On a nonlinear model for tumour growth with drug application

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Received 25 June 2014, revised 20 January 2015
Accepted for publication 9 March 2015
Published 21 April 2015

Abstract

We investigate the dynamics of a nonlinear system modelling tumour growth with drug application. The tumour is viewed as a mixture consisting of proliferating, quiescent and dead cells as well as a nutrient in the presence of a drug. The system is given by a multi-phase flow model: the densities of the different cells are governed by a set of transport equations, the density of the nutrient and the density of the drug are governed by rather general diffusion equations, while the velocity of the tumour is given by Brinkman’s equation. The domain occupied by the tumour in this setting is a growing continuum $\Omega$ with boundary $\partial \Omega$ both of which evolve in time. Global-in-time weak solutions are obtained using an approach based on penalization of the boundary behaviour, diffusion and viscosity in the weak formulation. Both the solutions and the domain are rather general, no symmetry assumption is required and the result holds for large initial data. This article is part of a research programme whose aim is the investigation of the effect of drug application in tumour growth.

Keywords: tumour growth models, cancer progression, mixed models, moving domain, penalization, existence
Mathematics Subject Classification: 35Q30, 76N10, 46E35

(Some figures may appear in colour only in the online journal)
1. Introduction

1.1. Motivation

The investigation of the effect of drug application in the treatment of cancer is the subject of intense scientific effort. A major cause of the failure of chemotherapeutic treatments for cancer is the development of resistance to drugs. This article is part of a research programme whose aim is the investigation of the effect of drug application on tumour growth. We investigate the dynamics of a nonlinear system describing the evolution of cancerous cells. In this setting, the tumour is viewed as a mixture consisting of proliferating, quiescent and dead cells in the presence of a nutrient (oxygen) and drug. The mathematical model presented here is governed by

- a system of transport equations, which describe the evolution of the densities of the cells that are present in the tumour: proliferating cells with density $P$, quiescent cells with density $Q$ and dead cells with density $D$ (this part of the tumour includes what is known also as waste or extra-cellular medium),
- two rather general diffusion equations which are used to describe the diffusion of the nutrient (oxygen) within the tumour region and the evolution of the drug within the same regime. In general, these equations obey Fick’s law: the nutrient is consumed at a rate proportional to the rate of cell mitosis, whereas the drug is consumed at a rate which is determined by the drug effectiveness,
- an extension of the Darcy law, known as Brinkman’s equation, which determines the velocity field. The continuous movement within the tumour region is due to proliferation, mitosis, apoptosis or removal of cells. Note, the tumour in the present context is viewed as a fluid-like porous medium.

Motivated by the experiment of Roda et al (2011, 2012) and the mathematical analysis in Friedman et al [13], [14], and Zhao in [26] our model is based on the following biological principles:

[P1] Living cells are either in a proliferating phase or in a quiescent phase.
[P2] Proliferating cells die as a result of apoptosis, which is a cell-loss mechanism. Quiescent cells die in part due to apoptosis and more often due to starvation. In fact the proliferation and the necrotic death rates of tumour cells depend on the oxygen level.
[P3] The dead tumour cells are obtained from necrosis and apoptosis of live tumour cells, and they are cleared by macrophages.
[P4] Living cells undergo mitosis, a process that takes place in the nucleus of a dividing cell.
[P5] Cells change from quiescent phase into proliferating phase at a rate which increases with the nutrient level, and they die at a rate which increases as the level of nutrient (oxygen) decreases.
[P6] Proliferating cells become quiescent and die at a rate which increases as the nutrient concentration decreases. The proliferation rate increases with the nutrient concentration.
[P7] Proliferating cells and quiescent cells become dead cells at a rate which depends on the drug concentration.

The tumour region $\Omega_t := \Omega(t)$ is contained in a fixed domain $B$ and the region $B \setminus \Omega_t$ represents the healthy tissue (see figure 1). The tumour region $\Omega_t$ and its boundary $\partial \Omega_t$ evolve with respect to time. Both live and dead tumour cells are assumed to be in the tumour region $\Omega_t$; oxygen molecules can diffuse throughout the whole domain $B$. Abnormal proliferation of tumour cells generates internal pressure in $\Omega(t)$, resulting to a velocity field $v \neq 0$ (while $v = 0$ in $B \setminus \Omega_t$).
1.2. Governing equations of cells, oxygen and drug

1.2.1. Transport equations for the evolution of the cell densities. All the cells are assumed to follow the general continuity equation:

\[ \frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) = G, \]

where \( \rho \) may represent densities of proliferating/quiescent and dead cells. The function \( G \) includes in general proliferation, apoptosis or clearance of cells, and chemotaxis terms as appropriate.

Due to proliferation and removal of cells, there is a continuous motion within the tumour represented by a velocity field \( \mathbf{v} \). We assume that there are three types of cells: proliferative cells with density \( P \), quiescent cells with density \( Q \) and dead cells with density \( D \) in the presence of a nutrient (oxygen) with density \( C \) and a drug with density \( W \). The rates of change from one phase to another are functions of the nutrient concentration \( C \):

- \( P \rightarrow Q \) at rate \( K_Q(C) \),
- \( Q \rightarrow P \) at rate \( K_P(C) \),
- \( P \rightarrow D \) at rate \( K_A(C) \),
- \( Q \rightarrow D \) at rate \( K_D(C) \),

where \( K_A \) stands for apoptosis. Finally, dead cells are removed at rate \( K_R \) (independent of \( C \)), and the rate of cell proliferation (new births) is \( K_B \).

1.2.2. The tumour tissue as a porous medium. Due to proliferation and removal of cells there is continuous motion of cells within the tumour; this movement is represented by the velocity field \( \mathbf{v} \) given by an alternative to Darcy’s equation known as Brinkman’s equation

\[ \nabla \sigma = -\frac{\mu}{K} \mathbf{v} + \mu \Delta \mathbf{v}, \quad (1.1) \]
where \( \sigma \) denotes the pressure, \( \mu \) is a positive constant describing the viscous like properties of tumour cells, whereas \( K \) denotes the permeability.

Relation (1.1) includes two viscous terms. The first term is the usual Darcy law and the second is analogous to the Laplacian term that appears in the Navier–Stokes equation. At a first look, (1.1) appears as an over damped force balance. A second interpretation of this relation states that the tumour tissue is ‘fluid like’ and that the tumour cells flow through the fixed extracellular matrix like a flow through a porous medium, obeying Brinkman’s law.

The mass conservation laws for the densities of the proliferative cells \( P \), quiescent cells \( Q \) and dead cells \( D \) in \( \Omega(t) \) take the following form:

\[
\begin{align*}
\frac{\partial P}{\partial t} + \text{div}(Pv) &= G_P, \\
\frac{\partial Q}{\partial t} + \text{div}(Qv) &= G_Q, \\
\frac{\partial D}{\partial t} + \text{div}(Dv) &= G_D.
\end{align*}
\]

Following Friedman [13], the source terms \( G_P, G_Q, G_D \) are of the following form:

\[
G_P = (K_BC - K_Q((C - C) - K_A((\bar{C} - C)) P + K_P C Q - i_1 G_1(W) P, 
\]

where \( G_1(\cdot) \) a smooth function and \( K_B, K_Q, K_A \) are positive constants. The first term in this equation accounts for the increase of the number of cells due to new births, loss due to change of phase from proliferating to quiescent and loss due to apoptosis. The second term reflects the increase of the number of proliferating cells generated from quiescent cells, whereas the third term accounts for the decrease of the number of cells due to death resulting from the effect of drug. In an analogous fashion

\[
G_Q = K_Q((\bar{C} - C) P - (K_P C + K_D((\bar{C} - C)) Q - i_2 G_2(W) Q, 
\]

with \( G_2(\cdot) \) a smooth function and \( K_P, K_Q, K_D \) positive constants. In the above relations (1.5)–(1.6) \( i_1 G_1(W) \) and \( i_2 G_2(W) \) denote the rates by which the proliferating cells and the quiescent cells become dead cells due to the drug. Finally,

\[
G_D = K_A((\bar{C} - C) P + K_D((\bar{C} - C) Q - K_D D + i_1 G_1(W) P + i_2 G_2(W) Q. 
\]

