

# On the vanishing viscosity approximation of a nonlinear model for tumor growth

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**ABSTRACT.** We investigate the dynamics of a nonlinear system modeling tumor growth with drug application. The tumor 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 tumor is given by Darcy's equation. The domain occupied by the tumor 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 the vanishing viscosity of the Brinkman's regularization. Both the solutions and the domain are rather general, no symmetry assumption is required and the result holds for large initial data.

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## 1. Introduction

**1.1. Motivation.** In recent years, there has been an increased interest in the mathematical modeling and numerical simulation of tumor growth to complement

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experimental and clinical studies and thereby improve the understanding of cancer progression. Mathematical models describing continuum cell populations and their development typically consider the interactions between the cell number densities and one or more chemical species that provide nutrients and drug or influence the cell cycle events of a tumor cell population.

In this work we investigate the dynamics of a nonlinear system describing the evolution of cancerous cells. The tumor is viewed as a *multiphase flow* consisting of proliferating cells, quiescent cells and dead cells (also known as extra-cellular cells) in the presence of a nutrient (oxygen) and drug. Here, and in what follows, we denote by  $P, Q$  and  $D$  the densities of proliferating, quiescent and dead cells respectively, and by  $C$  and  $W$  the nutrient and drug concentrations.

The mathematical model under consideration is governed by a system of transport equations for the evolution of cancerous cells; two rather general diffusion equations which are used to describe the diffusion of the nutrient (oxygen) within the tumor region and the evolution of the drug within the same regime and the Darcy law, which determines the velocity field. The continuous movement within the tumor region is due to proliferation, mitosis, apoptosis or removal of cells.

**1.2. Biological principles.** Our model is based on the following biological principles (cf. Roda *et al.* [11, 12], Friedman *et al.* [8], [9], Zhao [17]):

- Living cells are either in a *proliferating phase* or in a *quiescent phase*.
- 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 tumor cells depend on the oxygen level.
- The dead tumor cells are obtained from necrosis and apoptosis of live tumor cells, and they are cleared by macrophages.
- Living cells undergo *mitosis*, a process that takes place in the nucleus of a dividing cell.
- 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.
- Proliferating cells become quiescent and die at a rate which increases as the nutrient concentration decreases. The proliferation rate increases with the nutrient concentration.
- Proliferating cells and quiescent cells become dead cells at a rate which depends on the drug concentration.

We denote by  $\Omega_t := \Omega(t)$  the tumor region and its boundary  $\partial\Omega_t$  evolves with respect to time. Both live and dead tumor cells are assumed to be in the tumor region  $\Omega_t$ . Abnormal proliferation of tumor cells generates internal pressure in  $\Omega(t)$ , resulting to a velocity field  $\mathbf{v} \neq 0$ .

### 1.3. Governing equations of cells, oxygen and drug.

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

$$\frac{\partial n}{\partial t} + \operatorname{div}_x(n\mathbf{v}) = G(n),$$

where  $n$  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.

The change of phase of the cancerous cells generates a continuous movement within the tumor represented by a velocity field  $\mathbf{v}$ .

The rates of change from one phase to another are functions of the nutrient concentration  $C$ .

- $K_Q(C)$  denotes the rate of change of phase from  $P \rightarrow Q$ ;
- $K_P(C)$  denotes the rate of change from  $Q \rightarrow P$ ; while
- $K_A(C)$  and  $K_D(C)$  denote the change of phases from  $P \rightarrow D$  and  $Q \rightarrow D$  respectively.

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

1.3.2. *The tumor tissue as a porous medium.* Due to proliferation and removal of cells there is continuous motion of cells within the tumor; this movement is represented by the velocity field  $\mathbf{v}$  given by the Darcy's equation

$$(1.1) \quad \nabla_x \sigma = -\frac{\tilde{\mu}}{K} \mathbf{v}.$$

where  $\sigma$  denotes the pressure,  $\tilde{\mu}$  is a positive constant describing the viscous like properties of tumor cells, whereas  $K$  denotes the permeability. In the present context, (1.1) accounts for the friction of the tumor cells with the extracellular matrix

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:

$$(1.2) \quad \frac{\partial P}{\partial t} + \operatorname{div}(P\mathbf{v}) = \mathbf{G}_P,$$

$$(1.3) \quad \frac{\partial Q}{\partial t} + \operatorname{div}(Q\mathbf{v}) = \mathbf{G}_Q,$$

$$(1.4) \quad \frac{\partial D}{\partial t} + \operatorname{div}(D\mathbf{v}) = \mathbf{G}_D.$$

Following Friedman [8], the source terms  $\{\mathbf{G}_P, \mathbf{G}_Q, \mathbf{G}_D\}$  are of the following form:

$$(1.5) \quad \mathbf{G}_P = (K_B C - K_Q(\bar{C} - C) - K_A(\bar{C} - C)) P + K_P C Q - i_1 G_1(W) P,$$

