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► **To cite this version:**

Thierry Colin, Thomas Michel, Clair Poignard. Mathematical study and asymptotic analysis of a model for tumor drug resistance. [Research Report] RR-8784, Inria Bordeaux Sud-Ouest. 2015, 32 p. hal-01211770v2

HAL Id: hal-01211770

<https://inria.hal.science/hal-01211770v2>

Submitted on 1 Jul 2016

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**RESEARCH
REPORT**

N° 8784

October 2015

Project-Team MONC



Mathematical study and asymptotic analysis of a model for tumor drug resistance

Thierry Colin^{*†}, Thomas Michel^{‡†}, Clair Pognard^{§†}

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Research Report n° 8784 — October 2015 — 32 pages

Abstract: In this paper we study a partial differential equations model for tumor drug resistance. The aim is to take two different treatments into account: a specific tyrosine kinase inhibitor (TKI) targeted therapy, with a cytotoxic effect, that induces direct cell death, and a multi-targeted TKI, with both cytotoxic and anti-angiogenic effect, which prevents the creation of new blood vessels. The model is based on mass balance equations on cell densities coupled with a diffusion equation for the nutrients and oxygen concentration. We also consider a necrotic phase composed of dead cells, which are eliminated at a rate $1/\tau$. We first prove that, for any non-negative τ , the model is well-posed and in a second part we study the asymptotic behavior for small τ . Such a result is of great interest for the modeling, since it provides a family of τ -dependent models which is continuous with respect to τ .

Key-words: Tumor growth modeling; partial differential equations; asymptotic analysis.

* Bordeaux INP, IMB, UMR 5251, F-33400, Talence, France

† INRIA Bordeaux-Sud-Ouest, Team MONC, F-33400, Talence, France

‡ Université de Bordeaux, IMB, UMR 5251, F-33400, Talence, France

§ INRIA Bordeaux-Sud-Ouest, IMB, UMR 5251, F-33400, Talence, France

**RESEARCH CENTRE
BORDEAUX – SUD-OUEST**

200 avenue de la Vieille Tour
33405 Talence Cedex

Etude mathématique et analyse asymptotique d'un modèle de croissance tumorale avec résistance au traitement

Résumé : Dans cet article, nous étudions un modèle d'équations aux dérivées partielles pour la résistance de tumeurs aux traitements. L'objectif de ce modèle est de prendre en compte deux traitements différents. Le premier traitement est une thérapie ciblée inhibitrice de tyrosine kinase (TKI) qui présente un effet cytotoxique, induisant la mort cellulaire. Le second traitement est une thérapie ciblée TKI qui présente à la fois un effet cytotoxique et un effet anti-angiogénique, limitant la création de nouveaux vaisseaux sanguins. Le modèle est basé sur des équations de conservation de la masse pour les densités de cellules, couplées à une équation de diffusion pour la concentration en oxygène et en nutriments. Dans ce modèle, nous considérons également la présence d'une phase de nécrose, composée des cellules mortes et nous supposons que cette nécrose est évacuée à un taux $1/\tau$. Dans un premier temps, nous prouvons que pour tout τ strictement positif, le modèle est bien posé. Puis, dans un second temps, nous étudions le comportement asymptotique du modèle quand τ tend vers 0. Le résultat obtenu est intéressant du point de vue de la modélisation, puisqu'il assure l'existence d'une famille de modèles qui est continue par rapport au paramètre τ .

Mots-clés : Modélisation de la croissance tumorale, équations aux dérivées partielles, analyse asymptotique.

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1 Introduction

The impact of mathematical modeling in biology has increased dramatically during the last two decades. Particularly in oncology, the increase of biological knowledge combined with the data obtained by invasive and non invasive techniques makes it possible to elaborate more and more accurate models of tumor growth and to study the impact of treatments.

Several kinds of mathematical models for solid tumor growth have been developed over the last few decades. Among them, we can find discrete models or model based on ordinary differential equations (ODE models) or partial differential equations (PDE models). ODE models describe the time evolution of areas or masses of tumors but they account neither for the spatial behavior of the tumor nor for the spatial heterogeneity. Discrete models like cellular automata and agent-based models [10] make it possible to reproduce the growth at the cell-scale but cannot describe the cancer evolution at the organ level. Even though global PDE models at the organ level do not describe the cancer process at the cell scale, they seem adequate for accounting for both time and spatial behavior of the tumor at the macro scale. In this work, we attend to study clinical cases through medical imaging. There is a huge literature concerning the modeling of solid tumor growth with or without treatments and it is impossible to give an extensive list here. However, the reader can refer to [8, 12, 14, 19, 22] for PDE-type models and their mathematical analysis. Models based on reaction-diffusion equations are used to describe the active motion of tumor cells in the case of invasive tumors (see [13] or [20]). Models based on mass balance equations on cell densities are used when the growth is only a consequence of cell proliferation. Roughly speaking, on one hand, primary tumors are composed of degenerate cells of the host organ. These cells are in their original environment and it is hard to determine precisely the boundary of the tumor. On the other hand, metastases are composed of cells that come from a different tissue than the host organ. They are more regular, with sharp interfaces. These interfaces can be described using free boundary methods [17] or multiphase mixtures [7], which consider both cell densities and extracellular matrix [18, 21]. The model we study comes from [4] and is based on mass balance equations. It describes the spatial heterogeneity as a mixture of several cell populations. For

the closure of the model, we assume that the tumor behaves like a fluid in a porous media and we assume Darcy's law for the velocity field [2]. Other models like visco-elastic laws were also studied in [5]. These models may account for more complex phenomena, but their complexity is too high for clinical applications while Darcy's law is sufficient as a first approximation to address some clinical cases [9].

In [15], a model for GIST liver metastases has been studied numerically. This model, based on mass balance equations, enables to explain the tumor evolution observed on clinical images of metastases treated with two targeted therapies. It is well known that mutations will lead to the creation of tumor cells which are resistant to cytotoxic drugs. At the time being, it is not possible to know when such mutations may appear since this may depend on several parameters (such as treatment time, patient variability, external conditions). Therefore, it has been assumed in [15] that different populations of cells co-exist at the initial time of the model. We emphasize that this assumption is meaningful for clinical application since when the tumor is detected, it is very probable that mutations have already occurred. Other models for drug resistance can be studied, by considering that the transition from sensitive to resistant to a treatment is continuous [16]. One of the features of the model of [15] is that it describes the necrosis. Such a necrosis is composed of cells that die because of drugs or hypoxia (the lack of oxygen/nutrients). This necrosis is evacuated at a given rate $1/\tau$. Such a necrotic compartment is also important for other kinds of tumors. For example, thyroid metastases to the lung (Figure 1.a) or meningioma (Figure 1.b), in which few necrotic tissue is visible, and glioblastoma (Figure 1.d), a kind of tumor much more aggressive, the parts of which may contain only necrotic tissues. In contrast, compared to these tumors, the necrotic cells of GIST metastases to the liver (Figure 1.c) are more diffuse inside the tumor.

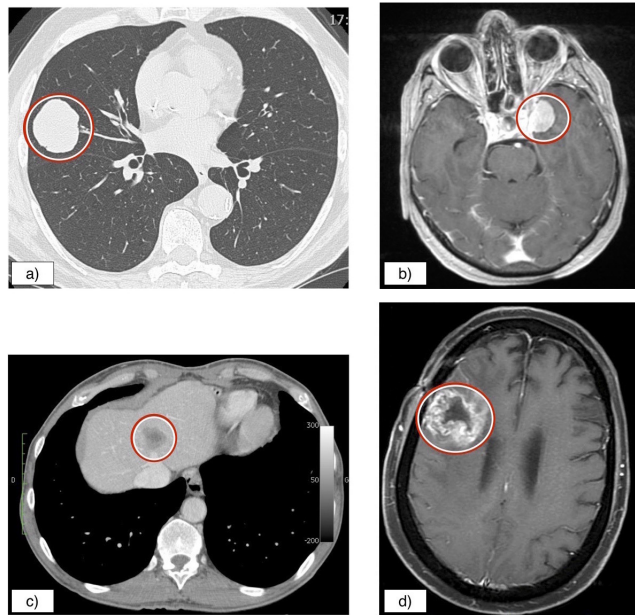


Figure 1: a) metastasis to the lung¹, b) brain meningioma², c) GIST metastasis to the liver¹, d) brain glioma³.

Once the model has been mathematically written, the main objective of this paper is to study

the well-posedness of the model [15] and to study its asymptotic behavior for small τ .

The outline of the paper is the following one. In Section 2 we briefly present the model. The model will be considered in a bounded domain in the case of dimension 2 or 3 in space. Then we present the model without necrosis which will be proved to be the limit model when the necrosis is immediately evacuated. In Section 3 we state the main results. Section 4 is devoted to preliminary results required for Sections 5 and 6. These results use classical estimates for hyperbolic, elliptic and parabolic equations. In Section 5, we prove the well-posedness of the model. The proof is based on a fixed-point method. Finally we perform the asymptotic analysis $\tau \rightarrow 0$ in Section 6. As it will be shown here after, it is a singular perturbation problem. The interesting fact is that, thanks to our analysis, we can describe the tumor growth evolution under treatment continuously with respect to τ .

2 The model

In this section we present the model of Lefebvre *et al.* provided in [15]. This model describes the evolution of three cancer cell's populations subjected to two different treatments. The first treatment \mathcal{T}_1 is a specific tyrosine kinase inhibitor (TKI), which has a cytotoxic effect in clinic. The second treatment \mathcal{T}_2 is a multi-targeted TKI, with both cytotoxic and anti-angiogenic effect. P_1 stands for the density of the proliferative cells which are assumed to be sensitive to both treatments \mathcal{T}_1 and \mathcal{T}_2 , while P_2 denotes the density of proliferative cells which are assumed to be resistant to \mathcal{T}_1 and sensitive to \mathcal{T}_2 . The density of cells that are affected neither by \mathcal{T}_1 nor \mathcal{T}_2 are denoted by P_3 . The nutrient (and oxygen) supply, coming from the healthy tissue, denoted by M , drives the proliferative rate $\gamma_1(M) - \gamma_2(M)$ of the three cancer cell species, where γ_1 and γ_2 are positive functions, standing respectively for the proliferative rate and the death rate due to hypoxia. In [15], they set

$$\gamma_1(M) = \frac{1 + \tanh(R_1(M - M_{hyp}))}{2}, \quad \gamma_2(M) = \frac{1 - \tanh(R_2(M - M_{hyp}))}{2}, \quad (1)$$

where R_1, R_2 are coefficients and M_{hyp} is the hypoxia threshold.