1.2.3. A linear diffusion equation for the evolution of nutrient. Tumour cells consume nutrients (oxygen). In contrast to the equations of cell densities, the equations of the oxygen molecules in the tumour include diffusion terms in the following form:

\[
\frac{\partial C}{\partial t} = \nabla \cdot (v_1 \nabla C) - (K_1 K_P C P + K_2 K_Q((\bar{C} - C)) Q) C.
\]

Assuming that \( v_1 \) is constant this equation (see [13]) becomes

\[
\frac{\partial C}{\partial t} = v_1 \Delta C - (K_1 K_P C P + K_2 K_Q((\bar{C} - C)) Q) C. 
\]

This equation describes the diffusion of the oxygen in the tumour region. According to (see [23, 24]) the nutrient is consumed at a rate proportional to the rate of cell mitosis, namely the second term on the right-hand side of the first equation in (1.8). We also refer the reader to [13] where a class of relevant tumour growth models are presented and the evolution of the nutrient is given by a related equation.
1.2.4. A linear diffusion equation for the evolution of drug. The evolution of the drug concentration in the tumour is given by a diffusion equation of the form

\[ \frac{\partial W}{\partial t} = \nabla \cdot (\nu \nabla W) - (\mu_1 G_1(W) P + \mu_2 G_2(W) Q) W, \]

with \( G_1(\cdot), G_2(\cdot) \) smooth functions.

Assuming that \( \nu_2 \) is constant this equation (see [26]) becomes

\[ \frac{\partial W}{\partial t} = \frac{\nu_2}{\Delta_1} W - (\mu_1 G_1(W) P + \mu_2 G_2(W) Q) W. \] (1.9)

This equation describes the diffusion of the drug within the tumour region. The second term of the right-hand side of (1.9) represents the drug consumption, the constants \( \mu_1, \mu_2 \) are two positive constants which can be viewed as a measure of the drug effectiveness. We refer the reader to [23, 25, 26] for further comments.

The total density of the mixture is denoted by \( \rho_f \) and is given by

\[ \rho_f = P + Q + D = \text{Constant}. \] (1.10)

Adding (1.2)–(1.4) and taking into consideration (1.10) we arrive at the following relation, which represents an additional constraint

\[ \rho_f \nabla \cdot \nu = G_p + G_Q + G_D = \kappa_b C P - \kappa_b D. \] (1.11)

Our aim is to study the system (1.1)–(1.11) in a spatial domain \( \Omega_t \), with a boundary \( \Gamma = \partial \Omega_t \) varying in time.

1.3. Boundary behaviour

The boundary of the domain \( \Omega_t \) occupied by the tumour is described by means of a given velocity \( V(t, x) \), where \( t \geq 0 \) and \( x \in \mathbb{R}^3 \). More precisely, assuming \( V \) is regular, we solve the associated system of differential equations

\[ \frac{d}{dt} X(t, x) = V(t, X)(t, x), \quad t > 0, \quad X(0, x) = x, \]

and set

\[ \begin{align*}
\Omega_t &= X(\tau, \Omega_0), \quad \text{where } \Omega_0 \subset \mathbb{R}^3 \text{ is a given domain}, \\
\Gamma_t &= \partial \Omega_t, \quad \text{and } Q_t = \{ (t, x) | t \in (0, \tau), x \in \Omega_t \}. 
\end{align*} \]

The model is closed by giving boundary conditions on the (moving) tumour boundary \( \Gamma_t \). More precisely, we assume that the boundary \( \Gamma_t \) is impermeable, meaning

\[ (v - V) \cdot n \big|_{\Gamma_t} = 0, \quad \text{for any } \tau \geq 0. \] (1.12)

In addition, for viscous fluids, Navier proposed the boundary condition of the form

\[ [S n]_{\text{tan}} \big|_{\Gamma_t} = 0, \] (1.13)

with \( S \) denoting the viscous stress tensor which in this context is assumed to be determined through Newton’s rheological law

\[ S = \mu \left( \nabla v + \nabla^\top v - \frac{3}{2} \text{div} v I \right) + \xi \text{div} v I, \]

where \( \mu > 0, \xi \geq 0 \) are respectively the shear and bulk viscosity coefficients. Condition (1.13) namely says that the tangential component of the normal viscous stress vanishes on \( \Gamma_t \).

The concentrations of the nutrient and the drug on the boundary satisfy the conditions:

\[ C(x, t) \big|_{\Gamma_t} = \bar{C}, \quad W(x, t) \big|_{\Gamma_t} = \bar{W}. \] (1.14)
Here, $\bar{C}$ and $\bar{W}$ denote positive constants reflecting the constant drug supply that the tumour receives from its boundary.

Finally, the problem (1.2)–(1.14) is supplemented by the initial conditions

$$
\begin{align*}
P(0, \cdot) &= P_0, 
Q(0, \cdot) &= Q_0, 
D(0, \cdot) &= D_0, 
C(0, \cdot) &= C_0 \leq \bar{C}, 
W(0, \cdot) &= W_0 \text{ in } \Omega_0.
\end{align*}
$$

Our main goal is to show the existence of global in time weak solutions to (1.1)–(1.15) for any finite energy initial data. Related works on the mathematical analysis of cancer models have been presented by Zhao [26] based on the framework introduced by Friedman et al [13, 14]. The analysis in [13, 14] yields existence and uniqueness of solution to a related model in the radial symmetric case for a small time interval $[0, T]$. The analysis in [26] treats a parabolic–hyperbolic free boundary problem and provides a unique global solution in the radially symmetric case. In the forth mentioned articles the tumour tissue is assumed to be a porous medium and the velocity field is determined by Darcy’s law

$$
\mathbf{v} = -\nabla x \sigma \text{ in } \Omega(t).
$$

In [9], Donatelli and Trivisa establish the global existence of weak solutions to a nonlinear system modelling tumour growth in a general moving domain $\Omega_t \subset \mathbb{R}^3$ without any symmetry assumption and for finite large initial data. The article [9] is according to our knowledge the first article treating the problem in a general setting. In [10] the same authors establish the global existence of weak solutions to a nonlinear system for tumour growth in the case of variable total density of cells within a cellular medium.

The present article extends earlier results in a variety of ways. First the effect of drug application is being considered within a moving domain in $\mathbb{R}^3$ without any symmetry considerations. Second, the transport equations are rather general capturing more effectively the biological setting. Our framework relies on biologically grounded principles $[P1]–[P7]$, which are motivated by experiments performed by Roda et al [5, 19, 20] and provide a description of the dynamics of the population of cells within the tumour.

We establish the global existence of weak solutions to (1.1)–(1.15) on time dependent domains, supplemented with slip boundary conditions. In the centre of our approach lie the so-called generalized penalty methods typically suitable for treating partial slip, free surface, contact and related boundary conditions in viscous flow analysis and simulations. As has been seen in earlier works (see [2–4, 9]), penalty methods provide an additional weakly enforce constraint in the problem. This form of boundary penalty approximation appeared by Courant in [6], in the context of slip conditions for stationary incompressible fluids by Stokes and Carrey in [22], and more recently in a series of articles (see [9–12]). The existence theory for the barotropic Navier–Stokes system on fixed spatial domains in the framework of weak solutions was developed in the seminal work of Lions [15].