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

$$(1.6) \quad \mathbf{G}_Q = K_Q(\bar{C} - C) P - (K_P C + K_D(\bar{C} - C)) Q - i_2 G_2(W) Q,$$

with  $G_2(\cdot)$  a smooth function and  $K_P, K_Q, K_D$  positive constants. In the above relations (1.5)-(1.6)  $i_1G_1(W)$  and  $i_2G_2(W)$  denote the rates by which the proliferating cells and the quiescent cells become dead cells due to the drug. Finally,

$$(1.7) \quad \mathbf{G}_D = K_A(\bar{C} - C)P + K_D(\bar{C} - C)Q - K_RD + i_1G_1(W)P + i_2G_2(W)Q.$$

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

$$\frac{\partial C}{\partial t} = \nabla \cdot (\nu_1 \nabla C) - (K_1 K_P C P + K_2 K_Q (\bar{C} - C) Q) C.$$

Assuming that  $\nu_1$  is constant this equation (cf. Friedman [8]) becomes

$$(1.8) \quad \frac{\partial C}{\partial t} = \nu_1 \Delta C - (K_1 K_P C P + K_2 K_Q (\bar{C} - C) Q) C.$$

This equation describes the diffusion of the oxygen in the tumor region. According to (cf. Ward and King [15], [16]) 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).

1.3.4. *A linear diffusion equation for the evolution of drug.* The evolution of the drug concentration in the tumor is given by a diffusion equation of the form

$$\frac{\partial W}{\partial t} = \nabla \cdot (\nu_2 \nabla W) - (\mu_1 G_1(W)P + \mu_2 G_2(W)Q) W,$$

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

Assuming that  $\nu_2$  is constant this equation (cf. Zhao [17]) becomes

$$(1.9) \quad \frac{\partial W}{\partial t} = \nu_2 \Delta W - (\mu_1 G_1(W)P + \mu_2 G_2(W)Q) W.$$

This equation describes the diffusion of the drug within the tumor 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.

The total density of the mixture is denoted by  $\varrho_f$  and is given by

$$(1.10) \quad \varrho_f = P + Q + D = \text{Constant}.$$

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

$$(1.11) \quad \rho_f \operatorname{div} \mathbf{v} = \mathbf{G}_P + \mathbf{G}_Q + \mathbf{G}_D = K_B C P - K_R D.$$

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.

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

$$\frac{d}{dt}\mathbf{X}(t, \mathbf{x}) = \mathbf{v}(t, \mathbf{X}(t, x)), \quad t > 0, \quad \mathbf{X}(0, x) = x,$$

and set

$$\begin{cases} \Omega_\tau = \mathbf{X}(\tau, \Omega_0), \text{ where } \Omega_0 \subset \mathbb{R}^3 \text{ is a given domain,} \\ \Gamma_\tau = \partial\Omega_\tau, \text{ and } Q_\tau = \{(t, x) | t \in (0, \tau), x \in \Omega_\tau\}. \end{cases}$$

Moreover, we assume that

$$(1.12) \quad \operatorname{div}_x \mathbf{v}(\tau, \cdot) = 0,$$

which by the transport theorem yields

$$|\Omega_\tau| = |\Omega_0| \text{ for any } \tau \geq 0.$$

The model is closed by giving boundary conditions on the (moving) tumor boundary  $\Gamma_\tau$ . More precisely, we assume that the boundary  $\Gamma_\tau$  is impermeable, meaning

$$(1.13) \quad (\mathbf{v} - \mathbf{v}) \cdot \mathbf{n}|_{\Gamma_\tau} = 0, \text{ for any } \tau \geq 0.$$

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

$$(1.14) \quad [\mathbb{S}\mathbf{n}]_{\tan}|_{\Gamma_\tau} = 0,$$

with  $\mathbb{S}$  denoting the viscous stress tensor which in this context is assumed to be determined through Newton's rheological law

$$\mathbb{S} = \mu \left( \nabla \mathbf{v} + \nabla^\perp \mathbf{v} - \frac{2}{3} \operatorname{div} \mathbf{v} \mathbb{I} \right) + \xi \operatorname{div} \mathbf{v} \mathbb{I},$$

where  $\mu > 0$ ,  $\xi \geq 0$  are respectively the shear and bulk viscosity coefficients. Condition (1.14) namely says that the tangential component of the normal viscous stress vanishes on  $\Gamma_\tau$ .

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

$$(1.15) \quad C(x, t)|_{\Gamma_t} = 0, \quad W(x, t)|_{\Gamma_t} = 0.$$

In contrast to the case of *avasacular tumors* where the nutrient typically diffuses within the tumor region through the boundary, here we assume that the diffusion of the nutrient occurs through the vessels present in the area.

