)}^2\le C\|\delta u\|_{L^4(Q)}^4, \qquad (6.19)
$$

for all t, $0\le t\le T$.

From (6.5), (6.6), (6.8) and (6.19) we obtain

$$\|\widehat{n}\|_{L^2(0,T;H^1(\Omega))} + \|\widehat{f}\|_{L^2(0,T;W^1_4(\Omega))} + \|\widehat{m}\|_{W^{2,1}_2(Q)} + \|\widehat{c}\|_{W^{2,1}_2(Q)} \le C\|\delta u\|^2_{L^4(Q)}, \tag{6.20}$$

where C depends on $T, \|n_1\|_{L^4(Q)}, \|u_1\|_{L^4(Q)}, \|f_0\|_{L^\infty(\Omega)}, \|\nabla f_0\|_{L^\infty(\Omega)}, \|f_0\|_{H^2(\Omega)}$ and other constants of the problem. □

Remark 6.3. According to the definition of the Fréchet-derivative the operator $F'(u) : L^4(Q) \to L^2(0,T; H^1(\Omega)) \times L^2(0,T;W^1_4(\Omega)) \times W^{2,1}_2(Q) \times W^{2,1}_2(Q)$, introduced in Theorem 6.1, is this derivative of F.

6.2. The optimal control problem

Let $\mathcal{G}_{ad}$ be a nonempty closed convex subset of the Banach space $L^4(Q)$.

Definition 6.4. $(n,f,m,c;u)$ is an admissible quintuple if (n,f,m,c) is in the space $L^2(0,T;H^1(\Omega)) \times L^2(0,T;W^1_4(\Omega)) \times W^{2,1}_2(Q) \times W^{2,1}_2(Q)$ and is a solution of (1.1)–(1.3) with $u \in \mathcal{G}_{ad}$. Then, the admissible set for (1.1)–(1.3) and (6.22) is

$$\mathcal{U}_{ad} = \big\{(n,f,m,c;u) : (n,f,m,c;u) \text{ is admissible}\big\}.$$

The optimal control problem will be: To obtain $(n,f,m,c;u_{opt}) \in \mathcal{U}_{ad}$ such that

$$J[n,f,m,c;u_{opt}] = \inf_{(v,g,h,q;u)\in\mathcal{U}_{ad}} J[v,g,h,q;u], \tag{6.21}$$

where

$$J[n,f,m,c;u] := \frac{\alpha_1}{2}\int_0^T\int_\Omega |n-n_d|^2dxdt + \frac{\alpha_2}{2}\int_0^T\int_\Omega |f-f_d|^2dxdt + \frac{\alpha_3}{2}\int_0^T\int_\Omega |m-m_d|^2dxdt$$
$$+ \frac{\alpha_4}{2}\int_0^T\int_\Omega |c-c_d|^2dxdt + \frac{\alpha_5}{2}\int_0^T\int_\Omega |u|^4dxdt. \tag{6.22}$$

Let F denote the solution operator of (1.1)–(1.3).

Theorem 6.5. *Let the same assumptions as in Theorems 2.2 and 2.7 be satisfied and assume that $n_d, f_d, m_d, c_d \in L^4(Q)$. Then there exists an optimal control $u_{opt} \in \mathcal{G}_{ad}$ minimizing the cost functional, i.e.*

$$J[n,f,m,c;u_{opt}] = \inf_{(v,g,h,q;u)\in\mathcal{U}_{ad}} J[v,g,h,q;u], \tag{6.23}$$

where $(n,f,m,c) = F(u_{opt})$ and $(v,g,h,q) = F(u)$.

Proof. For $(n_k,f_k,m_k,c_k;u_k)$, let $(n_k,f_k,m_k,c_k) = F(u_k)$ be a minimizing sequence. Since $J[n_k,f_k,m_k,c_k;u_k] \le C$ and owing to the particular structure of J we deduce

$$\|u_k\|_{L^4(Q)} \le C$$

and, in view of Theorem 2.2, see from the estimates (4.40) and (4.56), that the following estimates

$$\|n_k\|_{L^2(0,T;H^1(\Omega))} + \|f_k\|_{L^2(0,T;W_4^1(\Omega))} + \|m_k\|_{W_2^{2,1}(Q)} + \|c_k\|_{W_2^{2,1}(Q)} \le C \tag{6.24}$$

and

$$\|\partial_t n_k\|_{L^2(0,T;L^2(\Omega))} + \|\partial_t f_k\|_{L^2(\Omega)} \le C \tag{6.25}$$

hold. Therefore we can select a subsequence of (u_k) and (n_k, f_k, m_k, c_k), $(n_k, f_k, m_k, c_k) = F(u_k)$, again denoted by $(n_k, f_k, m_k, c_k; u_k)$ such that