### 1.4. Outline

The paper is organized as follows: section 1 presents the motivation, modelling and introduces the necessary preliminary material. Section 2 provides a weak formulation of the problem and states the main result. Section 3 is devoted to the penalization problem and to the construction of a suitable approximate scheme. The central component of the approximating procedure is the addition of a singular forcing term

$$
\frac{1}{\varepsilon} \int_{\Gamma(t)} (\mathbf{v} - \mathbf{V}) \cdot \mathbf{n} \varphi \cdot \mathbf{n} dS, \quad \varepsilon > 0 \text{ small},
$$

penalizing the normal component of the velocity on the boundary of the tumour domain in the variational formulation of Brinkman’s equation. We remark that applying a penalization
method to the slip boundary conditions is extremely delicate. Unlike for no-slip boundary condition, where the fluid velocity coincides with the field $V$ outside $\Omega_\tau$, it is only its normal component $v \cdot n$ that can be controlled in the case of slip. In order to treat the moving boundary, additional penalizations on the viscosity and diffusion parameters are required. In section 4 we give a sketch on the existence of solutions of the penalization scheme in the healthy tissue. In section 5 we collect all the uniform bounds satisfied by the solution of the penalization scheme. In section 6, the singular limits for $\varepsilon \to 0, \omega \to 0$ are performed successively. A key part in the penalization limit is to get rid of the terms supported in the healthy tissue part $((0, T) \times B) \setminus Q_T$. The main issue is to describe the evolution of the interface $\Gamma_\tau$. To that effect we employ elements from the so-called level set method (see [18]).

2. Weak formulation and main results

2.1. Weak solutions

Definition 2.1. We say that $(P, Q, D, v, C, W)$ is a weak solution of problem (1.1)–(1.7)–(1.12)–(1.14) supplemented with boundary data satisfying (1.15) provided that the following hold:

- $(P, Q, D) \geq 0$ represents a weak solution of (1.2)–(1.3)–(1.4) on $(0, T) \times \Omega_\tau$, i.e., for any test function $\varphi \in C^0_c((0, T) \times \mathbb{R}^3), T > 0$ the following integral relations hold:

\[
\int_{\Omega_\tau} P \varphi(\tau, \cdot) \, dx - \int_{\Omega_\tau} P_0 \varphi(0, \cdot) \, dx = \\
\int_0^T \int_{\Omega_\tau} \left( P \partial_\tau \varphi + P v \cdot \nabla_x \varphi + G_p \varphi(t, \cdot) \right) \, dx \, dt,
\]

\[
\int_{\Omega_\tau} Q \varphi(\tau, \cdot) \, dx - \int_{\Omega_\tau} Q_0 \varphi(0, \cdot) \, dx = \\
\int_0^T \int_{\Omega_\tau} \left( Q \partial_\tau \varphi + P v \cdot \nabla_x \varphi + G_Q \varphi(t, \cdot) \right) \, dx \, dt,
\]

\[
\int_{\Omega_\tau} D \varphi(\tau, \cdot) \, dx - \int_{\Omega_\tau} D_0 \varphi(0, \cdot) \, dx = \\
\int_0^T \int_{\Omega_\tau} \left( D \partial_\tau \varphi + D v \cdot \nabla_x \varphi + G_D \varphi(t, \cdot) \right) \, dx \, dt.
\]

(I)

In particular,

$P \in L^p([0, T]; \Omega_\tau)$, $Q \in L^p([0, T]; \Omega_\tau)$, $D \in L^p([0, T]; \Omega_\tau)$ for all $p \geq 1$.

We remark that in the weak formulation, it is convenient that the equations (1.2)–(1.4) hold in the whole space $\mathbb{R}^3$ provided that the densities $(P, Q, D)$ are extended to be zero outside the tumour domain.

- Brinkman’s equation (1.1) holds in the sense of distributions, i.e., for any test function $\varphi \in C^\infty_c(\mathbb{R}^3; \mathbb{R}^3)$ satisfying

$\varphi \cdot n|_{\Gamma_\tau} = 0$ for any $\tau \in [0, T],$

the following integral relation holds:

\[
\int_{\Omega_\tau} \sigma \text{div} \varphi \, dx - \int_{\Omega_\tau} \left( \mu \nabla_x v : \nabla_x \varphi + \frac{\mu}{K} v \varphi \right) \, dx = 0.
\]

(2.1)

All quantities in (2.1) are required to be integrable, so in particular,

$v \in W^{1,2}(\mathbb{R}^3; \mathbb{R}^3)$,
and
\[(v - V) \cdot n(\tau, \cdot)|_{\Gamma_\tau} = 0 \text{ for a.a. } \tau \in [0, T].\]

- \(C \geq 0\) is a weak solution of (1.8), i.e., for any test function \(\varphi \in C_c^\infty((0, T) \times \mathbb{R}^3), T > 0\) the following integral relations hold:
\[
\int_{\Omega_t} C\varphi(\tau, \cdot) \, dx - \int_{\Omega_0} C(0, \cdot) \, dx = \int_0^\tau \int_{\Omega_t} C \partial_t \varphi \, dx \, dt \\
- \int_0^\tau \int_{\Omega_t} \nu_1 \nabla_x C \cdot \nabla_x \varphi \, dx \, dt - \int_0^\tau \int_{\Omega_t} (K_1 K_1 C \, P + K_2 K_2 (\hat{C} - C) \, Q) \, C \varphi \, dx \, dt.
\]

- \(W \geq 0\) is a weak solution of (1.9), i.e., for any test function \(\varphi \in C_c^\infty((0, T) \times \mathbb{R}^3), T > 0\) the following integral relations hold:
\[
\int_{\Omega_t} W\varphi(\tau, \cdot) \, dx - \int_{\Omega_0} W(0, \cdot) \, dx = \int_0^\tau \int_{\Omega_t} W \partial_t \varphi \, dx \, dt \\
- \int_0^\tau \int_{\Omega_t} \nu_2 \nabla_x W \cdot \nabla_x \varphi \, dx \, dt - \int_0^\tau \int_{\Omega_t} (\mu_1 G_1(W) \, P + \mu_2 G_2(W) \, Q) \, W \, dx \, dt.
\]

The main result of the article now follows.

**Theorem 2.2.** Let \(\Omega_0 \subset \mathbb{R}^3\) be a bounded domain of class \(C^{2,\nu}\) and let \(V \in C^1([0, T]; C_c^1(\mathbb{R}^3; \mathbb{R}^3))\) be given. Let the initial data satisfy
\[P_0 \in L^p(\mathbb{R}^3), \quad Q_0 \in L^p(\mathbb{R}^3), \quad D_0 \in L^p(\mathbb{R}^3), \quad \text{for all } p \geq 1\]
and
\[C_0 \in L^2(\mathbb{R}^3) \cap L^\infty(\mathbb{R}^3), \quad W_0 \in L^2(\mathbb{R}^3) \cap L^\infty(\mathbb{R}^3),\]
with \((P_0, Q_0, D_0, C_0, W_0) \not\equiv 0, \quad (P_0, Q_0, D_0, C_0, W_0) \mid_{\mathbb{R} \setminus \Omega_0} = 0.\]

Then the problem (1.1)–(1.7), (1.8), (1.9)–(1.11) with initial data (1.15) and boundary data (1.12)–(1.14) admits a weak solution in the sense specified in definition 2.1.

### 3. Penalization

#### 3.1. General strategy

The main ingredients of our strategy can be formulated as follows:

- Our approach relies on **penalization** of the boundary behaviour, diffusion and viscosity in the weak formulation. A penalty approach to slip conditions for *stationary incompressible flow* was proposed by Stokes and Carey [22]. In the present setting, the variational (weak) formulation of the Brinkman equation is supplemented by a singular forcing term
\[
\frac{1}{\varepsilon} \int_{\Gamma_\tau} (v - V) \cdot n \varphi \cdot n \, dS_x, \quad \varepsilon > 0 \text{ small}, \tag{3.1}
\]
penalizing the normal component of the velocity on the boundary of the tumour domain.

- In addition to (3.1), we introduce a **variable** shear viscosity coefficient \(\mu = \mu_\omega\), as well as a **variable** diffusions \(\nu_i = \nu_{i\omega}, i = 1, 2\) with \(\mu_\omega, \nu_{i\omega}\) vanishing outside the tumour domain and remaining positive within the tumour domain.
• In constructing the approximating problem we employ the variables \( \epsilon \) and \( \omega \). Keeping \( \epsilon \) and \( \omega \) fixed, we solve the modified problem in a (bounded) reference domain \( B \subset \mathbb{R}^3 \) chosen in such way that
  \[ \bar{\Omega}_\tau \subset B \text{ for any } \tau \geq 0. \]
• We take the initial densities \( (P_0, Q_0, D_0) \) vanishing outside \( \Omega_\omega \), and letting the penalization \( \epsilon \to 0 \) for fixed \( \omega > 0 \) we obtain a ‘two-phase’ model consisting of the tumour region and the healthy tissue separated by impermeable boundary. We show that the densities vanish in part of the reference domain, specifically on \( ((0, T) \times B) \setminus Q_T \).
• We let first the penalization \( \epsilon \) vanish and next we perform the limit \( \omega \to 0 \).