Finally, the problem (1.2)-(1.15) is supplemented by the initial conditions

$$(1.16) \quad \begin{cases} P(0, \cdot) = P_0, \quad Q(0, \cdot) = Q_0, \quad D(0, \cdot) = D_0, \\ C(0, \cdot) = C_0 \leq \bar{C}, \quad W(0, \cdot) = W_0 \text{ in } \Omega_0. \end{cases}$$

The aim of this work is the establishment of the global existence of weak solutions to the nonlinear system (1.1)-(1.4), (1.8)-(1.9) for finite large initial data.

Related results on the mathematical analysis of cancer models have been presented by Zhao [17] based on the framework introduced by Friedman *et al.* [8], [9]. The analysis in [8], [9] 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 [17] treats a parabolic-hyperbolic free boundary problem and provides a unique global solution in the radially symmetric case.

In [3, 4], Donatelli and Trivisa establish the global existence of weak solutions to a nonlinear system modeling tumor growth in a general moving domain  $\Omega_t \subset \mathbb{R}^3$  without any symmetry assumption and for finite large initial data. In that context, the nonlinear system is governed by transport equations (1.2)-(1.9) for the evolution of cancerous cells, whereas the evolution of the velocity field  $\mathbf{v}$  of the tumor growth is given, by the Brinkman regularization of the Darcy Law, namely

$$\nabla_x \sigma = -\frac{\tilde{\mu}}{K} \mathbf{v} + \mu \Delta \mathbf{v}.$$

In the present article, we establish the global existence of weak solutions to the nonlinear system (S)

$$(S) \quad \left\{ \begin{array}{l} \nabla_x \sigma = -\frac{\tilde{\mu}}{K} \mathbf{v}, \\ \frac{\partial P}{\partial t} + \operatorname{div}(P \mathbf{v}) = \mathbf{G}_P, \\ \frac{\partial Q}{\partial t} + \operatorname{div}(Q \mathbf{v}) = \mathbf{G}_Q, \\ \frac{\partial D}{\partial t} + \operatorname{div}(D \mathbf{v}) = \mathbf{G}_D, \\ \frac{\partial C}{\partial t} = \nu_1 \Delta C - (K_1 K_P C P + K_2 K_Q (\bar{C} - C) Q) C, \\ \frac{\partial W}{\partial t} = \nu_2 \Delta W - (\mu_1 G_1(W) P + \mu_2 G_2(W) Q) W. \end{array} \right.$$

on time dependent domains supplemented with the boundary conditions (1.13), (1.14), (1.15) and the initial data (1.16), by establishing rigorously the vanishing viscosity limit  $\mu \rightarrow 0$  for the following system,

$$(S_\mu) \quad \left\{ \begin{array}{l} \nabla_x \sigma_\mu = -\frac{\tilde{\mu}}{K} \mathbf{v}_\mu + \mu \Delta \mathbf{v}_\mu, \\ \frac{\partial P_\mu}{\partial t} + \operatorname{div}(P_\mu \mathbf{v}_\mu) = \mathbf{G}_{P_\mu}, \\ \frac{\partial Q_\mu}{\partial t} + \operatorname{div}(Q_\mu \mathbf{v}_\mu) = \mathbf{G}_{Q_\mu}, \\ \frac{\partial D_\mu}{\partial t} + \operatorname{div}(D_\mu \mathbf{v}_\mu) = \mathbf{G}_{D_\mu}, \\ \frac{\partial C_\mu}{\partial t} = \nu_1 \Delta C_\mu - (K_1 K_P C_\mu P_\mu + K_2 K_Q (\bar{C} - C_\mu) Q_\mu) C_\mu, \\ \frac{\partial W_\mu}{\partial t} = \nu_2 \Delta W_\mu - (\mu_1 G_1(W_\mu) P + \mu_2 G_2(W_\mu) Q_\mu) W_\mu. \end{array} \right.$$

with the aid of a series of delicate estimates that enable us to treat the vanishing viscosity limit within the time-dependent kinematic boundary. The global existence of weak solutions to **(S)** is established for general solutions, that is no symmetry assumption is required and for large initial data.

**1.4. General strategy.** The main ingredients of our strategy can be formulated as follows:

- Starting from the nonlinear system  $(\mathbf{S}_\mu)$  the procedure, outlined in Section 2 below, provides a global weak solution

$$\{P_\mu, Q_\mu, D_\mu, \mathbf{v}_\mu, C_\mu, W_\mu\}.$$

The next step of the investigation involves the derivation of delicate a priori bounds (uniform in  $\mu$ ) within the time dependent kinematic boundary. In this part, the condition (1.12) imposed on the boundary behavior is critical.