The treatments efficiency is described thanks to the smooth functions of time μ_1 and μ_2 , which stand for the cytotoxic effect of treatments \mathcal{T}_1 and \mathcal{T}_2 respectively. We assume that the absorption is proportional to the rate of nutrient/oxygen.

When the cells die because of the treatment or hypoxia, they enter to a necrotic phase, whose density is denoted by N . The necrotic compartment is assumed to be evacuated at the rate $1/\tau$ where τ is the characteristic evacuation time.

S is the density of the healthy cells, which do not divide, since their metabolism is slow compared to the metabolism of proliferative cells.

The tumor grows at a speed \mathbf{v} whose divergence is obtained thanks to the saturation assumption:

$$P_1 + P_2 + P_3 + N + S = 1. \quad (2)$$

The factor ξ is introduced in order to account for the VEGF signal produced by the tumor cells to involve angiogenesis (see [11]). It is assumed to be global at any time and proportional to the number of cells dying by hypoxia, which are the fraction $\frac{\gamma_2(M)}{\max \gamma_2}$. There exist more complex

¹Courtesy of J. Palussière, MD at Institut Bergonié, 33000 Bordeaux, France.

²Courtesy of H. Loiseau, MD at Hôpital Pellegrin, CHU Bordeaux, 33000 Bordeaux, France.

³Courtesy of H. M. Fathallah-Shaykh, MD at University of Alabama at Birmingham, Birmingham, AL 35294, USA.

models of tumor-induced angiogenesis [3]. The smooth function of time ν_2 stands for the anti-angiogenic effect of treatment \mathcal{T}_2 and can be for example regularization of the time-characteristic function of treatment \mathcal{T}_2 . The parameter λ is the coefficient of absorption of this signal by the organism.

For further explanations on the model, see [4, 15].

For the sake of clarity, we introduce the following notations, which make it possible to write the problem in a factorized way.

Notation 2.1. For any $\alpha \in \mathbb{R}^n, \beta \in \mathbb{R}^d$ we denote by

$$\begin{aligned} (\alpha \otimes \beta)_{i,j} &= \alpha_i \beta_j, & \text{for } i = 1, \dots, n, j = 1, \dots, d, \\ \nabla \cdot (\alpha \otimes \beta) &= (\nabla \cdot \beta) \alpha + (\beta \cdot \nabla) \alpha. \end{aligned}$$

The vector \mathbf{u} stands for $(P_1, P_2, P_3, S)^t$ and we denote by $\gamma(M) := \gamma_1(M) - \gamma_2(M)$. Now we define

$$\begin{aligned} A(M) &:= \begin{pmatrix} \gamma(M) - (\mu_1 + \mu_2)M & 0 & 0 & 0 \\ 0 & \gamma(M) - \mu_2 M & 0 & 0 \\ 0 & 0 & \gamma(M) & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \\ \mathbf{b}(M) &:= (\gamma_1(M), \gamma_1(M), \gamma_1(M), 0)^t, \\ \mathbf{d}(M) &:= (\gamma_2(M) + (\mu_1 + \mu_2)M, \gamma_2(M) + \mu_2 M, \gamma_2(M), 0)^t, \\ \mathbf{p} &:= (1, 1, 1, 0)^t, \\ \mathbf{p}_{1,2} &:= (1, 1, 0, 0)^t, \\ \mathbf{s} &:= (0, 0, 0, 1)^t, \end{aligned}$$

and we denote by \mathbf{n} the outward normal to Ω , where Ω is a bounded domain in \mathbb{R}^2 or \mathbb{R}^3 .

The model of Lefebvre *et al.* can be written as

$$\partial_t \mathbf{u} + \nabla \cdot (\mathbf{u} \otimes \mathbf{v}) = A(M) \mathbf{u}, \quad (3a)$$

$$\mathbf{u} = \mathbf{s}, \quad \text{if } \mathbf{v} \cdot \mathbf{n} < 0 \text{ on } \partial\Omega, \quad (3b)$$

$$\partial_t N + \nabla \cdot (\mathbf{v} N) = \mathbf{d}(M) \cdot \mathbf{u} - (1/\tau)N, \quad (3c)$$

$$N = 0, \quad \text{if } \mathbf{v} \cdot \mathbf{n} < 0 \text{ on } \partial\Omega, \quad (3d)$$

$$\nabla \cdot \mathbf{v} = \mathbf{b}(M) \cdot \mathbf{u} - (1/\tau)N, \quad (3e)$$

$$\mathbf{v} = -k \nabla \Pi, \quad (3f)$$

$$\Pi|_{\partial\Omega} = 0, \quad (3g)$$

$$\partial_t M - \Delta M + \nabla \cdot (M \xi \nabla (\mathbf{p} \cdot \mathbf{u})) = -\eta M \mathbf{p} \cdot \mathbf{u} + C_0 \mathbf{s} \cdot \mathbf{u} (1 - M), \quad (3h)$$

$$M|_{\partial\Omega} = 1, \quad (3i)$$

$$\partial_t \xi = \alpha \int_{\Omega} \frac{\gamma_2(M)}{\max \gamma_2} (\mathbf{p} - \nu_2 \mathbf{p}_{1,2}) \cdot \mathbf{u} dx - \lambda \xi, \quad (3j)$$

with initial conditions for \mathbf{u}, N, M and ξ .

For tumors without necrosis, similar considerations lead to the following model:

$$\partial_t \mathbf{u} + \nabla \cdot (\mathbf{u} \otimes \mathbf{v}) = A(M) \mathbf{u}, \quad (4a)$$

$$\mathbf{u} = \mathbf{s}, \quad \text{if } \mathbf{v} \cdot \mathbf{n} < 0 \text{ on } \partial\Omega, \quad (4b)$$

$$\nabla \cdot \mathbf{v} = (\mathbf{b}(M) - \mathbf{d}(M)) \cdot \mathbf{u}, \quad (4c)$$

$$\mathbf{v} = -k \nabla \Pi, \quad (4d)$$

$$\Pi|_{\partial\Omega} = 0, \quad (4e)$$

$$\partial_t M - \Delta M + \nabla \cdot (M \xi \nabla (\mathbf{p} \cdot \mathbf{u})) = -\eta M \mathbf{p} \cdot \mathbf{u} + C_0 \mathbf{s} \cdot \mathbf{u} (1 - M), \quad (4f)$$

$$M|_{\partial\Omega} = 1, \quad (4g)$$

$$\partial_t \xi = \alpha \int_{\Omega} \frac{\gamma_2(M)}{\max \gamma_2} (\mathbf{p} - \nu_2 \mathbf{p}_{1,2}) \cdot \mathbf{u} dx - \lambda \xi. \quad (4h)$$

Note that we impose homogeneous Dirichlet condition on the pressure Π , which implicitly states that the tumor growth has no influence on the tissue far from the tumor location.

3 Main results and interpretation

In this paper we prove the local existence and uniqueness of the solution to the problems (3) and (4), under appropriate assumptions on the initial data and the boundary, as well as the asymptotic behavior of the solution to (3) when $\tau \rightarrow 0$.

In our study, we work in a $d = 2$ or 3 dimensional domain denoted by Ω . For the spatial regularity, we use the algebra structure of Sobolev space $H^s(\Omega)$ for s large enough.

Hypothesis 3.1. *Throughout the paper, the following hypothesis hold:*

- the domain Ω is a bounded domain in \mathbb{R}^2 or \mathbb{R}^3 with C^∞ boundary,
- the rates $\gamma_1(M)$ and $\gamma_2(M)$ are non-negative and smooth functions (this is the case for the examples given by (1)),
- the parameters μ_1 , μ_2 and ν_2 are smooth non-negative functions of time, such as regularization of the time-characteristic functions of treatment $\mathcal{T}_1, \mathcal{T}_2$,
- the parameters k , η , C_0 , α and λ are non-negative.

Before stating the Theorems, we introduce the following notations:

Notation 3.1. *The solution of each equation belongs to specific space:*

- for any $T > 0$, $p \in [1, +\infty]$ and $s \geq 0$, we denote by $L_T^p; H^s$ the space $L^p(0, T; H^s(\Omega))$ endowed with the norm

$$\|\varphi\|_{L_T^p; H^s} := \|\varphi\|_{L^p(0, T; H^s(\Omega))}, \quad \forall \varphi \in L_T^p; H^s,$$

for the sake of clarity, for $\mathbf{u} \in L^p(0, T; H^s(\Omega))^n$ we denote by $\|\mathbf{u}\|_{L_T^p; H^s}$ the norm of \mathbf{u} components by components,

- for any $T > 0$, $p_1, p_2 \in [1, +\infty]$ and $s_1, s_2 \geq 0$, we denote by $L_T^{p_1}; H^{s_1} \cap L_T^{p_2}; H^{s_2}$ the space $L^{p_1}(0, T; H^{s_1}(\Omega)) \cap L^{p_2}(0, T; H^{s_2}(\Omega))$ endowed with the norm

$$\|\varphi\|_{L_T^{p_1}; H^{s_1} \cap L_T^{p_2}; H^{s_2}} := \|\varphi\|_{L_T^{p_1}; H^{s_1}} + \|\varphi\|_{L_T^{p_2}; H^{s_2}}, \quad \forall \varphi \in L_T^{p_1}; H^{s_1} \cap L_T^{p_2}; H^{s_2},$$

- for any $s \geq 1$, we denote by \mathcal{E}_0^s the space $H^s(\Omega)^4 \times H^{s-1}(\Omega) \times \mathbb{R}$ endowed with the norm:

$$\|(\mathbf{u}_0, M_0, \xi_0)\|_{\mathcal{E}_0^s} := \|\mathbf{u}_0\|_{H^s} + \|M_0\|_{H^{s-1}} + |\xi_0|, \quad \forall (\mathbf{u}_0, M_0, \xi_0) \in \mathcal{E}_0^s,$$

- for any $T > 0$ and $s \geq 1$, we denote by \mathcal{E}_T^s the space $(L_T^\infty; H^s)^4 \times L_T^2; H^s \cap L_T^\infty; H^{s-1} \times \mathcal{C}^0([0, T])$ endowed with the norm:

$$\|(\mathbf{u}, M, \xi)\|_{\mathcal{E}_T^s} := \|\mathbf{u}\|_{L_T^\infty; H^s} + \|M\|_{L_T^2; H^s \cap L_T^\infty; H^{s-1}} + \|\xi\|_\infty, \quad \forall (\mathbf{u}, M, \xi) \in \mathcal{E}_T^s,$$

- for any $T > 0$ and $s \geq 0$, we denote by $\mathcal{E}_T^{2,s}$ the space $(L_T^2; H^s)^4 \times L_T^2; H^s \times L^2(0, T)$ endowed with the norm:

$$\|(\mathbf{u}, M, \xi)\|_{\mathcal{E}_T^{2,s}} := \|\mathbf{u}\|_{L_T^2; H^s} + \|M\|_{L_T^2; H^s} + \|\xi\|_{L^2(0, T)}, \quad \forall (\mathbf{u}, M, \xi) \in \mathcal{E}_T^{2,s}.$$

Then the local existence and uniqueness result is the following:

Theorem 3.2 (Well-posedness of problems (3) and (4)). *Assume the hypotheses 3.1 hold. Let $s \geq 3$.*

- (i) Let $\tau > 0$, $(\mathbf{u}_0, M_0, \xi_0) \in \mathcal{E}_0^s$ and $N_0 \in H^s(\Omega)$ satisfying the boundary conditions. Let us assume that the cells densities $\mathbf{u}_0 = (P_{1,0}, P_{2,0}, P_{3,0}, S_0)^t$ and N_0 satisfy

- $P_{1,0}, P_{2,0}, P_{3,0}$, and N_0 are compactly supported in Ω ,
- $P_{1,0}, P_{2,0}, P_{3,0}, S_0, N_0 \geq 0$,
- $P_{1,0} + P_{2,0} + P_{3,0} + N_0 + S_0 = 1$.