### 3.2. Penalization scheme

As typical in time dependent regimes the penalization can be applied to the interior of a fixed reference domains. In that way we obtain at the limit a two-phase model consisting of the tumour region \( \Omega_\tau \) and a healthy tissue \( B \setminus \Omega_\tau \) separated by an impermeable interface \( \Gamma_\tau \). As a result an extra stress is produced acting on the fluid by its complementary part outside \( \Omega_\tau \).

We choose \( R > 0 \) such that
\[
\mathbf{V}_{|(0, T) \times \{ |x| > R \}} = 0, \quad \bar{\Omega}_0 \subset \{ |x| < R \}
\]
and we take as the reference fixed domain
\[
B = \{ |x| < 2R \}.
\]

In order to eliminate this extra stresses we introduce a variable shear viscosity coefficient
\[
\mu = \mu_\omega(t, x), \quad \mu = \mu_\omega > 0 \quad \text{in } Q_T \quad \text{as } \omega \to 0,
\]
and a variable diffusion coefficients of the nutrient and the drug \( \nu_i = \nu_\omega(t, x), \quad i = 1, 2 \) remain strictly positive in \( Q_T \) as \( \omega \to 0 \), namely \( \nu_\omega \) are taken such that
\[
\nu_\omega \in C^\infty([0, T] \times \mathbb{R}^3), \quad 0 < \nu_\omega \leq \nu_\omega(t, x) \leq \nu_i \quad \text{in } [0, T] \times B,
\]
\[
\nu_\omega = \begin{cases} 
\nu_i = \text{const} > 0 & \text{in } Q_T \\
\nu_\omega & \text{a.e. in } (0, T) \times B \setminus Q_T.
\end{cases}
\]

Finally we modify the initial data for \( P, Q, D, C \) and \( W \) so that the following set of relations denoted by (IC-p) read
\[
\begin{align*}
&P_0 = P_{0, \omega, \epsilon} = P_{0, \omega}, \quad P_{0, \omega} \geq 0, \quad P_{0, \omega} \neq 0, \quad P_{0, \omega} |_{\mathbb{R} \setminus \Omega_0} = 0, \quad \int_B P_{0, \omega}^p \, dx = c, \\
&Q_0 = Q_{0, \omega, \epsilon} = Q_{0, \omega}, \quad Q_{0, \omega} \geq 0, \quad Q_{0, \omega} \neq 0, \quad Q_{0, \omega} |_{\mathbb{R} \setminus \Omega_0} = 0, \quad \int_B Q_{0, \omega}^p \, dx = c, \\
&D_0 = D_{0, \omega, \epsilon} = D_{0, \omega}, \quad D_{0, \omega} \geq 0, \quad D_{0, \omega} \neq 0, \quad D_{0, \omega} |_{\mathbb{R} \setminus \Omega_0} = 0, \quad \int_B D_{0, \omega}^p \, dx = c, \\
&C_0 = C_{0, \omega, \epsilon} = C_{0, \omega}, \quad C_{0, \omega} \geq 0, \quad C_{0, \omega} \neq 0, \quad C_{0, \omega} |_{\mathbb{R} \setminus \Omega_0} = 0, \quad \int_B C_{0, \omega}^p \, dx = c, \\
&W_0 = W_{0, \omega, \epsilon} = W_{0, \omega}, \quad W_{0, \omega} \geq 0, \quad W_{0, \omega} \neq 0, \quad W_{0, \omega} |_{\mathbb{R} \setminus \Omega_0} = 0, \quad \int_B W_{0, \omega}^p \, dx = c,
\end{align*}
\]
for all \( p \geq 1 \).
The weak formulation of the penalized problem reads:

- The integral relations (I) in definition (2.1) hold true for any $\tau \in [0, T]$ and $x \in B$ and any test function $\varphi \in C^\infty_c([0, T] \times \mathbb{R}^3)$, and for $G_{P_\omega,\varepsilon}, G_{Q_\omega,\varepsilon}, G_{D_\omega,\varepsilon}$ given in (1.5)–(1.7), namely

\[
\int_B P_{\omega,\varepsilon}(t, \cdot) \varphi(x) \, dx - \int_{\Omega_0} P_0 \varphi(0, \cdot) \, dx = 0,
\]

\[
\int_0^T \int_B (P_{\omega,\varepsilon} \partial_t \varphi + P_{\omega,\varepsilon} v_{\omega,\varepsilon} \cdot \nabla x \varphi + G_{P_{\omega,\varepsilon}} \varphi(t, \cdot)) \, dx \, dt = 0,
\]

\[
\int_B Q_{\omega,\varepsilon}(t, \cdot) \varphi(x) \, dx - \int_{\Omega_0} Q_0 \varphi(0, \cdot) \, dx = 0,
\]

\[
\int_0^T \int_B (Q_{\omega,\varepsilon} \partial_t \varphi + Q_{\omega,\varepsilon} v_{\omega,\varepsilon} \cdot \nabla x \varphi + G_{Q_{\omega,\varepsilon}} \varphi(t, \cdot)) \, dx \, dt = 0,
\]

\[
\int_B D_{\omega,\varepsilon}(t, \cdot) \varphi(x) \, dx - \int_{\Omega_0} D_0 \varphi(0, \cdot) \, dx = 0,
\]

\[
\int_0^T \int_B (D_{\omega,\varepsilon} \partial_t \varphi + D_{\omega,\varepsilon} v_{\omega,\varepsilon} \cdot \nabla x \varphi + G_{D_{\omega,\varepsilon}} \varphi(t, \cdot)) \, dx \, dt = 0.
\]

- The weak formulation for the penalized Brinkman’s equation reads

\[
\int_B \sigma_{\omega,\varepsilon} \text{div} \varphi \, dx - \int_B \left( \mu_{\omega} \nabla_s v_{\omega,\varepsilon} : \nabla x \varphi + \frac{\mu_{\omega}}{K} \nabla s v_{\omega,\varepsilon} \varphi \right) \, dx + \frac{1}{h} \int_{\Gamma_i} ((V - v_{\omega,\varepsilon}) \cdot n \varphi \cdot n) \, dS_i = 0
\]

for any test function $\varphi \in C^\infty_c(B; \mathbb{R}^3)$, where $v_{\omega,\varepsilon} \in W^{1,2}(B; \mathbb{R}^3)$, and $v_{\omega,\varepsilon}$ satisfies the no-slip boundary condition

\[
v_{\omega,\varepsilon}|_{\partial B} = 0 \quad \text{in the sense of traces.}
\]

- The weak formulation for $C_{\omega,\varepsilon}$ is as follows:

\[
\int_B C_{\omega,\varepsilon}(t, \cdot) \varphi(x) \, dx - \int_{\Omega_0} C_0 \varphi(0, \cdot) \, dx = \int_0^T \int_B C_{\omega,\varepsilon} \partial_t \varphi \, dx \, dt - \int_0^T \int_B v_{1_{\omega}} \nabla_s C_{\omega,\varepsilon} \cdot \nabla x \varphi \, dx \, dt
\]

\[
- \int_0^T \int_B (K_1 K_P C_{\omega,\varepsilon} P_{\omega,\varepsilon} + K_2 K_Q (C - C_{\omega,\varepsilon}) Q) C_{\omega,\varepsilon} \varphi \, dx \, dt,
\]

for any test function $\varphi \in C^\infty_c([0, T] \times \mathbb{R}^3)$ and $C_{\omega,\varepsilon}$ satisfies the boundary conditions

\[
\nabla C_{\omega,\varepsilon} \cdot n|_{\partial B} = 0 \quad \text{in the sense of traces.}
\]