- The uniform bounds in  $\mu$  will allow us to establish the necessary compactness in order to pass into the limit  $\mu \rightarrow 0$  obtaining the global existence of the solutions of the original problem **(S)**. An important tool in the analysis is the use of the extension operator for Sobolev spaces,  $E : W^{1,2}(\Omega_\tau) \rightarrow W^{1,2}(\mathbb{R}^3)$ , which is uniformly bounded with respect to  $t \in [0, T]$ . This operator allow us to deal with the moving domain  $\Omega_\tau$  in the following sense: since the limiting process takes place in a moving domain  $\Omega_\tau$  it will be easier to perform the limit, if we extend  $\mathbf{v}_\mu, C_\mu$  and  $W_\mu, P_\mu, Q_\mu, D_\mu$  on the whole domain  $\mathbb{R}^3$  by setting them equal to zero outside the tumor domain. Then, since the domain  $\Omega_\tau$  is regular at each time the extension operator  $E : W^{1,2}(\Omega_\tau) \rightarrow W^{1,2}(\mathbb{R}^3)$  can be of use.

**1.5. Outline.** The paper is organized as follows: Section 1 presents the motivation, modeling and introduces the necessary preliminary material. Section 2 provides weak formulation of the problem **(S)** and states the main result. Section 3 presents an outline of the global existence of weak solutions of the nonlinear system  $(\mathbf{S}_\mu)$ . In Section 4 we present delicate a priori bounds which yield the necessary compactness that is needed in order to perform rigorously the singular limit. In Section 5 the rigorous limit  $\mu \rightarrow 0$  is established and we complete the proof of our Main Theorem 2.2.

## 2. Weak formulation and main results

In this section we present the notion of weak solutions to the nonlinear system **(S)**.

### 2.1. Weak solutions.

**DEFINITION 2.1.** We say that  $(P, Q, D, \mathbf{v}, C, W)$  is a weak solution of problem **(S)** supplemented with boundary data satisfying (1.13)-(1.15) and initial data  $(P_0, Q_0, D_0, C_0, W_0)$  satisfying (1.16) provided that the following hold:

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

$$(2.1) \quad \left. \begin{aligned} & \int_{\Omega_\tau} P\varphi(\tau, \cdot) dx - \int_{\Omega_0} P_0\varphi(0, \cdot) dx = \\ & \quad \int_0^\tau \int_{\Omega_t} (P\partial_t\varphi + P\mathbf{v} \cdot \nabla_x\varphi + \mathbf{G}_P\varphi(t, \cdot)) dx dt, \\ & \int_{\Omega_\tau} Q\varphi(\tau, \cdot) dx - \int_{\Omega_0} Q_0\varphi(0, \cdot) dx = \\ & \quad \int_0^\tau \int_{\Omega_t} (Q\partial_t\varphi + P\mathbf{v} \cdot \nabla_x\varphi + \mathbf{G}_Q\varphi(t, \cdot)) dx dt, \\ & \int_{\Omega_\tau} D\varphi(\tau, \cdot) dx - \int_{\Omega_0} D_0\varphi(0, \cdot) dx = \\ & \quad \int_0^\tau \int_{\Omega_t} (D\partial_t\varphi + D\mathbf{v} \cdot \nabla_x\varphi + \mathbf{G}_D\varphi(t, \cdot)) dx dt. \end{aligned} \right\}$$

In particular,

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

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 tumor domain.

• Darcy's equation (1.1) holds in the sense of distributions, i.e., for any test function  $\varphi \in C_c^\infty(\mathbb{R}^3; \mathbb{R}^3)$  satisfying

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

the following integral relation holds

$$(2.2) \quad \int_{\Omega_\tau} \sigma \operatorname{div} \varphi dx - \frac{\tilde{\mu}}{K} \mathbf{v} \varphi dx = 0.$$

All quantities in (2.2) are required to be integrable, so in particular,

$$\mathbf{v} \in W^{1,2}(\mathbb{R}^3; \mathbb{R}^3),$$

and

$$(\mathbf{v} - \mathbf{V}) \cdot \mathbf{n}(\tau, \cdot)|_{\Gamma_\tau} = \mathbf{0} \text{ for a.a. } \tau \in [0, T].$$

•  $C \geq 0$  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

$$\begin{aligned} & \int_{\Omega_\tau} C\varphi(\tau, \cdot) dx - \int_{\Omega_0} C_0\varphi(0, \cdot) dx = \int_0^\tau \int_{\Omega_t} C\partial_t\varphi dx dt - \\ & \int_0^\tau \int_{\Omega_t} \nu_1 \nabla_x C \cdot \nabla_x \varphi dx dt - \int_0^\tau \int_{\Omega_t} (K_1 K_P C P + K_2 K_Q (\bar{C} - C) Q) C \varphi dx dt. \end{aligned}$$