There exist $R \geq \|(\mathbf{u}_0, M_0, \xi_0)\|_{\mathcal{E}_0^s} + \|N_0\|_{H^s}$ and a maximal time of existence $T^\tau > 0$ such that the problem (3) has a unique solution $((\mathbf{u}, M, \xi), \mathbf{v}, N)$ in $\mathcal{E}_{T^\tau}^s \times L_{T^\tau}^2; H^{s+1} \cap L_{T^\tau}^\infty; H^s \times L_{T^\tau}^\infty; H^s$. This solution satisfies

- (a) $\|(\mathbf{u}, M, \xi)\|_{\mathcal{E}_{T^\tau}^s} + \|N\|_{L_{T^\tau}^\infty; H^s} \leq R$,
- (b) $\mathbf{u}, N, \mathbf{v} \in \mathcal{C}^0([0, T^\tau]; H^{s-1}(\Omega))$, $M \in \mathcal{C}^0([0, T^\tau]; H^{s-2}(\Omega))$, $\xi \in \mathcal{C}^1([0, T^\tau])$,
- (c) the cell densities $\mathbf{u} = (P_1, P_2, P_3, S)^t$ and N satisfy
- for all $t < T^\tau$, $P_1(t, \cdot), P_2(t, \cdot), P_3(t, \cdot), N(t, \cdot)$ are compactly supported in Ω (i.e. the tumor does not hit the boundary),
 - $P_1, P_2, P_3, S, N \geq 0$,
 - $P_1 + P_2 + P_3 + N + S = 1$.

- (ii) Let $(\mathbf{u}_0, M_0, \xi_0) \in \mathcal{E}_0^s$ satisfying the boundary conditions. Let us assume that the cells densities $\mathbf{u}_0 = (P_{1,0}, P_{2,0}, P_{3,0}, S_0)^t$ satisfy

- $P_{1,0}, P_{2,0}, P_{3,0}$ are compactly supported in Ω ,
- $P_{1,0}, P_{2,0}, P_{3,0}, S_0 \geq 0$,
- $P_{1,0} + P_{2,0} + P_{3,0} + S_0 = 1$.

There exist $R \geq \|(\mathbf{u}_0, M_0, \xi_0)\|_{\mathcal{E}_0^s}$ and a maximal time of existence $T > 0$ such that the problem (4) has a unique solution $((\mathbf{u}, M, \xi), \mathbf{v})$ in $\mathcal{E}_T^s \times L_T^2; H^{s+1} \cap L_T^\infty; H^s$. This solution satisfies

- (a) $\|(\mathbf{u}, M, \xi)\|_{\mathcal{E}_T^s} \leq R$,

(b) $\mathbf{u}, \mathbf{v} \in \mathcal{C}^0([0, T]; H^{s-1}(\Omega))$, $M \in \mathcal{C}^0([0, T]; H^{s-2}(\Omega))$, $\xi \in \mathcal{C}^1([0, T])$,

(c) the cell densities $\mathbf{u} = (P_1, P_2, P_3, S)^t$ satisfy

- for all $t < T$, $P_1(t, \cdot), P_2(t, \cdot), P_3(t, \cdot)$ are compactly supported in Ω (i.e the tumor does not hit the boundary),
- $P_1, P_2, P_3, S \geq 0$,
- $P_1 + P_2 + P_3 + S = 1$.

Remark 3.1. For the sake of simplicity, we prove the theorem for s integer such that $s \geq 3$, then interpolation give the result for any real $s \geq 3$. The only hypothesis needed is that $s > d/2 + 1$ (which implies that the embedding $H^{s-1}(\Omega) \hookrightarrow L^\infty(\Omega)$ is continuous).

Remark 3.2 (Continuity with respect to initial conditions). Under the assumptions of Theorem 3.2 we have

(i) Let $\tau > 0$. For $i = 1, 2$, let $X_{0,i} := (\mathbf{u}_{0,i}, M_{0,i}, \xi_{0,i}) \in \mathcal{E}_0^s$ and $N_{0,i} \in H^s(\Omega)$ as in Theorem 3.2 (i) and assume that these initial conditions $X_{0,i}, N_{0,i}$ are bounded by $R > 0$. Let $((\mathbf{u}_i, M_i, \xi_i), \mathbf{v}_i, N_i)$ be the solution to problem (3) with initial conditions $\mathbf{u}_{0,i}, M_{0,i}, \xi_{0,i}$ and $N_{0,i}$. Denote by X_i the vector $(\mathbf{u}_i, M_i, \xi_i)$. Then there exists $C_R > 0$ such that

$$\|(X_1, \mathbf{v}_1, N_1) - (X_2, \mathbf{v}_2, N_2)\|_{\mathcal{E}_T^{2,s-1} \times L_T^{2\tau}; H^s \times L_T^{2\tau}; H^{s-1}}^2 \leq C_R \|(X_{0,1}, N_{0,1}) - (X_{0,2}, N_{0,2})\|_{\mathcal{E}_0^{s-1} \times H^{s-1}}^2.$$

(ii) For $i = 1, 2$, let $X_{0,i} := (\mathbf{u}_{0,i}, M_{0,i}, \xi_{0,i}) \in \mathcal{E}_0^s$ as in Theorem 3.2 (ii) and assume that these initial conditions $X_{0,i}$ are bounded by $R > 0$. Let $((\mathbf{u}_i, M_i, \xi_i), \mathbf{v}_i)$ be the solution to problem (4) with initial conditions $\mathbf{u}_{0,i}, M_{0,i}, \xi_{0,i}$. Denote by X_i the vector $(\mathbf{u}_i, M_i, \xi_i)$. Then there exists $C_R > 0$ such that

$$\|(X_1, \mathbf{v}_1) - (X_2, \mathbf{v}_2)\|_{\mathcal{E}_T^{2,s-1} \times L_T^{2\tau}; H^s}^2 \leq C_R \|X_{0,1} - X_{0,2}\|_{\mathcal{E}_0^{s-1}}^2.$$

The second result states that, if the initial data are well-prepared, the solution to problem (3) converges to the solution to problem (4) when $\tau \rightarrow 0$:

Theorem 3.3 (Asymptotic behavior). For any $\tau > 0$, let $\mathbf{u}_0^\tau, N_0^\tau, M_0^\tau$ and ξ_0^τ be as in Theorem 3.2 (i). Let \mathbf{u}_0, M_0 and ξ_0 be as in Theorem 3.2 (ii). Assume that

- $\lim_{\tau \rightarrow 0^+} \frac{1}{\sqrt{\tau}} \|N_0^\tau\|_{H^s} = 0$,
- $\lim_{\tau \rightarrow 0^+} (\mathbf{u}_0^\tau, M_0^\tau, \xi_0^\tau) = (\mathbf{u}_0, M_0, \xi_0)$ in \mathcal{E}_0^{s-1} .

Then there exists $T > 0$ (independent of τ) such that

- for any $\tau > 0$, the problem (3) has a unique solution on $[0, T]$ denoted by $((\mathbf{u}^\tau, M^\tau, \xi^\tau), \mathbf{v}^\tau, N^\tau)$ and the problem (4) has a unique solution on $[0, T]$ denoted by $((\mathbf{u}, M, \xi), \mathbf{v})$,
- there exists $C > 0$ such that for any $\tau > 0$ small enough

$$\frac{1}{\sqrt{\tau}} \|N^\tau\|_{L_T^\infty; H^s} + \frac{1}{\tau} \|N^\tau\|_{L_T^2; H^s} \leq C,$$

- $\lim_{\tau \rightarrow 0^+} ((\mathbf{u}^\tau, M^\tau, \xi^\tau), \mathbf{v}^\tau) = (\mathbf{u}, M, \xi, \mathbf{v})$ in $\mathcal{E}_T^{2,s-1} \times L_T^2; H^s$.

4 Preliminary results

Throughout the paper, we consider $d = 2, 3$ and $s \geq 3$. In this section, we prove estimates for the two models we study. The key argument to obtain these estimates is that if the initial data for P_1, P_2, P_3, N have compact support in Ω , then any solution to (3) or (4) is compactly supported. One can obtain *a priori* estimates on the system using non linear estimates in high order Sobolev spaces (similarly to non linear hyperbolic systems, see [1]) and usual parabolic estimates for M . The strategy is therefore to construct a suitable mapping such that this property remains true. In a first step, we start to define the operators which give the solution of each equation and we construct the mappings on which we apply the fixed-point strategy.