- The weak formulation for $W_{\omega,\varepsilon}$ is as follows:

\[
\int_B W_{\omega,\varepsilon}(t, \cdot) \varphi(x) \, dx - \int_{\Omega_0} W_0 \varphi(0, \cdot) \, dx = \int_0^T \int_B W_{\omega,\varepsilon} \partial_t \varphi \, dx \, dt - \int_0^T \int_B v_{2_{\omega}} \nabla_s W_{\omega,\varepsilon} \cdot \nabla x \varphi \, dx \, dt
\]

\[
- \int_0^T \int_B (\mu_1 G_1(W_{\omega,\varepsilon}) P_{\omega,\varepsilon} + \mu_2 G_2(W_{\omega,\varepsilon}) Q_{\omega,\varepsilon}) W_{\omega,\varepsilon} \varphi \, dx \, dt,
\]

for any test function $\varphi \in C^\infty_c([0, T] \times \mathbb{R}^3)$ and $W_{\omega,\varepsilon}$ satisfies the boundary conditions

\[
\nabla W_{\omega,\varepsilon} \cdot n|_{\partial B} = 0 \quad \text{in the sense of traces.}
\]

Here, $\varepsilon$ and $\omega$ are positive parameters.
4. Existence of approximate solutions within $B$

The construction of the approximate solutions

$$(P_{ω,ε}, Q_{ω,ε}, D_{ω,ε}, v_{ω,ε}, C_{ω,ε}, W_{ω,ε})$$

within the fixed reference domain $B$ relies

– on the regularization of the three transport equations (1.2)–(1.4) with the aid of an artificial viscosity parameter $η$ transforming the three transport (hyperbolic) equations into parabolic partial differential equations, and

– on the use of the so-called Faedo Garlerkin approximations on Brinkman’s equation which involves replacing (1.1) by an integral relation. The approximation at this level involves a parameter $n$, denoting the dimension of the basis used in this process.

Given the approximate velocity, and the nutrient and drug concentrations one solves the three parabolic equations corresponding to (1.2)–(1.4) via a fixed point argument. Next, one solves the diffusion equations obtaining the nutrient and the drug concentrations.

The loop closes by performing a fixed point argument on the integral form of Brinkman’s equation yielding the approximate velocity. The existence of the approximate solutions $\{P_{ω,ε}, Q_{ω,ε}, D_{ω,ε}, v_{ω,ε}, C_{ω,ε}, W_{ω,ε}\}$ within $B$ is established by letting $n \to \infty$ and $η \to 0$ in the spirit of the analysis in [7].

We emphasize at this point that by adding the three parabolic equations of the approximate cell densities corresponding to (1.2)–(1.4) one obtains a parabolic equation for the sum of cell densities $[P + Q + D]_{ω,ε,n}$. At this point we omit the indices for simplicity in the presentation.

We recall that in $Ω_ε$, (1.10) holds, namely $P + Q + D = ϱf$. A simple argument shows that this sum is constant within the fixed reference domain $B$ as well. At this level one can argue by contradiction, namely assume that

$$P + Q + D = R(t) \neq ϱf$$

and write the equation verified by $R(t)$ which is the following linear parabolic equation:

$$\partial_t R(t) + v \nabla R(t) = η Δ R(t) + \frac{1}{ϱf} [K_BCP - K_RD][ϱf - R(t)]$$  (4.1)

supplemented with the initial data

$$R(0) = ϱf.$$  (4.2)

Applying Gronwall’s inequality now yields uniqueness of solutions for (4.1)–(4.2). Observing now, that $R(t) = ϱf$ is a solution of (4.1)–(4.2) leads to contradiction.

5. Uniform bounds

In this section we collect all the uniform bounds satisfied by the solutions of the penalization schemes defined in the section 3. Let us mention that we will denote by $c$ a constant that depends on the initial data (1.15), the boundary conditions (1.13)–(1.14), $ϱf$, $∥C_{ω,ε}∥_{L^∞(t,x)}$, $∥W_{ω,ε}∥_{L^∞(t,x)}$.

From the previous section we get that

$$0 \leq P_{ω,ε}, Q_{ω,ε}, D_{ω,ε} \leq ϱf$$  in $[0, T] \times B$,  \hspace{1cm} (5.1)

this entails that for any $p \geq 1$

$$P_{ω,ε}, Q_{ω,ε}, D_{ω,ε} \text{ are uniformly bounded in } L^p([0, T] \times B).$$  \hspace{1cm} (5.2)
Since the nutrient \( C_{\omega,\varepsilon} \) and the drug concentration satisfy a parabolic equation, by a standard application of the maximum principle \([1]\) we have that almost everywhere in \( B \times (0, T) \)
\[
C_{\omega,\varepsilon}(x, t) \in L^\infty([0, T] \times B),
\]
(5.3)
\[
W_{\omega,\varepsilon}(x, t) \in L^\infty([0, T] \times B).
\]
(5.4)

Now, by multiplying (1.8) by \( C_{\omega,\varepsilon} \), by integrating by parts and by taking into account (5.1), (5.2), (5.3) we get that \( C_{\omega,\varepsilon} \) satisfies the following energy estimate:
\[
\frac{\partial}{\partial t} \int_B \frac{1}{2} C_{\omega,\varepsilon}^2 \, dx + \int_B v_1 \omega |\nabla C_{\omega,\varepsilon}|^2 \, dx \leq c \int_B C_{\omega,\varepsilon}^2 \, dx,
\]
(5.5)
similarly, taking into account that \( G_1 \) and \( G_2 \) are smooth functions we have also
\[
\frac{\partial}{\partial t} \int_B \frac{1}{2} W_{\omega,\varepsilon}^2 \, dx + \int_B v_2 \omega |\nabla W_{\omega,\varepsilon}|^2 \, dx \leq c \int_B W_{\omega,\varepsilon}^2 \, dx.
\]
(5.6)

As a consequence of (5.3), (5.4), (5.5), (5.6) we get the following uniform bounds with respect to \( \varepsilon, \omega \).
\[
\|C_{\omega,\varepsilon}\|_{L^2_t L^2} + \|v_1 \omega \nabla C_{\omega,\varepsilon}\|_{L^2_t L^2} \leq c,
\]
(5.7)
\[
\|W_{\omega,\varepsilon}\|_{L^2_t L^2} + \|v_2 \omega \nabla W_{\omega,\varepsilon}\|_{L^2_t L^2} \leq c,
\]
(5.8)
where \( L^q_t L^p \) stands for \( L^q(0, T; L^p(B)) \). By combining (5.2), (5.3) with (1.11) we have that
\[
\text{div}\, v_{\omega,\varepsilon} = G, \quad \text{with } G \in L^2(0, T; L^2(B)).
\]
(5.9)

Next, by applying regularity theory concerning the divergence equation in Sobolev spaces (see lemma 2.1.1 (a) in \([21]\) or remark 3.19 in \([16]\), for more details see also \([9]\)) we end up with
\[
\|\nabla v_{\omega,\varepsilon}\|_{L^2} \leq c \|\nabla G\|_{L^2}.
\]
(5.10)

uniformly with respect to \( \varepsilon, \omega \).