$$u_k \rightharpoonup u \quad \text{weakly in } L^4(Q), \tag{6.26}$$
$$f_k \rightharpoonup f \quad \text{weakly in } L^2\big(0,T; W_4^1(\Omega)\big), \tag{6.27}$$
$$\partial_t f_k \rightharpoonup \partial_t f \quad \text{weakly in } L^2(Q), \tag{6.28}$$
$$n_k \rightharpoonup n \quad \text{weakly in } L^2\big(0,T; H^1(\Omega)\big), \tag{6.29}$$
$$\partial_t n_k \rightharpoonup \partial_t n \quad \text{weakly in } L^2(Q), \tag{6.30}$$
$$m_k \to m \quad \text{weakly in } W_2^{2,1}(Q), \tag{6.31}$$
$$c_k \to c \quad \text{weakly in } W_2^{2,1}(Q). \tag{6.32}$$

By the embedding theorems we obtain

$$f_k \rightharpoonup f \quad \text{strongly in } L^2(Q), \tag{6.33}$$
$$n_k \rightharpoonup n \quad \text{strongly in } L^2(Q), \tag{6.34}$$
$$m_k \to m \quad \text{strongly in } L^2(Q), \tag{6.35}$$
$$c_k \to c \quad \text{strongly in } L^2(Q). \tag{6.36}$$

One can check that $(n, f, m, c) = F(u)$, in the since give by Theorem 2.2 and that

$$\liminf_{k\to\infty} J[n_k, f_k, m_k, c_k; u_k] \ge J[n, f, m, c; u].$$

Thus $u_{opt} := u$ is an optimal solution of (6.23). □

Now we will prove necessary optimality conditions for each optimal control u.

Theorem 6.6. *Let u be an optimal control for problem (6.23). Then there exists functions $(n, f, m, c, p, q, r, z; u)$ satisfying:*

$$\partial_t n - D_n \Delta n = -\chi \nabla(n \nabla f) \quad \textit{in } Q,$$
$$\partial_t f = -\alpha m f \quad \textit{in } Q,$$
$$\partial_t m - D_m \Delta m = \mu n - \lambda m + u \quad \textit{in } Q,$$
$$\partial_t c - D_c \Delta c = \beta f - \gamma n - \sigma c \quad \textit{in } Q,$$
$$-\partial_t p - D_n \Delta p = -\gamma z + \mu r + \chi \nabla p \cdot \nabla f + \alpha_1 (n - n_d) \quad \textit{in } Q,$$
$$-\partial_t q = -\alpha m q + \beta z - \chi \nabla(n \nabla p) + \alpha_2 (f - f_d) \quad \textit{in } Q,$$
$$-\partial_t r - D_m \Delta r = -\lambda r - \alpha f q + \alpha_3 (m - m_d) \quad \textit{in } Q,$$
$$-\partial_t z - D_c \Delta z = -\sigma z + \alpha_4 (c - c_d) \quad \textit{in } Q,$$

$$
\begin{gathered}
(D_n \nabla n - \chi n \nabla f)\eta = \frac{\partial m}{\partial \eta} = \frac{\partial c}{\partial \eta} = 0 \quad on\ S, \\
\frac{\partial p}{\partial \eta} = \frac{\partial r}{\partial \eta} = \frac{\partial z}{\partial \eta} = 0 \quad on\ S, \\
n(0) = n_0, \qquad f(0) = f_0, \qquad m(0) = m_0, \qquad c(0) = c_0 \quad in\ \Omega, \\
p(T) = q(T) = r(T) = z(T) = 0 \quad in\ \Omega
\end{gathered} \tag{6.37}
$$

and

$$
\int_0^T \int_\Omega \left(r + 2\alpha_5 u^3\right)(v - u)\,dxdt \geq 0, \tag{6.38}
$$

for all $v \in \mathcal{G}_{ad}$.

Proof. Let $u := u_{opt}$ and $(n, f, m, c) = F(u)$. From Theorem 6.1 and Remark 6.3 we know that F is Fréchet differentiable. Therefore,

$$
\begin{aligned}
&\frac{d}{d\xi} J\left[F\left(u + \xi(v - u)\right); u + \xi(v - u)\right]\Big|_{\xi=0} \\
&= \alpha_1 \int_0^T \int_\Omega (n - n_d)n^* dxdt + \alpha_2 \int_0^T \int_\Omega (f - f_d) f^* dxdt + \alpha_3 \int_0^T \int_\Omega (m - m_d) m^* dxdt \\
&\quad + \alpha_4 \int_0^T \int_\Omega (c - c_d) c^* dxdt + 2\alpha_5 \int_0^T \int_\Omega u^3 (v - u)\,dxdt,
\end{aligned} \tag{6.39}
$$