Definition 4.1. *We consider the following operators*

- $\mathcal{V} : f \mapsto \mathbf{v}$, where \mathbf{v} is the solution to

$$\begin{cases} \nabla \cdot \mathbf{v} = f, & (\text{in } \Omega) \\ \mathbf{v} = -k\nabla\Pi, & (\text{in } \Omega) \\ \Pi = 0, & (\text{on } \partial\Omega) \end{cases} \quad (5)$$

- $\mathcal{U} : (\mathbf{u}_0, \mathbf{v}, M) \mapsto \mathbf{u}$, where \mathbf{u} is the solution to

$$\begin{cases} \partial_t \mathbf{u} + \nabla \cdot (\mathbf{u} \otimes \mathbf{v}) = A(M)\mathbf{u}, & (\text{in } \Omega) \\ \mathbf{u} = \mathbf{s}, & (\text{if } \mathbf{v} \cdot \mathbf{n} < 0 \text{ on } \partial\Omega) \\ \mathbf{u}|_{t=0} = \mathbf{u}_0, & (\text{in } \Omega) \end{cases} \quad (6)$$

- $\mathcal{N} : (N_0, \mathbf{u}_0, \mathbf{v}, M, \tau) \mapsto N$, where N is the solution to

$$\begin{cases} \partial_t N + \nabla \cdot (\mathbf{v}N) = \mathbf{d}(M) \cdot \mathbf{u} - (1/\tau)N, & (\text{in } \Omega) \\ N = 0, & (\text{if } \mathbf{v} \cdot \mathbf{n} < 0 \text{ on } \partial\Omega) \\ N|_{t=0} = N_0, & (\text{in } \Omega) \end{cases} \quad (7)$$

with $\mathbf{u} := \mathcal{U}(\mathbf{u}_0, \mathbf{v}, M)$.

- $\mathcal{M} : (M_0, \mathbf{u}, \xi) \mapsto M$, where M is the solution to

$$\begin{cases} \partial_t M - \Delta M + \nabla \cdot (M\xi\nabla(\mathbf{p} \cdot \mathbf{u})) = -\eta M \mathbf{p} \cdot \mathbf{u} + C_0 \mathbf{s} \cdot \mathbf{u}(1 - M), & (\text{on } \Omega) \\ M|_{\partial\Omega} = 1, \\ M|_{t=0} = M_0, \end{cases} \quad (8)$$

- $\Xi : (\xi_0, \mathbf{u}, M) \mapsto \xi$, where ξ is the solution to

$$\begin{cases} \partial_t \xi = \alpha \int_{\Omega} \frac{\gamma_2(M)}{\max \gamma_2} (\mathbf{p} - \nu_2 \mathbf{p}_{1,2}) \cdot \mathbf{u} dx - \lambda \xi, \\ \xi|_{t=0} = \xi_0. \end{cases} \quad (9)$$

To apply the fixed-point strategy for problem (3), we define the operator Φ as follows: for any $X_0 := (\mathbf{u}_0, M_0, \xi_0), N_0$ and $X := (\mathbf{u}, M, \xi), N$, we define

$$(\tilde{X}, \tilde{N}) := \Phi((X, N), (X_0, N_0), \tau),$$

where $\tilde{X} := (\tilde{\mathbf{u}}, \tilde{M}, \tilde{\xi})$ with

$$\begin{aligned}\tilde{\mathbf{u}} &:= \mathcal{U}(\mathbf{u}_0, \mathcal{V}(\mathbf{b}(M) \cdot \mathbf{u} - (1/\tau)N), M), \\ \tilde{N} &:= \mathcal{N}(N_0, \mathbf{u}_0, \mathcal{V}(\mathbf{b}(M) \cdot \mathbf{u} - (1/\tau)N), M), \\ \tilde{M} &:= \mathcal{M}(M_0, \mathbf{u}, \xi), \\ \tilde{\xi} &:= \Xi(\xi_0, \mathbf{u}, M),\end{aligned}$$

To apply the fixed-point strategy for problem (4), we define the operator Ψ as follows: for any $X_0 := (\mathbf{u}_0, M_0, \xi_0)$ and $X := (\mathbf{u}, M, \xi)$, we define

$$\tilde{X} := \Psi(X, X_0),$$

where $\tilde{X} := (\tilde{\mathbf{u}}, \tilde{M}, \tilde{\xi})$ with

$$\begin{aligned}\tilde{\mathbf{u}} &:= \mathcal{U}(\mathbf{u}_0, \mathcal{V}((\mathbf{b}(M) - \mathbf{d}(M)) \cdot \mathbf{u}), M), \\ \tilde{M} &:= \mathcal{M}(M_0, \mathbf{u}, \xi), \\ \tilde{\xi} &:= \Xi(\xi_0, \mathbf{u}, M).\end{aligned}$$

In order to prove the well-posedness of problems (3) and (4), we use the facts that

- if it exists, the solution to (3) satisfies $(X^\tau, N^\tau) = \Phi((X^\tau, N^\tau), (X_0, N_0), \tau)$,
- if the solution to (4) exists, it satisfies $X = \Psi(X, X_0)$.

It is crucial to exhibit the stability and contraction properties of the operators Φ and Ψ . Such properties will be deduced after analysis of the operators $\mathcal{V}, \mathcal{U}, \mathcal{N}, \mathcal{M}$ and Ξ .

4.1 Estimates for operator \mathcal{V}

Since Ω is smooth, the following estimates on \mathcal{V} are consequences of classical results for linear elliptic equations that can be found in [6]. For the sake of conciseness, the proof of the following property is left to the reader.

Proposition 4.1 (Estimates for \mathcal{V}). *Let $s' \leq s$, $p \in [1, +\infty]$ and $f \in L_T^p; H^{s'}$ be given. Then the solution \mathbf{v} to (5) belongs to $L_T^p; H^{s'+1}$ and satisfies*

$$\|\mathbf{v}\|_{L_T^p; H^{s'+1}}^2 \leq C \|f\|_{L_T^p; H^{s'}}^2.$$

Moreover, if $f \in \mathcal{C}^0([0, T]; H^{s-2}(\Omega))$ then $\mathbf{v} \in \mathcal{C}^0([0, T]; H^{s-1}(\Omega))$.

4.2 Estimates for operators \mathcal{U}, \mathcal{N}

Let $\mathbf{u}_0 \in H^s(\Omega)^4$, $N_0 \in H^s(\Omega)$, $\mathbf{v} \in (L_T^2; H^{s+1})^d$ and $M \in L_T^2; H^s$ be given. We consider \mathbf{u} and N the solutions to (6) and (7). In order to derive explicit formulas for \mathbf{u} and N , we use the characteristic method. The difficulty lies in the fact that $\nabla \cdot \mathbf{v}$ is not necessarily non-negative and thus we must be able to move forward and backward along the characteristic curves. We use the assumption that $\mathbf{u}_0 - \mathbf{s}$ (where $\mathbf{s} = (0, 0, 0, 1)^t$) and N_0 are compactly supported in Ω and we choose T so that the tumor does not reach the boundary $\partial\Omega$. More precisely we introduce the following domains:

Definition 4.2. Let Ω_0 be an open set compactly embedded in Ω and assume that $\text{supp}(\mathbf{u}_0 - \mathbf{s}) \cup \text{supp}(N_0) \subset \Omega_0$. For $i = 1, 2, 3$, we define the open domain Ω_i (see Figure 2) by

$$\Omega_i := \left\{ x \in \Omega, d(x, \Omega_0) < \frac{i}{4} d(\partial\Omega, \Omega_0) \right\}, \quad \text{for } i = 1, 2, 3.$$

In order to prevent that characteristic curves go out of Ω we assume in the following that T is small enough such that

$$\sqrt{T} \|\mathbf{v}\|_{L_T^2; H^{s+1}} < \frac{1}{4} d(\partial\Omega, \Omega_0). \quad (10)$$

The upper bound (10) on T ensures that

- The characteristic curves are well-defined for any $t, t' \in [0, T]$ and $x \in \Omega_3$ by

$$\begin{cases} \partial_{t'} \tilde{x}(t', t, x) &= \mathbf{v}(t', \tilde{x}(t', t, x)), \\ \tilde{x}(t, t, x) &= x, \end{cases}$$

- For $i = 0, 1, 2$, the characteristic curves coming from Ω_i at $t = 0$ stay in Ω_{i+1} for any $t \leq T$. Indeed for any $t, t' \in [0, T]$ and $x \in \Omega_2$, we have

$$|\tilde{x}(t', t, x) - x| \leq \sqrt{|t - t'|} \|\mathbf{v}\|_{L_T^2; H^{s+1}} < \sqrt{\frac{|t - t'|}{T}} \frac{1}{4} d(\partial\Omega, \Omega_0).$$

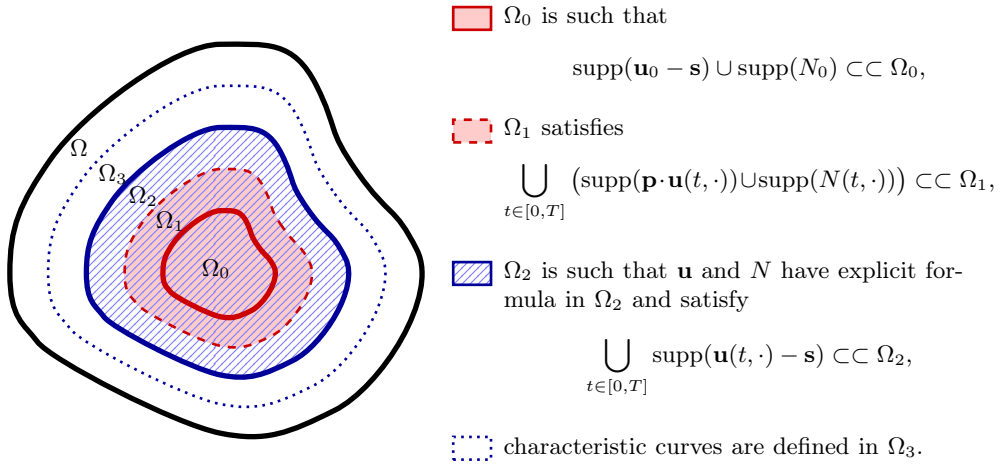


Figure 2: The domains defined for the characteristic method

Thanks to the change of coordinates along the characteristic curves, we can come back from Ω_3 to Ω_2 and obtain the following explicit formulas for the solutions to (6) and (7) in Ω_2 :

$\forall(t, x) \in [0, T] \times \Omega_2,$

$$\mathbf{u}(t, x) = \exp \left(\int_0^t (A(M) - \nabla \cdot \mathbf{v})(t', \tilde{x}(t', t, x)) dt' \right) \mathbf{u}_0(\tilde{x}(0, t, x)), \quad (11)$$

$$\begin{aligned} N(t, x) = & \exp \left(- \int_0^t \left(\nabla \cdot \mathbf{v} + \frac{1}{\tau} \right) (t', \tilde{x}(t', t, x)) dt' \right) N_0(\tilde{x}(0, t, x)) \\ & + \int_0^t \exp \left(- \int_{t'}^t \left(\nabla \cdot \mathbf{v} + \frac{1}{\tau} \right) (t'', \tilde{x}(t'', t, x)) dt'' \right) (\mathbf{d}(M) \cdot \mathbf{u})(t', \tilde{x}(t', t, x)) dt'. \end{aligned} \quad (12)$$

This leads to the following property:

Proposition 4.2. *Let $\mathbf{u}_0 \in H^s(\Omega)^4$, $N_0 \in H^s(\Omega)$, $\mathbf{v} \in (L_T^2; H^{s+1})^d$ and $M \in L_T^2; H^s$. Assume the 3 following facts:*

- (i) N_0 and the components of \mathbf{u}_0 are non-negative,
- (ii) $\text{supp}(\mathbf{u}_0 - \mathbf{s}) \cup \text{supp}(N_0)$ is compactly embedded in Ω_0 ,
- (iii) $\bigcup_{t \in [0, T]} \text{supp}((\nabla \cdot \mathbf{v})(t, \cdot))$ is compactly embedded in Ω_1 .