•  $W \geq 0$  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

$$\begin{aligned} & \int_{\Omega_\tau} W\varphi(\tau, \cdot) dx - \int_{\Omega_0} W_0\varphi(0, \cdot) dx = \int_0^\tau \int_{\Omega_t} W\partial_t\varphi dx dt - \\ & \int_0^\tau \int_{\Omega_t} \nu_2 \nabla_x W \cdot \nabla_x \varphi dx dt - \int_0^\tau \int_{\Omega_t} (\mu_1 G_1(W) P + \mu_2 G_2(W) Q) W dx dt. \end{aligned}$$



The main result of the article now follows.

**THEOREM 2.2.** *Let  $\Omega_0 \subset \mathbb{R}^3$  be a bounded domain of class  $C^{2+\nu}$ . Assume that the vector field  $\mathbf{v}$  belongs to the class*

$$\mathbf{v} \in C^1([0, T]; C_c^3(\mathbb{R}^3; \mathbb{R}^3)), \quad \operatorname{div}_x \mathbf{v}(\tau, \cdot) = 0 \text{ for all } \tau \in [0, T].$$

*Let the initial data satisfy*

$$P_0 \in L^p(\mathbb{R}^3), \quad Q_0 \in L^p(\mathbb{R}^3), \quad D_0 \in L^p(\mathbb{R}^3), \text{ for all } p \geq 1$$

*and*

$$\begin{aligned} C_0 &\in L^2(\mathbb{R}^3) \cap L^\infty(\mathbb{R}^3), \quad W_0 \in L^2(\mathbb{R}^3) \cap L^\infty(\mathbb{R}^3), \\ \text{with } (P_0, Q_0, D_0, C_0, W_0) &\geq 0, \quad (P_0, Q_0, D_0, C_0, W_0) \not\equiv 0, \\ P_0 + Q_0 + D_0 &= \varrho_f, \quad (P_0, Q_0, D_0, C_0, W_0)|_{\mathbb{R}^3 \setminus \Omega_0} = 0. \end{aligned}$$

*Then the problem (S) with initial data (1.16) and boundary data (1.13)-(1.15) admits a weak solution in the sense specified in Definition 2.1.*

### 3. Global Existence of Weak Solutions to the system $\mathbf{S}_\mu$

As already said in Section 1, we will prove the Theorem 2.2 by performing the vanishing viscosity limit of the system  $(\mathbf{S}_\mu)$ . Therefore we consider the system  $(\mathbf{S}_\mu)$  endowed with the following initial data

$$(3.1) \quad \begin{cases} P_\mu(0, \cdot) = P_{\mu 0} = P_0, \quad Q_\mu(0, \cdot) = Q_{\mu 0} = Q_0, \quad D_\mu(0, \cdot) = D_{\mu 0} = D_0, \\ C_\mu(0, \cdot) = C_{\mu 0} = C_0 \leq \bar{C}, \quad W_\mu(0, \cdot) = W_{\mu 0} = W_0 \text{ in } \Omega_0. \end{cases}$$

and the following boundary data:

$$(3.2) \quad (\mathbf{v}_\mu - \mathbf{v}) \cdot \mathbf{n}|_{\Gamma_\tau} = 0, \text{ for any } \tau \geq 0.$$

$$(3.3) \quad [\mathbf{S}\mathbf{n}]_{\tan}|_{\Gamma_\tau} = 0,$$

$$(3.4) \quad C_\mu(x, t)|_{\Gamma_t} = 0, \quad W_\mu(x, t)|_{\Gamma_t} = 0.$$

In this section, for completeness, we discuss briefly the global existence of weak solutions to the nonlinear system  $(\mathbf{S}_\mu)$  presented in [4]. The following result established in [4] will be essential in the sequel.

**THEOREM 3.1.** *Let  $\Omega_0 \subset \mathbb{R}^3$  be a bounded domain of class  $C^{2+\nu}$  and let*

$$\mathbf{v} \in C^1([0, T]; C_c^3(\mathbb{R}^3; \mathbb{R}^3))$$

*be given. Let the initial data satisfy*

$$P_{\mu 0} \in L^p(\mathbb{R}^3), \quad Q_{\mu 0} \in L^p(\mathbb{R}^3), \quad D_{\mu 0} \in L^p(\mathbb{R}^3), \text{ for all } p \geq 1$$