Since the vector field \( V \) vanishes on the boundary of the reference domain \( B \) it may be used as a test function in the weak formulation of the Brinkman’s equation for the penalized problem (3.2), namely
\[
\int_B \sigma_{\omega,\varepsilon} \text{div} V \, dx - \int_B \left( \mu_{\omega} \nabla \cdot v_{\omega,\varepsilon} : \nabla V + \frac{\mu_{\omega}}{K} v_{\omega,\varepsilon} \cdot V \right) \, dx
\]
\[
+ \frac{1}{\varepsilon} \int_{\Gamma_t} \left( (V - v_{\omega,\varepsilon}) \cdot n \right) \, dS_x = 0.
\]
(5.11)

By combining standard computations with (5.11), the velocity field \( v_{\omega,\varepsilon} \) satisfies the following estimate:
\[
\int_B \mu_{\omega} |\nabla v_{\omega,\varepsilon}|^2 + \frac{1}{K} |v_{\omega,\varepsilon}|^2 \, dx + \frac{1}{\varepsilon} \int_{\Gamma_t} |(v_{\omega,\varepsilon} - V) \cdot n|^2 \, dS
\]
\[
\leq \int_B \mu_{\omega} \nabla \cdot v_{\omega,\varepsilon} : \nabla V + \mu_{\omega} v_{\omega,\varepsilon} \cdot V \, dx + \int_B \sigma_{\omega,\varepsilon} (\text{div} v_{\omega,\varepsilon} - \text{div} V) \, dx.
\]

Since the vector field \( V \) is smooth by means of (5.9), and by considering the weak formulation of Brinkmann’s equation for the penalized problem (3.2) in \( B \) once more with a special test function (solving a Poisson-type equation for the pressure) we get the following uniform bounds with respect to \( \varepsilon, \omega \).
\[
\|\sigma_{\omega,\varepsilon}\|_{L^2} \leq c,
\]
(5.12)
\[
\|\mu_{\omega} v_{\omega,\varepsilon}\|_{L^2} + \|\mu_{\omega} \nabla v_{\omega,\varepsilon}\|_{L^2} \leq c,
\]
(5.13)
\[
\int_{\Gamma_t} |(v_{\omega,\varepsilon} - V) \cdot n|^2 \, dS \leq c\varepsilon.
\]
(5.14)
6. Singular limits

In this section we perform the limits of our two level penalization approximation. The first step is to keep $\omega$ fixed and let $\varepsilon \to 0$. The main issue of this step is to get rid of the quantities that are supported by the healthy tissue $B \setminus \Omega_2$. This will be done by means of the lemmas 6.1 and 6.3 that we will prove in the section. The second and final step is the vanishing viscosity limit $\omega \to 0$ that we perform in section 6.2 and this completes the proof of our main result theorem 2.2.

6.1. Vanishing penalization $\varepsilon \to 0$

As a consequence of the uniform bound (5.2) and the equations (1.2), (1.3), (1.4) we get that the weak solutions of our approximation system satisfy

\[
\begin{align*}
P_{\omega, \varepsilon} & \to P_{\omega} \\
Q_{\omega, \varepsilon} & \to Q_{\omega} \\
D_{\omega, \varepsilon} & \to D_{\omega}
\end{align*}
\]

in $C_{\text{weak}}(0, T; L^p(B))$, $p \geq 1$. (6.1)

From the bound (5.7), (5.8) and (5.13) we get

\[
\begin{align*}
C_{\omega, \varepsilon} & \rightharpoonup C_{\omega} \quad \text{weakly in } L^2(0, T; W^{1,2}_0(B)), \\
W_{\omega, \varepsilon} & \rightharpoonup W_{\omega} \quad \text{weakly in } L^2(0, T; W^{1,2}_0(B)), \\
v_{\omega, \varepsilon} & \rightharpoonup v_{\omega} \quad \text{weakly in } W^{1,2}_0(B),
\end{align*}
\]

while from (5.14) we have that

\[
\begin{align*}
(v_{\omega, \varepsilon} - V) \cdot n & = 0 \quad \text{for a.a } \tau \in [0, T].
\end{align*}
\]

By combining together (5.2), (5.13) and the compact embedding of $L^2(B)$ in $W^{-1,2}(B)$ we get

\[
\begin{align*}
P_{\omega, \varepsilon}v_{\omega, \varepsilon} & \rightharpoonup P_{\omega}v_{\omega} \\
Q_{\omega, \varepsilon}v_{\omega, \varepsilon} & \rightharpoonup Q_{\omega}v_{\omega} \\
D_{\omega, \varepsilon}v_{\omega, \varepsilon} & \rightharpoonup D_{\omega}v_{\omega}
\end{align*}
\]

in $C_{\text{weak}}([T_1, T_2]; L^{2q/6+q}(B))$, $2 \leq q < 6$. (6.5)

Finally from the equations (1.2)–(1.4) it follows that

\[
\begin{align*}
P_{\omega, \varepsilon}C_{\omega, \varepsilon} & \rightharpoonup P_{\omega}C_{\omega} \\
Q_{\omega, \varepsilon}C_{\omega, \varepsilon} & \rightharpoonup Q_{\omega}C_{\omega} \\
D_{\omega, \varepsilon}C_{\omega, \varepsilon} & \rightharpoonup D_{\omega}C_{\omega}
\end{align*}
\]

in $C_{\text{weak}}([T_1, T_2]; L^{2q/6+q}(B))$, $2 \leq q < 6$. (6.6)

Since the embedding of $W^{1,2}_0(B)$ in $L^6(B)$ is compact we have that

\[
v_{\omega, \varepsilon} \otimes v_{\omega, \varepsilon} \rightharpoonup v_{\omega} \otimes v_{\omega} \quad \text{weakly in } L^{6q/6+q}(B) \text{ for any } 2 \leq q < 6.
\]

Taking into account (5.2), (5.7), (5.8) and, as before, the compact embedding of $L^2(B)$ in $W^{-1,2}(B)$ we get

\[
\begin{align*}
P_{\omega, \varepsilon}W_{\omega, \varepsilon} & \rightharpoonup P_{\omega}W_{\omega} \\
Q_{\omega, \varepsilon}W_{\omega, \varepsilon} & \rightharpoonup Q_{\omega}W_{\omega}
\end{align*}
\]

in $C_{\text{weak}}([T_1, T_2]; L^{2q/6+q}(B))$, $2 \leq q < 6$. (6.7)

By using (5.12) and (6.4) we into the limit in the weak formulation (3.2) of the Brinkman's equation we get

\[
\int_B \sigma_{\omega} \text{div} \psi \, dx = \int_B \left( \mu_{\omega} \nabla_{\omega} v_{\omega} : \nabla_{\omega} \psi + \frac{\mu_{\omega}}{K} v_{\omega} \psi \right) \, dx = 0,
\]

for any test function $\psi \in C^\infty_c(B; \mathbb{R}^3)$, $\psi \cdot n|_B = 0$. (6.8)
By using (5.13), (6.1)–(6.7) we can pass to the limit in the weak formulations (Ip), (3.4), (3.6) and we obtain

\[
\int_{B} P_{\omega} \varphi(\tau, \cdot) \, dx - \int_{B} P_{0} \varphi(0, \cdot) \, dx = \\
\int_{0}^{\tau} \int_{B} (P_{\omega} \partial_{t} \varphi + P_{\omega} v \cdot \nabla_{x} \varphi + G_{P_{\omega}} \varphi) \, dx \, dt,
\]

\[
\int_{B} Q_{\omega} \varphi(\tau, \cdot) \, dx - \int_{B} Q_{0} \varphi(0, \cdot) \, dx = \\
\int_{0}^{\tau} \int_{B} (Q_{\omega} \partial_{t} \varphi + Q_{\omega} v \cdot \nabla_{x} \varphi + G_{Q_{\omega}} \varphi) \, dx \, dt,
\]

\[
\int_{B} D_{\omega} \varphi(\tau, \cdot) \, dx - \int_{B} D_{0} \varphi(0, \cdot) \, dx = \\
\int_{0}^{\tau} \int_{B} (D_{\omega} \partial_{t} \varphi + D_{\omega} v \cdot \nabla_{x} \varphi + G_{D_{\omega}} \varphi) \, dx \, dt.
\]

(IIp)

\[
\int_{B} C_{\omega} \varphi(\tau, \cdot) \, dx - \int_{B} C_{0} \varphi(0, \cdot) \, dx = \\
\int_{0}^{\tau} \int_{B} C_{\omega} \partial_{t} \varphi \, dx \, dt - \int_{0}^{\tau} \int_{B} v_{1_{\omega}} \nabla_{x} C_{\omega} \cdot \nabla_{x} \varphi \, dx \, dt
\]

\[- \int_{0}^{\tau} \int_{B} (K_{1} K_{P_{\omega}} C_{\omega} + K_{2} K_{Q}(\bar{C} - C_{\omega}) \bar{Q}) C_{\omega} \varphi \, dx \, dt.
\]