Then $\mathbf{u} := \mathcal{U}(\mathbf{u}_0, \mathbf{v}, M)$ and $N := \mathcal{N}(N_0, \mathbf{u}_0, \mathbf{v}, M, \tau)$ satisfy

- (i) N and the components of \mathbf{u} are non-negative,
- (ii) $\bigcup_{t \in [0, T]} \left(\text{supp}(\mathbf{p} \cdot \mathbf{u}(t, \cdot)) \cup \text{supp}(N(t, \cdot)) \right)$ is compactly embedded in Ω_1 ,
- (iii) $\bigcup_{t \in [0, T]} \text{supp}(\mathbf{u}(t, \cdot) - \mathbf{s})$ is compactly embedded in Ω_2 .

Remark 4.1. *The property that $\bigcup_{t \in [0, T]} \left(\text{supp}(\mathbf{p} \cdot \mathbf{u}(t, \cdot)) \cup \text{supp}(N(t, \cdot)) \right)$ is compactly embedded in Ω_1 implies the 2 followings points:*

- $\bigcup_{t \in [0, T]} \left(\text{supp}((\nabla \cdot \mathcal{V}(\mathbf{b}(M) \cdot \mathbf{u} - (1/\tau)N)(t, \cdot)) \right)$ is compactly embedded in Ω_1 ,
- $\bigcup_{t \in [0, T]} \left(\text{supp}((\nabla \cdot \mathcal{V}((\mathbf{b}(M) - \mathbf{d}(M)) \cdot \mathbf{u})(t, \cdot)) \right)$ is compactly embedded in Ω_1 ,

which will be useful for the fixed point in Section 5.

Proof. The property that the components of \mathbf{u} are non-negative is a consequence of assumption on \mathbf{u}_0 and explicit formula (11). Then since $\mathbf{d}(M) \cdot \mathbf{u}$ is non-negative, explicit formula (12) and assumption on N_0 lead to the property that N_0 is non-negative.

Denote by $\mathcal{K}_0 \subset \Omega_0$ the compact $\text{supp}(\mathbf{u}_0 - \mathbf{s}) \cup \text{supp}(N_0)$ and denote by $\mathcal{K}_1 \subset \Omega_1$ a compact such that

- $\bigcup_{t \in [0, T]} \left(\text{supp}((\nabla \cdot \mathbf{v})(t, \cdot)) \right) \subset \mathcal{K}_1$,
- $\{x \in \Omega, d(x, \mathcal{K}_0) \leq \frac{1}{4}d(\partial\Omega, \Omega_0)\} \subset \mathcal{K}_1$.

We consider also \mathcal{K}_2 the compact $\{x \in \Omega, d(x, \mathcal{K}_1) \leq \frac{1}{4}d(\partial\Omega, \Omega_0)\} \subset \Omega_2$.

Let us focus on (11). For any $t \in [0, T]$ and $x \in \Omega_2 \setminus \mathcal{K}_1$, assumption (10) on T ensures that $\mathbf{u}_0(\tilde{x}(0, t, x)) = \mathbf{s}$. The fact that $A(M)\mathbf{s} = 0$, which implies that $\exp(A(M))\mathbf{s} = \mathbf{s}$, leads to

$$\mathbf{u}(t, x) = \exp\left(\int_0^t -(\nabla \cdot \mathbf{v})(t', \tilde{x}(t', t, x))dt'\right)\mathbf{s}, \quad \text{for any } t \in [0, T] \text{ and } x \in \Omega_2 \setminus \mathcal{K}_1, \quad (13)$$

and we obtain that $\mathbf{p} \cdot \mathbf{u}(t, \cdot) = 0$ in $\Omega_2 \setminus \mathcal{K}_1$ for any $t \in [0, T]$.

Since $\tilde{x}(t', t, x) \in \Omega \setminus \mathcal{K}_1$ for any $t, t' \in [0, T]$ and $x \in \Omega_2 \setminus \mathcal{K}_2$, we deduce from the above formula that $\mathbf{u}(t, \cdot) = \mathbf{s}$ in $\Omega_2 \setminus \mathcal{K}_2$ for any $t \in [0, T]$.

From the explicit expressions for N and \mathbf{u} respectively given in (12) and (11), we deduce that $\mathbf{d}(M) \cdot \mathbf{u}(t', \tilde{x}(t', t, x)) = 0$ for any $t, t' \in [0, T]$ and $x \in \Omega_2 \setminus \mathcal{K}_1$. Since $N_0(\tilde{x}(0, t, x)) = 0$ for any $t \in [0, T]$ and $x \in \Omega_2 \setminus \mathcal{K}_1$, we conclude that $N(t, \cdot) = 0$ in $\Omega_2 \setminus \mathcal{K}_1$.

In conclusion, the solutions \mathbf{u} and N given by the characteristic method in Ω_2 satisfy $\mathbf{u} = \mathbf{s}$ and $N = 0$ in a neighborhood of $\partial\Omega_2$. Thanks to equations (6) and (7), \mathbf{u} can be smoothly extended by $\mathbf{u} = \mathbf{s}$ in $\Omega \setminus \Omega_2$ and N can be smoothly extended by $N = 0$ in $\Omega \setminus \Omega_2$. This concludes the proof of the Proposition. \square

The following Lemma gives estimates on $\partial_x^m \nabla \cdot (\mathbf{v}u) \partial_x^m u$ in terms of $\|\mathbf{u}\|_{H^m}$ for $u \in H^m(\Omega)$:

Lemma 4.1. *Let $s' > d/2$ and $K \in \mathbb{R}$ be given. Let $m \in \mathbb{N}$ such that $m \leq s'$. Let $\mathbf{v} \in H^{s'+1}(\Omega)$. We assume that $u \in H^m(\Omega)$ is such that $u = K$ in a neighborhood of $\partial\Omega$, therefore $\partial_x^k u|_{\partial\Omega} = 0$ for any $1 \leq k \leq m$. Then the following estimate holds:*

$$\left| \int_{\Omega} \partial_x^m \nabla \cdot (\mathbf{v}u) \partial_x^m u \right| \leq C \|\mathbf{v}\|_{H^{s'+1}} (K^2 \delta_{m,0} + \|u\|_{H^m}^2),$$

where $\delta_{m,0}$ is the Kronecker delta equal to 1 for $m = 0$ and equal to 0 elsewhere.

Proof. In the proof, we use the Gagliardo-Nirenberg interpolation inequality that can be found in [1]. We start by applying Leibniz formula on the left-hand side

$$\left| \int_{\Omega} \partial_x^m \nabla \cdot (\mathbf{v}u) \partial_x^m u \right| \leq \sum_{k=0}^m C_m^k \underbrace{\left| \int_{\Omega} \nabla \cdot (\partial_x^k \mathbf{v} \partial_x^{m-k} u) \partial_x^m u \right|}_{=I_m^k}.$$

- If $k = 0$,

$$I_m^0 = \int_{\Omega} \nabla \cdot (\mathbf{v} \partial_x^m u) \partial_x^m u = \int_{\Omega} (\nabla \cdot \mathbf{v}) (\partial_x^m u)^2 + \int_{\Omega} \mathbf{v} \cdot \frac{1}{2} \nabla ((\partial_x^m u)^2),$$

then integrate by parts the second integral to obtain successively

$$\begin{aligned} I_m^0 &= \int_{\Omega} (\nabla \cdot \mathbf{v}) (\partial_x^m u)^2 + \frac{1}{2} \left(K^2 \delta_{m,0} \int_{\partial\Omega} \mathbf{v} \cdot \mathbf{n} d\sigma - \int_{\Omega} (\nabla \cdot \mathbf{v}) (\partial_x^m u)^2 \right), \\ &= \frac{1}{2} \int_{\Omega} (\nabla \cdot \mathbf{v}) (K^2 \delta_{m,0} + (\partial_x^m u)^2). \end{aligned}$$

Thanks to the continuous embedding $H^{s'}(\Omega) \hookrightarrow L^\infty(\Omega)$ we infer

$$|I_m^0| \leq C \|\mathbf{v}\|_{H^{s'+1}} (K^2 \delta_{m,0} + \|u\|_{H^m}^2).$$

- If $1 \leq k \leq m$, I_m^k can be rewritten as

$$I_m^k = \underbrace{\int_{\Omega} (\nabla \cdot \partial_x^k \mathbf{v}) \partial_x^{m-k} u \partial_x^m u}_{I_1} + \underbrace{\int_{\Omega} \partial_x^k \mathbf{v} \cdot \nabla (\partial_x^{m-k} u) \partial_x^m u}_{I_2}.$$

Let first estimate I_1 .

- (i) If $m \geq 2$ and $k = m$:

$$|I_1| \leq \|\nabla \cdot \partial_x^m \mathbf{v}\|_{L^2} \|u\|_{L^\infty} \|\partial_x^m u\|_{L^2},$$

and we use the continuous embedding $H^m \hookrightarrow L^\infty$ to obtain

$$|I_1| \leq \|\mathbf{v}\|_{H^{s'+1}} \|u\|_{H^m}^2.$$

- (ii) Otherwise I_1 satisfies

$$|I_1| \leq \|\nabla \cdot \partial_x^k \mathbf{v}\|_{L^4} \|\partial_x^{m-k} u\|_{L^4} \|\partial_x^m u\|_{L^2},$$

Gagliardo-Nirenberg inequality and using the fact that $s' + 1 \geq 3$ lead to

$$|I_1| \leq \|\mathbf{v}\|_{H^{s'+1}} \|u\|_{H^m}^2.$$

Then we focus on I_2 .