*and*

$$\begin{aligned} C_{\mu 0} &\in L^2(\mathbb{R}^3) \cap L^\infty(\mathbb{R}^3), \quad W_{\mu 0} \in L^2(\mathbb{R}^3) \cap L^\infty(\mathbb{R}^3), \\ \text{with } (P_{\mu 0}, Q_{\mu 0}, D_{\mu 0}, C_{\mu 0}, W_{\mu 0}) &\geq 0, \quad (P_{\mu 0}, Q_{\mu 0}, D_{\mu 0}, C_{\mu 0}, W_{\mu 0}) \not\equiv 0, \\ P_{\mu 0} + Q_{\mu 0} + D_{\mu 0} &= \varrho_f, \quad (P_{\mu 0}, Q_{\mu 0}, D_{\mu 0}, C_{\mu 0}, W_{\mu 0})|_{\mathbb{R}^3 \setminus \Omega_0} = 0. \end{aligned}$$

*Then the problem  $(\mathbf{S}_\mu)$  with initial data (3.1) and boundary data (3.2)-(3.4) admits a weak solution satisfying the constraint*

$$(3.5) \quad P_\mu + Q_\mu + D_\mu = \varrho_f$$

**PROOF.** We present here the main ingredients of the proof of the Theorem 3.1 presented in [4] (in order to simplify the notations we drop the index  $\mu$ ).

- Our approach involves the construction of a suitable approximating scheme which relies on the *penalization* of the boundary behavior, diffusion and viscosity in the weak formulation. The approximating scheme employs the variables  $\varepsilon$  (for the penalization of the boundary behavior) and  $\omega$  (for the penalization of the diffusion and viscosity).

**a.** In the center of the 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. This form of boundary penalty approximation appeared by Courant in [2], in the context of slip conditions for stationary incompressible fluids by Stokes and Carrey in [14], and more recently in a series of articles (cf. [3], [5], [4],[6], [7]).

More specifically, the boundary condition (1.13) is treated as a *weakly enforced constraint*, in the sense that the variational (weak) formulation of the Brinkman equation is supplemented by a singular forcing term

$$\frac{1}{\varepsilon} \int_{\Gamma_t} (\mathbf{v} - \mathbf{v}) \cdot \mathbf{n} \varphi \cdot \mathbf{n} dS_x, \quad \varepsilon > 0 \text{ small,}$$

penalizing the normal component of the velocity on the boundary of the tumor domain.

- b.** A *variable* shear viscosity coefficient  $\mu = \mu_\omega$ , as well as a *variable* diffusions  $\nu_i = \nu_{i\omega}$ ,  $i = 1, 2$  with  $\mu_\omega, \nu_{i\omega}$  are introduced, with the property that they vanish outside the tumor domain and remain positive within the tumor domain. The addition, of the variable  $\omega$  allows us the treat the moving domain.
- Keeping  $\varepsilon$  and  $\omega$  fixed, we solve the modified problem in a (bounded) reference domain  $B \subset \mathbb{R}^3$  chosen in such way that

$$\bar{\Omega}_\tau \subset B \text{ for any } \tau \geq 0$$

with the aid of a Faedo-Galerkin approximation. We refer the reader to [4] for the details. The solution  $\{P_{\omega,\varepsilon}, Q_{\omega,\varepsilon}, D_{\omega,\varepsilon}, \mathbf{v}_{\omega,\varepsilon}\}$  constructed satisfy the following uniform bounds:

$$(3.6) \quad 0 \leq P_{\omega,\varepsilon}, Q_{\omega,\varepsilon}, D_{\omega,\varepsilon} \leq \varrho_f \quad \text{in } [0, T] \times B,$$

this entails that for any  $p \geq 1$

$$(3.7) \quad P_{\omega,\varepsilon}, Q_{\omega,\varepsilon}, D_{\omega,\varepsilon} \quad \text{are uniformly bounded in } L^p([0, T] \times B).$$

Moreover we have the following uniform bounds for nutrient  $C_{\omega,\varepsilon}$ , the drug concentration  $W_{\omega,\varepsilon}$  the velocity  $\mathbf{v}_{\omega,\varepsilon}$  and the pressure  $\sigma_{\omega,\varepsilon}$

$$(3.8) \quad C_{\omega,\varepsilon}(x, t) \in L^\infty([0, T] \times B).$$

$$(3.9) \quad W_{\omega,\varepsilon}(x, t) \in L^\infty([0, T] \times B).$$

$$(3.10) \quad \|C_{\omega,\varepsilon}\|_{L_t^2 L_x^2} + \|\nu_{1\omega} \nabla_x C_{\omega,\varepsilon}\|_{L_t^2 L_x^2} \leq c,$$

$$(3.11) \quad \|W_{\omega,\varepsilon}\|_{L_t^2 L_x^2} + \|\nu_{2\omega} \nabla_x W_{\omega,\varepsilon}\|_{L_t^2 L_x^2} \leq c,$$

where  $L_t^q L_x^p$  stands for  $L^q(0, T; L^2(B))$ . In addition,

$$(3.12) \quad \|\sigma_{\omega, \varepsilon}\|_{L_x^\beta} \leq c, \quad 1 < \beta \leq 2$$

$$(3.13) \quad \|\mu_\omega \mathbf{v}_{\omega, \varepsilon}\|_{L_x^2} + \|\mu_\omega \nabla_x \mathbf{v}_{\omega, \varepsilon}\|_{L_x^2} \leq c,$$

$$(3.14) \quad \int_{\Gamma_t} |(\mathbf{v}_{\omega, \varepsilon} - \mathbf{v}) \cdot \mathbf{n}|^2 dS_x \leq c\varepsilon.$$