where $(n^*, f^*, m^*, c^*) = F'(u)(v - u)$ is a solution of the following system

$$
\begin{gathered}
\partial_t n^* - D_n \Delta n^* = -\chi \nabla\left[n^* \nabla f + n \nabla f^*\right] \quad \text{in } Q, \\
\partial_t f^* = -\alpha\left(m^* f + m f^*\right) \quad \text{in } Q, \\
\partial_t m^* - D_m \Delta m^* = \mu n^* - \lambda m^* + v - u \quad \text{in } Q, \\
\partial_t c^* - D_c \Delta c^* = \beta f^* - \gamma n^* - \sigma c^* \quad \text{in } Q, \\
\left(D_n \nabla n^* - \chi\left(n^* \nabla f + n \nabla f^*\right)\right)\eta = \frac{\partial m^*}{\partial \eta} = \frac{\partial c^*}{\partial \eta} = 0 \quad \text{on } S, \\
n^*(0) = f^*(0) = m^*(0) = c^*(0) = 0 \quad \text{in } \Omega.
\end{gathered} \tag{6.40}
$$

Moreover, since u is an optimal solution we have

$$
\frac{d}{d\xi} J\left[F\left(u + \xi(v - u)\right); u + \xi(v - u)\right]\Big|_{\xi=0} \geq 0
$$

for all $v \in \mathcal{G}_{ad}$; i.e.

$$
\begin{aligned}
&\alpha_1 \int_0^T \int_\Omega (n - n_d)n^* dxdt + \alpha_2 \int_0^T \int_\Omega (f - f_d) f^* dxdt + \alpha_3 \int_0^T \int_\Omega (m - m_d) m^* dxdt + \alpha_4 \int_0^T \int_\Omega (c - c_d) c^* dxdt \\
&\quad + 2\alpha_5 \int_0^T \int_\Omega u^3 (v - u)\,dxdt \geq 0
\end{aligned} \tag{6.41}
$$

for all $v \in \mathcal{G}_{ad}$.

We transform (6.41) into another form by introducing the costate variables (p, q, r, z) as solutions of the problem:

$$\begin{aligned}
-\partial_t p - D_n \Delta p &= -\gamma z + \mu r + \chi \nabla p \cdot \nabla f + \alpha_1 (n - n_d) \quad \text{in } Q, \\
-\partial_t q &= -\alpha m q + \beta z - \chi \nabla (n \nabla p) + \alpha_2 (f - f_d) \quad \text{in } Q, \\
-\partial_t r - D_m \Delta r &= -\lambda r - \alpha f q + \alpha_3 (m - m_d) \quad \text{in } Q, \\
-\partial_t z - D_c \Delta z &= -\sigma z + \alpha_4 (c - c_d) \quad \text{in } Q, \\
\frac{\partial p}{\partial \eta} = \frac{\partial r}{\partial \eta} &= \frac{\partial z}{\partial \eta} = 0 \quad \text{on } S, \\
p(T) = q(T) &= r(T) = z(T) = 0 \quad \text{in } \Omega.
\end{aligned} \tag{6.42}$$

Remark 6.7. Problem (6.42) is a linear system. It has a unique solution (p, q, r, z) at least on $L^2(0, T; H^1(\Omega)) \times L^2(0, T; H^1(\Omega)) \times W_2^{2,1}(Q) \times W_2^{2,1}(Q)$.

Testing the first equation in (6.42) with n^*, the second with f^*, the third with m^* and the forth with c^*, when integrating in Q, using Green's formula and summing we obtain

$$\begin{aligned}
\int_0^T \int_\Omega r(v - u) dx dt = \alpha_1 \int_0^T \int_\Omega (n - n_d) n^* dx dt + \alpha_2 \int_0^T \int_\Omega (f - f_d) f^* dx dt + \alpha_3 \int_0^T \int_\Omega (m - m_d) m^* dx dt \\
+ \alpha_4 \int_0^T \int_\Omega (c - c_d) c^* dx dt.
\end{aligned} \tag{6.43}$$

Therefore, from (6.41) and (6.43) we conclude that

$$\int_0^T \int_\Omega \big(r + 2\alpha_5 u^3\big)(v - u) dx dt \geq 0,$$

for all $v \in \mathcal{G}_{ad}$. This complete the proof of theorem. □

Remark 6.8. If $\mathcal{G}_{ad} = L^4(Q)$ from (6.38) we have

$$u_{opt} := -\left(\frac{1}{2\alpha_5} r\right)^{\frac{1}{3}}. \tag{6.44}$$

Acknowledgments

The authors are grateful to the Professor Dale William Bean-Iceb-Ufop for your fine work in correction of English text in our manuscript and referees for their valuable suggestions which improved this article.