- (i) If $k = 1$:

$$|I_2| \leq \|\partial_x \mathbf{v}\|_{L^\infty} \|\nabla (\partial_x^{m-1} u)\|_{L^2} \|\partial_x^m u\|_{L^2},$$

here again the embedding $H^2(\Omega) \hookrightarrow L^\infty(\Omega)$ and the fact that $s' + 1 \geq 3$ lead to

$$|I_2| \leq \|\mathbf{v}\|_{H^{s'+1}} \|u\|_{H^m}^2.$$

- (ii) Otherwise, for $k \geq 2$, I_2 satisfies

$$|I_2| \leq \|\partial_x^k \mathbf{v}\|_{L^4} \|\nabla (\partial_x^{m-k} u)\|_{L^4} \|\partial_x^m u\|_{L^2},$$

Gagliardo-Nirenberg inequality leads to

$$|I_2| \leq \|\mathbf{v}\|_{H^{s'+1}} \|u\|_{H^m}^2.$$

□

The previous Lemma makes it possible to prove the following estimate on the solution to scalar advection equation (14):

Proposition 4.3. *Let $K \in \mathbb{R}$, $u_0 \in H^s(\Omega)$, $\mathbf{v} \in (L_T^2; H^{s+1})^d$, $a, b_1, b_2 \in L_T^2; H^s$. Let u be a solution to*

$$\begin{cases} \partial_t u + \nabla \cdot (\mathbf{v}u) &= au + b_1 + b_2, \\ u|_{t=0} &= u_0, \\ u|_{\partial\Omega} &= K, \end{cases} \quad \text{if } \mathbf{v} \cdot \mathbf{n} < 0 \text{ on } \partial\Omega \quad (14)$$

and assume that $u = K$ in a neighborhood of Ω . Then for all $s' \in \mathbb{N}$ such that $d/2 < s' \leq s$, we have

$$\begin{aligned} \|u\|_{L_T^\infty; H^{s'}}^2 &\leq \left(\|u_0\|_{H^{s'}}^2 + C\sqrt{T} \left(K^2 \|\mathbf{v}\|_{L_T^2; H^{s'+1}} + \|b_1\|_{L_T^2; H^{s'}} \right) + \|b_2\|_{L_T^2; H^{s'}}^2 \right) \\ &\quad \times \exp \left(CT + C\sqrt{T} (\|\mathbf{v}\|_{L_T^2; H^{s'+1}} + \|a\|_{L_T^2; H^{s'}} + \|b_1\|_{L_T^2; H^{s'}}) \right). \end{aligned} \quad (15)$$

Remark 4.2. *A priori, b_1 and b_2 play the same role. However for stability of the operator \mathcal{N} and the contraction of \mathcal{U} and \mathcal{N} , it is important to discriminate their roles. More precisely, the term $\|b_2\|_{L_T^2; H^{s'}}$ does not appear in the exponential term in (15), which will be crucial in the following.*

Proof. Let $m \in \mathbb{N}$, $m \leq s'$, apply the derivative ∂_x^m to (14), multiply by $\partial_x^m u$ and integrate over Ω . First observe that since $H^{s'}$ is an algebra, we have

$$\begin{aligned} \left| \int_{\Omega} \partial_x^m (au) \partial_x^m u \right| &\leq \|au\|_{H^{s'}} \|u\|_{H^{s'}}, \\ &\leq C \|a\|_{H^{s'}} \|u\|_{H^{s'}}^2. \end{aligned}$$

Then we have

$$\begin{aligned} \left| \int_{\Omega} \partial_x^m b_1 \partial_x^m u \right| &\leq \|b_1\|_{H^{s'}} \|u\|_{H^{s'}}, \\ &\leq \|b_1\|_{H^{s'}} (1 + \|u\|_{H^{s'}}^2), \end{aligned}$$

and similarly

$$\left| \int_{\Omega} \partial_x^m b_2 \partial_x^m u \right| \leq \frac{1}{2} (\|b_2\|_{H^{s'}}^2 + \|u\|_{H^{s'}}^2).$$

By summing the above inequalities, thanks to Lemma 4.1 we obtain straightforwardly

$$\begin{aligned} \partial_t \|u\|_{H^{s'}}^2 &\leq C \left[(1 + \|\mathbf{v}\|_{H^{s'+1}} + \|a\|_{H^{s'}} + \|b_1\|_{H^{s'}}) \|u\|_{H^{s'}}^2 \right. \\ &\quad \left. + K^2 \|\mathbf{v}\|_{H^{s'+1}} + \|b_1\|_{H^{s'}} + \|b_2\|_{H^{s'}}^2 \right], \end{aligned}$$

then integrating between time 0 and $t < T$ and applying Gronwall's inequality lead to the result. \square

Thanks Proposition 4.3, we deduce the stability and contraction of the operators \mathcal{U} and \mathcal{N} .

Proposition 4.4 (Estimate for \mathcal{U} , \mathcal{N}). *Operators \mathcal{U} and \mathcal{N} satisfy the following properties:*

(i) (Stability) *Let $\mathbf{u}_0 \in H^s(\Omega)^4$, $N_0 \in H^s(\Omega)$, $\mathbf{v} \in (L_T^2; H^{s+1})^d \cap (L_T^\infty; H^s)^d$ and $M \in L_T^2; H^s \cap L_T^\infty; H^{s-1}$ satisfying the assumptions of Proposition 4.2. Then $\mathbf{u} := \mathcal{U}(\mathbf{u}_0, \mathbf{v}, M)$ satisfies*

$$\|\mathbf{u}\|_{L_T^\infty; H^s}^2 \leq \left(\|\mathbf{u}_0\|_{H^s}^2 + C\sqrt{T} \|\mathbf{v}\|_{L_T^2; H^{s+1}} \right) \exp \left(C\sqrt{T} (\|\mathbf{v}\|_{L_T^2; H^{s+1}} + \|M\|_{L_T^2; H^s}) \right),$$

and $N := \mathcal{N}(N_0, \mathbf{u}_0, \mathbf{v}, M, \tau)$ satisfies

$$\begin{aligned} \|N\|_{L_T^\infty; H^s}^2 &\leq \left(\|N_0\|_{H^s}^2 + C\sqrt{T} (\|\mathbf{v}\|_{L_T^2; H^{s+1}} + \|\mathbf{u}\|_{L_T^\infty; H^s} \|M\|_{L_T^2; H^s}) \right) \\ &\quad \exp \left(C\sqrt{T} (\|\mathbf{v}\|_{L_T^2; H^{s+1}} + \|\mathbf{u}\|_{L_T^\infty; H^s} \|M\|_{L_T^2; H^s}) \right). \end{aligned}$$

moreover $\mathbf{u}, N \in \mathcal{C}^0([0, T]; H^{s-1}(\Omega))$.

(ii) (Contraction) *For $i = 1, 2$, let $\mathbf{u}_{0,i}$, $N_{0,i}$, \mathbf{v}_i , M_i be as previously and let $\mathbf{u}_i := \mathcal{U}(\mathbf{u}_{0,i}, \mathbf{v}_i, M_i)$ and $N_i := \mathcal{N}(N_{0,i}, \mathbf{u}_{0,i}, \mathbf{v}_i, M_i, \tau)$. Assume there exists $R > 0$ such that*

$$\|(\mathbf{u}_i, M_i, \xi_i)\|_{\mathcal{E}_T^s} + \|N_i\|_{L_T^\infty; H^s} \leq R,$$

then we have

$$\begin{aligned} \|\mathbf{u}_1 - \mathbf{u}_2\|_{L_T^\infty; H^{s-1}}^2 &\leq C_R \left(\|\mathbf{u}_{0,1} - \mathbf{u}_{0,2}\|_{H^{s-1}}^2 \right. \\ &\quad \left. + \|\mathbf{v}_1 - \mathbf{v}_2\|_{L_T^2; H^s}^2 + \|M_1 - M_2\|_{L_T^2; H^{s-1}}^2 \right), \end{aligned}$$

and

$$\begin{aligned} \|N_1 - N_2\|_{L_T^\infty; H^{s-1}}^2 &\leq C_R \left(\|N_{0,1} - N_{0,2}\|_{H^{s-1}}^2 + \|\mathbf{v}_1 - \mathbf{v}_2\|_{L_T^2; H^s}^2 \right. \\ &\quad \left. + \|M_1 - M_2\|_{L_T^2; H^{s-1}}^2 + \|\mathbf{u}_1 - \mathbf{u}_2\|_{L_T^2; H^{s-1}}^2 \right). \end{aligned}$$

Proof. (i) We apply Proposition 4.3 with $s' = s$, b_1 and b_2 identically null. For $1 \leq i \leq 4$, let u be the i^{th} component of \mathbf{u} and a equals to the i^{th} diagonal component of $A(M)$ (recall that $A(M)$ is diagonal) and apply Proposition 4.3 to obtain the estimate for \mathbf{u} .

Apply Proposition 4.3 with $s' = s$, b_1 equals to $\mathbf{d}(M) \cdot \mathbf{u}$, a and b_2 identically null leads to the estimate for N^1 .

To prove the time continuity, the assumptions on \mathbf{v} and M and equation (6) imply that $\partial_t \mathbf{u}$ belongs to $(L_T^\infty; H^{s-1})^d$. By integrating $\partial_t \mathbf{u}$ between t_1 and t_2 (with $0 \leq t_1 \leq t_2 \leq T$) and using the fact that $\mathbf{u}_0 \in H^s(\Omega)$, we obtain that $\mathbf{u} \in C^0([0, T]; H^{s-1}(\Omega))$ (even Lipschitz continuous). The same result holds for N .