- Letting the penalization  $\varepsilon \rightarrow 0$  for fixed  $\omega > 0$  we obtain a “two-phase” model consisting of the *tumor region* and the *healthy tissue* separated by impermeable boundary. We show that the densities vanish in part of the reference domain, specifically on  $((0, T) \times B) \setminus Q_T$ . 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*.
- The final result is obtained by performing the limit  $\omega \rightarrow 0$ .

□

#### 4. A Priori Estimates

In this section we collect all the a priori estimates uniform in  $\mu$  satisfied by the solutions of the system  $(\mathbf{S}_\mu)$ . Let us mention that, in the sequel, we will denote by  $c$  any constant that depends on  $\varrho_f, \bar{C}, \bar{W}$ , the initial data (1.16) and the boundary conditions (1.14)-(1.15). First of all we observe that because of the condition (3.5) we get that

$$(4.1) \quad 0 \leq P_\mu, Q_\mu, D_\mu \leq \varrho_f \quad \text{in } [0, T] \times \Omega_\tau,$$

from which it follows that for any  $p \geq 1$

$$(4.2) \quad P_\mu, Q_\mu, D_\mu \quad \text{are uniformly bounded in } L^p([0, T] \times \Omega_\tau).$$

By a standard application of the maximum principle to the parabolic equations satisfied by the nutrient  $C_\mu$  and the drug concentration  $W_\mu$  we have that

$$(4.3) \quad \sup_{t \in [0, T]} \|C_\mu\|_{L^\infty(\Omega_t)} \leq \bar{C}, \quad \sup_{t \in [0, T]} \|W_\mu\|_{L^\infty(\Omega_t)} \leq \bar{W}$$

Now, by multiplying (1.8) by  $C_\mu$ , by integrating by parts and by taking into account (4.1), (4.2), (4.3) we get that  $C_\mu$  satisfies the following energy estimate,

$$(4.4) \quad \int_{\Omega_\tau} \frac{1}{2} |C_\mu|^2 dx + \nu_1 \int_0^\tau \int_{\Omega_t} |\nabla_x C_\mu|^2 dx dt \leq c \int_{\Omega_\tau} |C_0|^2 dx + \int_0^\tau \int_{\Omega_t} |C_\mu|^2 dx dt,$$

similarly, taking into account that  $G_1$  and  $G_2$  are smooth functions we have also

$$(4.5) \quad \int_{\Omega_\tau} \frac{1}{2} |W_\mu|^2 dx + \nu_2 \int_0^\tau \int_{\Omega_t} |\nabla_x W_\mu|^2 dx dt \\ \leq c \int_{\Omega_\tau} |W_0|^2 dx + \int_0^\tau \int_{\Omega_t} |W_\mu|^2 dx dt,$$

As a consequence of (4.4) and (4.5) we get the following uniform bounds

$$(4.6) \quad \int_0^T \|C_\mu\|_{W^{1,2}(\Omega_t)}^2 dt \leq c, \quad \int_0^T \|W_\mu\|_{W^{1,2}(\Omega_t)}^2 dt \leq c.$$

Now we focus our attention on the velocity field  $\mathbf{v}_\mu$ . First we notice that by adding up the equations  $(\mathbf{S}_\mu)_2 - (\mathbf{S}_\mu)_4$  we have

$$(4.7) \quad \rho_f \operatorname{div} \mathbf{v}_\mu = K_B C_\mu P_\mu - K_R D_\mu = \mathbf{G},$$

where by using (4.2) we have that  $\mathbf{G} \in L^p(\Omega_\tau)$ ,  $p \geq 1$ . Next, by applying regularity theory concerning the divergence equation in Sobolev spaces (see Lemma 2.1.1 (a) in [13] or Remark 3.19 in [10], for more details see also [3]) we end up with

$$(4.8) \quad \|\nabla_x \mathbf{v}_\mu\|_{L_x^p} \leq c \|\mathbf{G}\|_{L_x^p}, \quad p > 1.$$