(6.9)

\[
\int_{B} W_{\omega} \varphi(\tau, \cdot) \, dx - \int_{B} W_{0} \varphi(0, \cdot) \, dx = \\
\int_{0}^{\tau} \int_{B} W_{\omega} \partial_{t} \varphi \, dx \, dt - \int_{0}^{\tau} \int_{B} v_{1_{\omega}} \nabla_{x} W_{\omega} \cdot \nabla_{x} \varphi \, dx \, dt
\]

\[- \int_{0}^{\tau} \int_{B} (\mu_{2} G_{1}(W_{\omega}) P_{\omega} + \mu_{2} G_{2}(W_{\omega}, \epsilon) Q_{\omega}) W_{\omega} \varphi \, dx \, dt.
\]

(6.10)

6.1.1. Vanishing density terms in the ‘healthy tissue’. The next step in the penalization limit is to get rid of the terms supported in the healthy tissue part \(((0, T) \times B) \setminus \Omega_{T}\). The main issue is to describe the evolution of the interface \(\Gamma_{T}\). To that effect we employ elements from the so-called level set method. The level set method is a numerical method for tracking interfaces and shapes (see [18]). It turns out that the interface \(\Gamma_{T}\) can be identified with a component of the set

\[\{ \Phi(\tau, \cdot) = 0 \},\]

while the set \(B \setminus \Omega_{T}\) correspond to \(\{ \Phi(\tau, \cdot) > 0 \}\), with \(\Phi = \Phi(t, x)\) denoting the unique solution of the transport equation

\[\partial_{t} \Phi + \nabla_{x} \Phi(t, x) \cdot V = 0, \quad (6.11)\]

with initial data

\[\Phi_{0}(x) = \begin{cases} > 0 & \text{for } x \in B \setminus \Omega_{0}, \\ < 0 & \text{for } x \in \Omega_{0} \cup ([R^{3} \setminus B]) \cap \Gamma_{0}. \end{cases}, \quad \nabla_{x} \Phi_{0} \neq 0 \text{ on } \Gamma_{0}.
\]

Finally,

\[\nabla_{x} \Phi(\tau, x) = \lambda(\tau, x)n(x) \quad \text{for any } x \in \Gamma_{\tau}, \quad \lambda(\tau, x) \geq 0 \quad \text{for } \tau \in [0, T]. \quad (6.12)\]

First we deal with the nutrient \(C_{\omega}\) and the drug concentration \(W_{\omega}\). In order to study their behaviour on the healthy tissue we need to prove the following lemma.
Lemma 6.1. Let \( Z \in L^\infty(0, T; W^{1,2}(B)) \), \( Z \geq 0 \), satisfying the following parabolic equation in \([0, T] \times B\)

\[
\frac{\partial Z}{\partial t} = \nu \Delta Z + H(x, t)Z
\]  

(6.13)

where \( H(x, t) \in L^\infty([0, T] \times B) \). Moreover assume that

\( Z_0 \in L^2(\mathbb{R}^3), \quad Z_0|_{B\setminus \Omega_0} = 0. \)

Then

\[ Z(\tau, \cdot)|_{B\setminus \Omega_\tau} = 0 \quad \text{for any} \quad \tau \in [0, T]. \]  

(6.14)

**Proof.** In the proof it is crucial the construction of an appropriate test function to be used in the weak formulation of (6.13). For given \( \eta > 0 \) we use

\[ \varphi = \left[ \min \left\{ \frac{1}{\eta} \Phi; 1 \right\} \right]^+ \]  

(6.15)

and we obtain

\[
\int_{B\setminus \Omega_\tau} Z \varphi \, dx = \frac{1}{\eta} \int_0^\tau \int_{\{0 \leq \Phi(t, x) \leq \eta\}} (Z \partial_t \Phi - \nu \nabla_x Z \cdot \nabla_x \Phi - H(x, t)Z \Phi) \, dx \, dt
\]

\[
+ \int_0^\tau \int_{\{\Phi(t, x) > \eta\}} H(x, t)Z \, dx \, dt
\]

We introduce now the following distance function:

\[ \delta(t, x) = \text{dist}_{\mathbb{R}^3 \setminus x} \partial(B\setminus \Omega_\tau) \quad \text{for} \quad t \in [0, \tau], x \in B\setminus \Omega_\tau. \]  

(6.16)

Since \( V \) is regular we have that

\[ \frac{\sqrt{\delta(t, x)}}{\eta} \leq c, \quad \text{when} \quad 0 \leq \Phi(t, x) \leq \eta. \]  

(6.17)

By using (6.11) and (6.16) we have that

\[
\int_{B\setminus \Omega_\tau} Z \varphi \, dx \leq -\frac{1}{\eta} \int_0^\tau \int_{\{0 \leq \Phi(t, x) \leq \eta\}} \frac{\sqrt{\delta}}{\sqrt{\delta}} (ZV + \nu \nabla_x Z \cdot \nabla_x \Phi) \, dx \, dt
\]

\[
- \frac{1}{\eta} \int_0^\tau \int_{\{0 \leq \Phi(t, x) \leq \eta\}} \frac{\sqrt{\delta}}{\sqrt{\delta}} H(x, t) \Phi \, dx \, dt - \int_0^\tau \int_{B\setminus \Omega_\tau} H(x, t)Z \, dx \, dt,
\]  

(6.18)

and letting \( \eta \to 0 \) in (6.18) and by using (6.17) the fact that \( Z/\sqrt{\delta} \in L^1([0, \tau] \times B\setminus \Omega_\tau), \ Z_\omega, \ \nabla_x Z_\omega \in L^2(0, T; L^2(B)) \) and that \( H(x, t) \) is bounded, by Gronwall’s inequality we conclude with (6.14).

Now we are ready to prove that the nutrient and the drug concentration are vanishing outside \( \Omega_\tau \).

**Proposition 6.2.** Assume that \( C_\omega \), \( W_\omega \) satisfy (6.9) and (6.10), respectively and that (IC-p) holds, then

\[ C_\omega(\tau, \cdot)|_{B\setminus \Omega_\tau} = 0, \quad W_\omega(\tau, \cdot)|_{B\setminus \Omega_\tau} = 0. \]  

(6.19)
Proof. The proof of (6.19) follows by applying the Lemma 6.1 to $Z = C_0$ and $H(x,t) = K_1 K_0 C_0 P_0 + K_2 K_0 (\bar{C} - C_0) Q$ or $Z = W_0$ and $H(x,t) = \mu_1 G_1 (W_0) P_0 + \mu_2 G_2 (W_0, \varepsilon) Q_0$. Then, by taking into account (5.2), (5.3), (5.4), (5.7), (5.8), all the hypothesis of the Lemma 6.1 are fulfilled.

Now, thanks to the Proposition 6.2, the weak formulation (6.9) assumes the following form:

\[
\int_{\Omega_t} C_0 \phi(\tau, \cdot) \, dx - \int_{\Omega_0} C_0 \phi(0, \cdot) \, dx
= \int_0^\tau \int_{\Omega_t} C_0 \phi \, dt - \int_0^\tau \int_{\Omega_t} v_{10} \nabla_x C_0 \cdot \nabla_x \phi \, dx \, dt
- \int_0^\tau \int_{\Omega_t} (K_1 K_0 C_0 P_0 + K_2 K_0 (\bar{C} - C_0) Q_0) C_0 \phi(\tau, \cdot) \, dx \, dt, \tag{6.20}
\]

while the drug concentration formulation (6.10) becomes

\[
\int_{\Omega_t} W_0 \phi(\tau, \cdot) \, dx - \int_{\Omega_0} W_0 \phi(0, \cdot) \, dx
= \int_0^\tau \int_{\Omega_t} W_0 \phi \, dt - \int_0^\tau \int_{\Omega_t} v_{20} \nabla_x W_0 \cdot \nabla_x \phi \, dx \, dt
- \int_0^\tau \int_{\Omega_t} (\mu_1 G_1 (W_0) P_0 + \mu_2 G_2 (W_0, \varepsilon) Q_0) W_0 \phi(\tau, \cdot) \, dx \, dt. \tag{6.21}
\]

In order to prove that the proliferating, quiescent and dead cells are vanishing in the healthy tissue we need to prove the following lemma.