(ii) Let $\mathbf{u}_1, \mathbf{u}_2$ be as in Proposition 4.4, then $\mathbf{u}_1 - \mathbf{u}_2$ satisfies the following equation:

$$\begin{aligned} \partial_t(\mathbf{u}_1 - \mathbf{u}_2) + \nabla \cdot ((\mathbf{u}_1 - \mathbf{u}_2) \otimes \mathbf{v}_1) &= A(M_1)(\mathbf{u}_1 - \mathbf{u}_2) \\ &\quad - \nabla \cdot (\mathbf{u}_2 \otimes (\mathbf{v}_1 - \mathbf{v}_2)) + (A(M_1) - A(M_2))\mathbf{u}_2. \end{aligned}$$

For $1 \leq i \leq 4$, we apply Proposition 4.3 with $s' = s - 1$, $\mathbf{v} = \mathbf{v}_1$, u equals to the i^{th} component of $\mathbf{u}_1 - \mathbf{u}_2$, a equals to the i^{th} diagonal component of $A(M_1)$, b_1 identically null and b_2 equals to the i^{th} component of $-\nabla \cdot (\mathbf{u}_2 \otimes (\mathbf{v}_1 - \mathbf{v}_2)) + (A(M_1) - A(M_2))\mathbf{u}_2$. Observing that

$$\begin{aligned} \|\nabla \cdot (\mathbf{u}_2 \otimes (\mathbf{v}_1 - \mathbf{v}_2))\|_{H^{s-1}}^2 &\leq \|\mathbf{u}_2 \otimes (\mathbf{v}_1 - \mathbf{v}_2)\|_{H^s}^2 \\ &\leq C \|\mathbf{u}_2\|_{H^s}^2 \|\mathbf{v}_1 - \mathbf{v}_2\|_{H^s}^2, \\ &\leq C_R \|\mathbf{v}_1 - \mathbf{v}_2\|_{H^s}^2, \end{aligned}$$

and integrating between time 0 and T , we obtain

$$\|\nabla \cdot (\mathbf{u}_2 \otimes (\mathbf{v}_1 - \mathbf{v}_2))\|_{L_T^2; H^{s-1}}^2 \leq C_R \|\mathbf{v}_1 - \mathbf{v}_2\|_{L_T^2; H^s}^2.$$

Similarly, we get the following estimate on $A(M_1) - A(M_2)$:

$$\|(A(M_1) - A(M_2))\mathbf{u}_2\|_{L_T^2; H^{s-1}}^2 \leq C_R \|M_1 - M_2\|_{L_T^2; H^{s-1}}^2.$$

Then we apply Proposition 4.3 to obtain

$$\begin{aligned} \|\mathbf{u}_1 - \mathbf{u}_2\|_{L_T^\infty; H^{s-1}}^2 &\leq \left(\|\mathbf{u}_{0,1} - \mathbf{u}_{0,2}\|_{H^{s-1}}^2 + C_R \left(\|\mathbf{v}_1 - \mathbf{v}_2\|_{L_T^2; H^s}^2 + \|M_1 - M_2\|_{L_T^2; H^{s-1}}^2 \right) \right) \\ &\quad \times \exp \left(CT + C_R \sqrt{T} \right). \end{aligned}$$

¹Note that the linear term $-(1/\tau)N$ in equation (7) is easy to handle: it provides a constant $e^{-t/\tau} \leq 1$ for any $0 \leq t \leq T$.

Finally, since T is bounded by some arbitrary constant, we have proved the estimate on $\mathbf{u}_1 - \mathbf{u}_2$.

We use the same ideas to get the estimate on $N_1 - N_2$. □

4.3 Estimate for \mathcal{M}

To prove estimates on \mathcal{M} , we start to prove estimates on the following equation:

$$\begin{cases} \partial_t \tilde{M} - \Delta \tilde{M} + \nabla \cdot (\mathbf{w}_1 \tilde{M} + \mathbf{w}_2) & = a \tilde{M} + b, \\ \tilde{M}|_{\partial\Omega} & = 0, \\ \tilde{M}|_{t=0} & = \tilde{M}_0, \end{cases} \quad (16)$$

where \tilde{M}_0 satisfies the boundary condition, $\mathbf{w}_1, \mathbf{w}_2$ and b are compactly supported in Ω . The estimates on \tilde{M} make it possible to prove stability and contraction estimates on \mathcal{M} . To prove estimate on \tilde{M} , we build \tilde{M} by a Galerkin approximation using the eigenvalues of the operator $(-\Delta)$ endowed with the Dirichlet boundary conditions. This makes it possible to assume in the next computations that for any $k \in \mathbb{N}$, $(-\Delta)^k \tilde{M} = 0$ on the boundary (we can also see this from the equation satisfied by \tilde{M}). In order to prove the estimate on \tilde{M} , we need the following Lemma:

Lemma 4.2. *Let $\tilde{M}_0 \in H^{s-1}(\Omega)$. Let $\mathbf{w}_1 \in (L_T^2; H^{s-1})^d, a \in L_T^2; H^{s-1}$ and $\mathbf{w}_2 \in (L_T^2; L^2)^d, b \in L_T^2; L^2$. Assume that $\tilde{M}_0|_{\partial\Omega} = 0$ and that $\mathbf{w}_1, \mathbf{w}_2$ and b are compactly supported in Ω . Then the solution \tilde{M} to (16) satisfies*

(i) *for any $k \in \mathbb{N}$, such that $2k + 1 \leq s$ and $\mathbf{w}_2 \in (L_T^2; H^{2k})^d, b \in L_T^2; H^{2k}$, we have*

$$\begin{aligned} \partial_t \|(-\Delta)^k \tilde{M}\|_{L^2}^2 + \|(-\Delta)^k \nabla \tilde{M}\|_{L^2}^2 &\leq C \left[\|\mathbf{w}_2\|_{H^{2k}}^2 + \|b\|_{H^{2k}}^2 \right. \\ &\quad \left. + (1 + \|\mathbf{w}_1\|_{H^{s-1}}^2 + \|a\|_{H^{s-1}}^2) \|(-\Delta)^k \tilde{M}\|_{L^2}^2 \right], \end{aligned} \quad (17)$$

(ii) *for any $k \in \mathbb{N}$, such that $2k + 2 \leq s$ and $\mathbf{w}_2 \in (L_T^2; H^{2k+1})^d, b \in L_T^2; H^{2k+1}$, we have*

$$\begin{aligned} \partial_t \|(-\Delta)^k \nabla \tilde{M}\|_{L^2}^2 + \|(-\Delta)^{k+1} \tilde{M}\|_{L^2}^2 &\leq C \left[\|\mathbf{w}_2\|_{H^{2k+1}}^2 + \|b\|_{H^{2k+1}}^2 \right. \\ &\quad \left. + (1 + \|\mathbf{w}_1\|_{H^{s-1}}^2 + \|a\|_{H^{s-1}}^2) \|\nabla (-\Delta)^k \tilde{M}\|_{L^2}^2 \right]. \end{aligned} \quad (18)$$

Proof. We first prove the result for $k = 0$ since it uses different estimates than general case.

- For $k = 0$.

To prove (17), multiply the equation (16) by \tilde{M} and integrate by parts:

$$\frac{1}{2} \partial_t \|\tilde{M}\|_{L^2}^2 + \|\nabla \tilde{M}\|_{L^2}^2 \leq \left| \int_{\Omega} (\mathbf{w}_1 \tilde{M} + \mathbf{w}_2) \cdot \nabla \tilde{M} \right| + \left| \int_{\Omega} (a \tilde{M} + b) \tilde{M} \right|.$$

Using Young's inequality leads to

$$\begin{aligned} \frac{1}{2} \partial_t \|\tilde{M}\|_{L^2}^2 + \|\nabla \tilde{M}\|_{L^2}^2 &\leq \frac{1}{2} \left(\|\mathbf{w}_1 \tilde{M} + \mathbf{w}_2\|_{L^2}^2 + \|\nabla \tilde{M}\|_{L^2}^2 \right. \\ &\quad \left. + \|a \tilde{M}\|_{L^2}^2 + \|\tilde{M}\|_{L^2}^2 + \|b\|_{L^2}^2 + \|\tilde{M}\|_{L^2}^2 \right), \end{aligned}$$

then we use the continuous embedding $H^2(\Omega) \hookrightarrow L^\infty(\Omega)$ for \mathbf{w}_1 and get (17) for $k = 0$.

To prove (18), we apply the operator $(-\Delta)$ to (16), multiply by \tilde{M} and integrate by parts:

$$\frac{1}{2}\partial_t\|\nabla\tilde{M}\|_{L^2}^2 + \|\Delta\tilde{M}\|_{L^2}^2 \leq \left| \int_{\Omega} \nabla \cdot (\mathbf{w}_1\tilde{M} + \mathbf{w}_2)\Delta\tilde{M} \right| + \left| \int_{\Omega} \nabla(a\tilde{M} + b) \cdot \nabla\tilde{M} \right|.$$

Using Young's inequality leads to

$$\begin{aligned} \frac{1}{2}\partial_t\|\nabla\tilde{M}\|_{L^2}^2 + \|\Delta\tilde{M}\|_{L^2}^2 &\leq \frac{1}{2} \left(\|\nabla \cdot (\mathbf{w}_1\tilde{M} + \mathbf{w}_2)\|_{L^2}^2 + \|\Delta\tilde{M}\|_{L^2}^2 \right. \\ &\quad \left. + \|\nabla(a\tilde{M})\|_{L^2}^2 + \|\nabla b\|_{L^2}^2 + 2\|\nabla\tilde{M}\|_{L^2}^2 \right). \end{aligned}$$

Observe that

$$\begin{aligned} \|\nabla \cdot (\mathbf{w}_1\tilde{M})\|_{L^2} &\leq \|(\nabla \cdot \mathbf{w}_1)\tilde{M}\|_{L^2} + \|\mathbf{w}_1 \cdot \nabla\tilde{M}\|_{L^2}, \\ &\leq \|(\nabla \cdot \mathbf{w}_1)\|_{L^4} \|\tilde{M}\|_{L^4} + \|\mathbf{w}_1 \cdot \nabla\tilde{M}\|_{L^2}, \end{aligned}$$

using Gagliardo-Nirenberg inequality for the first term and the continuous embedding $H^2(\Omega) \hookrightarrow L^\infty(\Omega)$ for the second term leads to

$$\|\nabla \cdot (\mathbf{w}_1\tilde{M})\|_{L^2} \leq C\|\mathbf{w}_1\|_{H^2}\|\nabla\tilde{M}\|_{L^2},$$

The same idea applied on $\nabla(a\tilde{M})$ makes it possible to infer

$$\|\nabla(a\tilde{M})\|_{L^2} \leq C\|a\|_{H^2}\|\nabla\tilde{M}\|_{L^2}.$$

- For $k \geq 1$.

To prove (17), apply $(-\Delta)^k$ to (16), multiply by $(-\Delta)^k\tilde{M}$ and integrate by parts:

$$\begin{aligned} \frac{1}{2}\partial_t\|(-\Delta)^k\tilde{M}\|_{L^2}^2 + \|(-\Delta)^k\nabla\tilde{M}\|_{L^2}^2 &\leq \left| \int_{\Omega} (-\Delta)^k(\mathbf{w}_1\tilde{M} + \mathbf{w}_2) \cdot (-\Delta)^k\nabla\tilde{M} \right| \\ &\quad + \left| \int_{\Omega} (-\Delta)^k(a\tilde{M} + b)(-\Delta)^k\tilde{M} \right|. \end{aligned}$$

Using Young's inequality leads to

$$\begin{aligned} \frac{1}{2}\partial_t\|(-\Delta)^k\tilde{M}\|_{L^2}^2 + \|(-\Delta)^k\nabla\tilde{M}\|_{L^2}^2 &\leq \frac{1}{2} \left(\|(-\Delta)^k(\mathbf{w}_1\tilde{M} + \mathbf{w}_2)\|_{L^2}^2 + \|(-\Delta)^k\nabla\tilde{M}\|_{L^2}^2 \right. \\ &\quad + \|(-\Delta)^k(a\tilde{M})\|_{L^2}^2 + \|(-\Delta)^k\tilde{M}\|_{L^2}^2 \\ &\quad \left. + \|(-\Delta)^kb\|_{L^2}^2 + \|(-\Delta)^k\tilde{M}\|_{L^2}^2 \right), \end{aligned}$$

then use the fact that $H^{2k}(\Omega)$ is an algebra to deduce (17).