On the other hand by considering the equation  $(\mathbf{S}_\mu)_1$ , by taking into account (4.7) and (4.8) and by a standard application of elliptic regularity theory (see again [3]) we conclude with the following uniform bound with respect to  $\mu$ ,

$$(4.9) \quad \|\sigma_\mu\|_{L_x^2} \leq c.$$

Now, by using (4.7), (4.9) and by multiplying the equation  $(\mathbf{S}_\mu)_1$  by  $\mathbf{v}_\mu$  and by integrating by parts we have

$$(4.10) \quad \frac{\tilde{\mu}}{K} \int_{\Omega_\tau} |\mathbf{v}_\mu|^2 dx + \mu \int_{\Omega_\tau} |\nabla_x \mathbf{v}_\mu|^2 dx \leq c.$$

We remark that the soleindal condition (1.12) on  $\mathbf{v}$  was essential in order to get the estimates (4.4), (4.5), (4.10).

## 5. Vanishing viscosity limit $\mu \rightarrow 0$

In this section we perform the limit  $\mu \rightarrow 0$  in order to recover the system (S). Since our limiting process takes place in a moving domain  $\Omega_\tau$  it is more convenient to extend  $\mathbf{v}_\mu$ ,  $C_\mu$  and  $W_\mu$ ,  $P_\mu$ ,  $Q_\mu$ ,  $D_\mu$  on the whole domain  $\mathbb{R}^3$  by setting them equal to zero outside the tumor domain. In fact in this way one performs the limit in a “time independent domain”. Then, since the domain  $\Omega_\tau$  is regular at each time we use the standard extension operator for Sobolev spaces,  $E : W^{1,2}(\Omega_\tau) \rightarrow W^{1,2}(\mathbb{R}^3)$ , uniformly bounded with respect to  $t \in [0, T]$ , (for details on the operator E see [1]).

From the uniform bounds (4.6), (4.10) we get

$$(5.1) \quad EC_\mu \rightarrow C \quad \text{weakly in } L^2(0, T; W^{1,2}(\mathbb{R}^3)),$$

$$(5.2) \quad EW_\mu \rightarrow W \quad \text{weakly in } L^2(0, T; W^{1,2}(\mathbb{R}^3)),$$

$$(5.3) \quad E\mathbf{v}_\mu \rightarrow \mathbf{v} \quad \text{weakly in } W^{1,2}(\mathbb{R}^3).$$

By taking into account (4.2) and (4.10) we have we get

$$(5.4) \quad \left. \begin{aligned} P_\mu \mathbf{v}_\mu &\rightarrow P\mathbf{v} \\ Q_\mu \mathbf{v}_\mu &\rightarrow Q\mathbf{v} \\ D_\mu \mathbf{v}_\mu &\rightarrow D\mathbf{v} \end{aligned} \right\} \text{ weakly-}(\ast) \text{ in } L^\infty(T_1, T_2; L^{2q/q+2}(K)), \quad 2 \leq q < 6, .$$

where  $K \subset \Omega_\tau$  is a compact subset. Moreover, from the equations  $(\mathbf{S}_\mu)_2 - (\mathbf{S}_\mu)_4$  it follows that

$$(5.5) \quad \left. \begin{aligned} P_\mu \mathbf{v}_\mu &\rightarrow P\mathbf{v} \\ Q_\mu \mathbf{v}_\mu &\rightarrow Q\mathbf{v} \\ D_\mu \mathbf{v}_\mu &\rightarrow D\mathbf{v} \end{aligned} \right\} \text{ in } C_{\text{weak}}([T_1, T_2]; L^{2q/q+2}(K)), \quad 2 \leq q < 6.$$

Now, by using (4.2), (4.6), as before we get also

$$(5.6) \quad \left. \begin{aligned} P_\mu C_\mu &\rightarrow PC \\ Q_\mu C_\mu &\rightarrow QC \\ D_\mu C_\mu &\rightarrow DC \\ P_\mu W_\mu &\rightarrow PW \\ Q_\mu W_\mu &\rightarrow QW \end{aligned} \right\} \text{ weakly-}(\ast) \text{ in } L^\infty(0, T; L^{2q/q+2}(K)), \quad 2 \leq q < 6.$$

REMARK 5.1. Since the compact set  $K$  can be chosen arbitrarily close to the the boundary of  $Q_T$ , the above convergences (5.4), (5.5), (5.6) take place in the whole cylinder  $Q_T$ .

Now, by standard computations, and by taking into account (4.10) we have

$$\sqrt{\mu} \int_{\Omega_\tau} \sqrt{\mu} \nabla_x \mathbf{v}_\omega : \nabla_x \varphi dx \longrightarrow 0 \quad \text{as } \mu \rightarrow 0.$$

At this point it is straightforward to pass into the limit in the weak formulations of the system  $(\mathbf{S}_\mu)$  and to conclude the proof of the Theorem 2.2.

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