Lemma 6.3. Let $Z \in L^\infty(0, T; L^2(B))$, $Z \geq 0$, $v \in W^{1,2}_0(B)$ satisfying the following equation

\[
\int_B (Z_0(\tau, \cdot) - Z_0 \phi(0, \cdot)) \, dx
= \int_0^\tau \int_B \left( Z \partial_t \phi + Z v \cdot \nabla_x \phi + (G + G_Z) \phi \right) \, dx \, dt, \tag{6.22}
\]

for any $\tau \in [0, T]$ and any test function $\phi \in C^1_0([0, T] \times \mathbb{R}^3)$ and $G_Z$ a linear function of $Z$, while $G \in L^\infty([0, T] \times B)$, $G(\tau, \cdot)|_{B \setminus \Omega_t} = 0$. Moreover assume that

\[
(v - V)(\tau, \cdot) \cdot n \big|_{\Gamma_{\tau t}} = 0 \quad \text{a.e. } \tau \in (0, T) \tag{6.23}
\]

and that

\[
Z_0 \in L^2(\mathbb{R}^3), \quad Z_0 \geq 0 \quad Z_0 \big|_{B \setminus \Omega_0} = 0.
\]

Then

\[
Z(\tau, \cdot) \big|_{B \setminus \Omega_t} = 0 \quad \text{for any } \tau \in [0, T]. \tag{6.24}
\]

Proof. By taking the function (6.15) as a test function in the weak formulation (6.22) we obtain

\[
\int_B Z \phi \, dx = \frac{1}{\eta} \int_0^\tau \int_{\Phi_{\tau t} \leq \eta} (Z \partial_t \Phi + Z v \cdot \nabla_x \Phi + (G + G_Z) \Phi) \, dx \, dt
+ \int_0^\tau \int_{\Phi_{\tau t} > \eta} G_Z \, dx \, dt. \tag{6.25}
\]
We have that
\[ Z \partial_t \Phi + Z v \cdot \nabla_x \Phi = Z (\partial_t \Phi + v \cdot \nabla_x \Phi) = Z (v - V) \cdot \nabla_x \Phi, \]
where by (6.12) and (6.23) we get
\[ (v - V) \cdot \nabla_x \Phi \in W^{1,2}_0(B \setminus \Omega_t) \quad \text{for a.e. } t \in (0, \tau). \] (6.26)

By using again the distance function (6.16) from (6.26) and an application of Hardy’s inequality (see theorem 21.5 in [17]) it follows that
\[ \frac{1}{\delta} (v - V) \cdot \nabla_x \Phi \in L^2([0, \tau] \times B \setminus \Omega_t). \] (6.27)

On the other hand by taking into account that \( G \) is bounded and that \( G_Z \) is a linear function of \( Z \) and \( Z \in L^\infty(0, T; L^2(B)) \) and that (6.16) is defined in \( \mathbb{R}^3 \) we have also
\[ \frac{V + G_Z}{\sqrt{\delta}} \in L^1([0, \tau] \times B \setminus \Omega_t). \] (6.28)

Since \( V \) is regular we have that
\[ \frac{\delta(t, x)}{\eta} \leq C, \quad \text{when } 0 \leq \Phi(t, x) \leq \eta. \] (6.29)

Going back to (6.25) we get
\[
\begin{align*}
\int_{B \setminus \Omega_t} Z \varphi \, dx &\leq \frac{1}{\eta} \int_0^\tau \int_{\{0 \leq \Phi(t, x) \leq \eta\}} \frac{Z (v - V) \cdot \nabla_x \Phi}{\delta} \, dx \, dt \\
& \quad + \frac{1}{\eta} \int_0^\tau \int_{\{0 \leq \Phi(t, x) \leq \eta\}} \frac{\sqrt{\delta} G + G_Z}{\sqrt{\delta}} \Phi \, dx \, dt + \int_0^\tau \int_{B \setminus \Omega_t} G_Z \, dx \, dt \\
& \leq 0
\end{align*}
\] (6.30)

and letting \( \eta \to 0 \) in (6.30) and by taking into account (6.15), (6.27), (6.28), (6.17) and that \( G_Z \) is a linear function of \( Z \) and \( Z \in L^\infty(0, T; L^2(B)) \), by applying Gronwall’s inequality we conclude with
\[ \int_{B \setminus \Omega_t} Z \, dx = 0. \]

Therefore by using the fact that \( Z \geq 0 \) and \( Z \in L^\infty(0, T; L^2(B)) \) we end up with (6.24). \( \square \)

By means of the previous lemma we are able to prove now that the proliferating, quiescent, dead cells are vanishing in the healthy tissue.

**Proposition 6.4.** Assume that \( P_{\omega}, Q_{\omega}, D_{\omega}, \) and \( C_{\omega} \) satisfy (II-p) and that (IC-p) holds, then
\[ P_{\omega}(\tau, \cdot)_{|B\setminus\Omega_t} = 0, \quad Q_{\omega}(\tau, \cdot)_{|B\setminus\Omega_t} = 0, \quad D_{\omega}(\tau, \cdot)_{|B\setminus\Omega_t} = 0. \] (6.31)

**Proof.** We start the proof with \( P_{\omega} \): by using the lemma 6.1 and the uniform bounds of the section 5 we see \( P_{\omega} \) verifies the hypotheses of the lemma 6.3 if we take \( G = K_p C_{\omega} Q_{\omega} \) and \( G_z = (K_d C_{\omega} - K_Q (C_c - C_{\omega}) - K_A (C_c - C_{\omega})) P_{\omega} - i_1 G_1 (W_{\omega}) P_{\omega} \), so we have that \( P_{\omega}(\tau, \cdot)_{|B\setminus\Omega_t} = 0 \). Having obtained the result for \( P_{\omega} \), the remaining part of the proof follows with the same type of arguments applied to \( Q_{\omega} \) and \( D_{\omega} \). \( \square \)

Now, taking into account the proposition 6.4, \( P_{\omega}, Q_{\omega}, D_{\omega} \) satisfy the weak formulation (I) as \( \varepsilon \to 0 \).
6.2. Vanishing viscosity limit $\omega \to 0$

The last step in the proof is to perform the limit $\omega \to 0$ in order to get rid of the last viscosity terms of (6.8) in $B \setminus \Omega_1$. By using (5.13) we have that

$$
\int_{\Omega_1} \mu \left( |\nabla x v_\omega|^2 + |v_\omega|^2 \right) \, dx \leq c
$$

$$
\int_{B \setminus \Omega_1} \mu_\omega \left( |\nabla x v_\omega| + |v_\omega| \right) \, dx \leq c.
$$

The estimates (6.32) with a standard computations yields that

$$
\int_{B \setminus \Omega_1} \mu_\omega \left( \nabla_x v_\omega : \nabla_x \varphi + v_\omega, t \varphi \right) \, dx \to 0 \quad \text{as } \omega \to 0.
$$

(6.33)

By combining (6.8) with (6.33) we get

$$
\int_{B \setminus \Omega_1} \sigma_\omega \mathrm{div} \varphi \, dx \, dt = 0,
$$

for any test function $\varphi$. Now in the same spirit of [8] we can let $\omega \to 0$ in the weak formulations (6.8), (6.20), (6.21) and we complete the proof of theorem 2.2.

Acknowledgments

The work of DD was supported by the Ministry of Education, University and Research (MIUR), Italy under the grant PRIN 2012- Project N. 2012L5WXHJ, Nonlinear Hyperbolic Partial Differential Equations, Dispersive and Transport Equations: theoretical and applicative aspects. KT gratefully acknowledges the support in part by the National Science Foundation under the grant DMS-1211519 and by the Simons Foundation under the Simons Fellows in Mathematics Award 267399. Part of this research was performed during the visit of KT at University of L’Aquila which was supported under the grant PRIN 2012- Project N. 2012L5WXHJ, Nonlinear Hyperbolic Partial Differential Equations, Dispersive and Transport Equations: theoretical and applicative aspects. This work was completed while KT was resident at École Normale Supérieure de Cachan as a Simons Fellow. KT is grateful to C Bardos, L Desvillettes and the CMLA Lab for providing a very stimulating environment for scientific research and to C Villani and the Institute Henri Poincaré for the hospitality.

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