References

[1] R.A. Adams, Sobolev Spaces, Academic Press, New York, 1975.

[2] A.R.A. Anderson, A hybrid mathematical model of solid tumour invasion: the importance of cell adhesion, Math. Med. Biol. 22 (2005) 163–186.

[3] K. Bahrami, M. Kim, Optimal control of multiplicative control systems arising from cancer therapy, IEEE Trans. Automat. Control AC-20 (1975) 537–542.

[4] D. Balding, D.L.S. McElwain, A mathematical model of tumor-induced capillary growth, J. Theoret. Biol. 114 (1985) 53–73.

[5] H. Brezis, Functional Analysis, Sobolev Spaces and Partial Differential Equations, Springer, 2010.

[6] M.A.J. Chaplain, A.R.A. Anderson, Mathematical modelling of tissue invasion, in: L. Preziosi (Ed.), Cancer Modelling and Simulation, Chapman & Hall/CRT, 2003.

[7] M.A.J. Chaplain, S.R. McDougall, A.R.A. Anderson, Mathematical modeling of tumor-induced angiogenesis, Annu. Rev. Biomed. Eng. 8 (2006) 233–257.

[8] M. Chiu, J.-L. Yu, An optimal adaptive time-stepping scheme for solving reaction–diffusion–chemotaxis systems, Math. Biosci. Eng. 4 (2) (2007) 187–203.

[9] L. Corrias, B. Perthame, H. Zaag, Global solutions of some chemotaxis and angiogenesis systems in high space dimensions, Milan J. Math. 72 (2004) 1–28.

[10] L. Corrias, B. Perthame, H. Zaag, Lp and L1a priori estimates for some chemotaxis models and applications to the Cauchy problem, in: The Mechanism of the Spatio-Temporal Pattern Arising Reaction Diffusion System, Kyoto, 2004, preprint available at http://www.math.univ-paris13.fr/zaag/publications/CPZkyoto04.pdf.

[11] A.M. Czochra, M. Ptashnyk, Boundedness on solutions of a haptotaxis model, Math. Models Methods Appl. Sci. 20 (3) (2010) 449–476.

[12] M. Eisen, Mathematical Models in Cell Biology and Cancer Chemotherapy, Lect. Notes Biomath., vol. 30, Springer Verlag, 1979.

[13] L.C. Evans, Partial Differential Equations, Amer. Math. Soc., 1998.

[14] K.R. Fister, M.L. Mccarthy, Identification of a chemotactic sensitivity in a coupled system, Math. Med. Biol. 25 (2008) 215–232.

[15] A. Friedman, Partial Differential Equations, Robert E. Krieger Publishing Co., 1976.

[16] O. Ladyzhenskaya, V. Solonnikov, N. Uraltseva, Linear and Quasilinear Equations of Parabolic Type, Amer. Math. Soc., 1968.

[17] D. Lebiedz, U. Brandt-Pollmann, Manipulation of self-aggregation patterns and waves in a reaction–diffusion system by optimal boundary control strategies, Phys. Rev. Lett. 91 (20) (2003).

[18] J.L. Lions, Quelques Méthodes de Résolutions des Problèmes aux Limites Non-Linéaires, Dunod, Paris, 1969.

[19] V.P. Mikhailov, Partial Differential Equations, Mir, Moscow, 1978.

[20] C. Morales-Rodrigo, Local existence and uniqueness of regular solutions in a model of tissue invasion by solid tumours, Math. Comput. Modelling 47 (2008) 604–613.

[21] Sang-Uk Ryu, Optimal control for a parabolic system modelling chemotaxis, Trends Math. Inf. Center Math. Sci. 6 (1) (2003) 45–49.

[22] Sang-Uk Ryu, A. Yagi, Optimal control of Keller–Segel equations, J. Math. Anal. Appl. 256 (2001) 45–66.

[23] J. Simon, Compacts sets in the space $L^p(0,T;B)$, Ann. Mat. Pura Appl. 146 (1987) 65–96.

[24] G.W. Swan, Role of optimal control in cancer chemotherapy, Math. Biosci. 101 (1990) 237–284.

[25] G.W. Swan, T.L. Vincent, Optimal control analysis in the chemotherapy of IgG multiple myeloma, Bull. Math. Biol. 39 (1977) 317–337.

[26] C. Vilas, E. Balsa-Canto, J.R. Banga, A.A. Alonso, Robust and efficient numerical methods for the optimal control of spatially distributed biological systems, in: 20th Mediterranean Conference on Control and Automation, MED, Barcelona, Spain, July 2012, pp. 3–6.