To prove (18), apply $(-\Delta)^{k+1}$ to (16), multiply by $(-\Delta)^k\tilde{M}$ and integrate by parts:

$$\begin{aligned} \frac{1}{2}\partial_t\|(-\Delta)^k\nabla\tilde{M}\|_{L^2}^2 + \|(-\Delta)^{k+1}\tilde{M}\|_{L^2}^2 &\leq \left| \int_{\Omega} (-\Delta)^k\nabla \cdot (\mathbf{w}_1\tilde{M} + \mathbf{w}_2)(-\Delta)^{k+1}\tilde{M} \right| \\ &\quad + \left| \int_{\Omega} (-\Delta)^k\nabla(a\tilde{M} + b) \cdot (-\Delta)^k\nabla\tilde{M} \right|. \end{aligned}$$

Using Young's inequality leads to

$$\begin{aligned} \frac{1}{2} \partial_t \|(-\Delta)^k \nabla \tilde{M}\|_{L^2}^2 + \|(-\Delta)^{k+1} \tilde{M}\|_{L^2}^2 &\leq \frac{1}{2} \left(\|(-\Delta)^k \nabla \cdot (\mathbf{w}_1 \tilde{M} + \mathbf{w}_2)\|_{L^2}^2 + \|(-\Delta)^{k+1} \tilde{M}\|_{L^2}^2 \right. \\ &\quad + \|(-\Delta)^k \nabla (a \tilde{M})\|_{L^2}^2 + \|(-\Delta)^k \nabla \tilde{M}\|_{L^2}^2 \\ &\quad \left. + \|(-\Delta)^k \nabla b\|_{L^2}^2 + \|(-\Delta)^k \nabla \tilde{M}\|_{L^2}^2 \right), \end{aligned}$$

then use the fact that $H^{2k+1}(\Omega)$ is an algebra to obtain (18). □

The previous Lemma leads to the following Proposition, which makes it possible to prove estimates on \mathcal{M} :

Proposition 4.5. *Under the assumption of Lemma 4.2, for any $s' \in \mathbb{N}$ such that $s' \leq s$, we have the following estimates*

$$\begin{aligned} \|\tilde{M}\|_{L_T^\infty; H^{s'-1}}^2 &\leq \left(\|\tilde{M}_0\|_{H^{s'-1}}^2 + C(\|\mathbf{w}_2\|_{L_T^2; H^{s'-1}}^2 + \|b\|_{L_T^2; H^{s'-1}}^2) \right) \\ &\quad \times \exp \left[C \left(T + \|\mathbf{w}_1\|_{L_T^2; H^{s-1}}^2 + \|a\|_{L_T^2; H^{s-1}}^2 \right) \right]. \end{aligned} \quad (19)$$

$$\begin{aligned} \|\tilde{M}\|_{L_T^2; H^{s'}}^2 &\leq \|\tilde{M}_0\|_{H^{s'-1}}^2 + C \left[\|\mathbf{w}_2\|_{L_T^2; H^{s'-1}}^2 + \|b\|_{L_T^2; H^{s'-1}}^2 \right. \\ &\quad \left. + \left(T + \|\mathbf{w}_1\|_{L_T^2; H^{s-1}}^2 + \|a\|_{L_T^2; H^{s-1}}^2 \right) \|\tilde{M}\|_{L_T^\infty; H^{s'-1}}^2 \right]. \end{aligned} \quad (20)$$

Proof. We use Lemma 4.2 and the facts that for $k \in \mathbb{N}$, $\|\tilde{M}\|_{L^2} + \|(-\Delta)^k \tilde{M}\|_{L^2}$ is equivalent to $\|\tilde{M}\|_{H^{2k}}$ and $\|\tilde{M}\|_{L^2} + \|(-\Delta)^k \nabla \tilde{M}\|_{L^2}$ is equivalent to $\|\tilde{M}\|_{H^{2k+1}}$.

- If $s' = 2m + 1$, with $m \in \mathbb{N}^*$, we apply (17) for $k = 0$ and $k = m$ and sum them.
- If $s' = 2m + 2$, $m \in \mathbb{N}^*$, we apply (17) for $k = 0$ and (18) for $k = m$ and sum them.

These calculations lead to the following estimates:

$$\begin{aligned} \partial_t \|\tilde{M}\|_{H^{s'-1}}^2 + \|\tilde{M}\|_{H^{s'}}^2 &\leq C \left[\|\mathbf{w}_2\|_{H^{s'-1}}^2 + \|b\|_{H^{s'-1}}^2 \right. \\ &\quad \left. + (1 + \|\mathbf{w}_1\|_{H^{s-1}}^2 + \|a\|_{H^{s-1}}^2) \|\tilde{M}\|_{H^{s'-1}}^2 \right]. \end{aligned} \quad (21)$$

We start by omitting the term $\|\tilde{M}\|_{H^s}^2 \geq 0$ and we integrate between time 0 and $t \leq T$. Applying Gronwall's inequality leads to (19). To prove (20), we go back to (21), integrate between time 0 and T and omit the term $\|\tilde{M}(T, \cdot)\|_{H^{s'-1}}^2$. □

Now we can prove the main estimates on operator \mathcal{M} :

Proposition 4.6. *Operator \mathcal{M} satisfies the following properties:*

(i) (Stability) Let $M_0 \in H^{s-1}(\Omega)$ such that $M_0 = 1$ on $\partial\Omega$. Let $\mathbf{u} \in (L_T^\infty; H^s)^4$ such that $\mathbf{p} \cdot \mathbf{u}$ is compactly supported in Ω , where $\mathbf{p} = (0, 0, 0, 1)^t$. Let $\xi \in C^0([0, T])$. Then $M := \mathcal{M}(M_0, \mathbf{u}, \xi)$ satisfies

$$\begin{aligned} \|M\|_{L_T^\infty; H^{s-1}}^2 &\leq 1 + \left(\|M_0\|_{H^{s-1}}^2 + CT(\|\mathbf{u}\|_{L_T^\infty; H^s}^2 + \|\xi\|_\infty^2) \right) \\ &\quad \times \exp \left[CT \left(1 + \|\mathbf{u}\|_{L_T^\infty; H^s}^2 + \|\xi\|_\infty^2 \right) \right], \end{aligned}$$

$$\begin{aligned} \|M\|_{L_T^2; H^s}^2 &\leq 1 + \|M_0\|_{H^{s-1}}^2 + CT \left[\|\mathbf{u}\|_{L_T^\infty; H^s}^2 + \|\xi\|_\infty^2 \right. \\ &\quad \left. + \left(1 + \|\mathbf{u}\|_{L_T^\infty; H^s}^2 + \|\xi\|_\infty^2 \right) \|M\|_{L_T^\infty; H^{s-1}}^2 \right]. \end{aligned}$$

Furthermore M belongs to $C^0([0, T]; H^{s-2}(\Omega))$.

(ii) (Contraction) For $i = 1, 2$, let $M_{0,i}, \mathbf{u}_i, \xi_i$ be as previously and let $M_i := \mathcal{M}(M_{0,i}, \mathbf{u}_i, \xi_i)$. Assume there exists $R > 0$ such that

$$\|(\mathbf{u}_i, M_i, \xi_i)\|_{\mathcal{E}_T^s} \leq R,$$

then we have

$$\|M_1 - M_2\|_{L_T^2; H^{s-1}}^2 \leq C_R \left(\|M_{0,1} - M_{0,2}\|_{H^{s-2}}^2 + \|\mathbf{u}_1 - \mathbf{u}_2\|_{L_T^2; H^{s-1}}^2 + \|\xi_1 - \xi_2\|_{L_T^2}^2 \right).$$

Proof. (i) The proof is a consequence of Proposition 4.5 with $s' = s$ and

$$\begin{aligned} \tilde{M} &:= 1 - M, \\ \tilde{M}_0 &:= 1 - M_0, \\ \mathbf{w}_1 &:= \xi \nabla(\mathbf{p} \cdot \mathbf{u}), \\ \mathbf{w}_2 &:= \mathbf{w}_1, \\ a &:= -(\eta \mathbf{p} + C_0 \mathbf{s}) \cdot \mathbf{u}, \\ b &:= \eta \mathbf{p} \cdot \mathbf{u}. \end{aligned}$$

(ii) We consider

$$\begin{aligned} \tilde{M} &:= M_1 - M_2, \\ \tilde{M}_0 &:= M_{0,1} - M_{0,2}, \\ \mathbf{w}_1 &:= \xi_1 \nabla(\mathbf{p} \cdot \mathbf{u}_1), \\ \mathbf{w}_2 &:= -((\xi_1 \nabla(\mathbf{p} \cdot \mathbf{u}_1) - \xi_2 \nabla(\mathbf{p} \cdot \mathbf{u}_2))M_2), \\ a &:= -(\eta \mathbf{p} + C_0 \mathbf{s}) \cdot \mathbf{u}_1, \\ b &:= -(\eta \mathbf{p} + C_0 \mathbf{s}) \cdot (\mathbf{u}_1 - \mathbf{u}_2)M_2 + \eta \mathbf{p} \cdot (\mathbf{u}_1 - \mathbf{u}_2), \end{aligned}$$

and we apply Proposition 4.5 with $s' = s - 1$. Assumptions and equation (19) leads to

$$\begin{aligned} \|M_1 - M_2\|_{L_T^\infty; H^{s-2}}^2 &\leq \left(\|M_{0,1} - M_{0,2}\|_{H^{s-2}}^2 + C_R(\|\mathbf{u}_1 - \mathbf{u}_2\|_{L_T^2; H^{s-1}}^2 + \|\xi_1 - \xi_2\|_{L_T^2}^2) \right) \\ &\quad \times \exp(C_R T), \end{aligned}$$

then from (20) we infer

$$\begin{aligned} \|M_1 - M_2\|_{L_T^2; H^{s-1}}^2 &\leq \|M_{0,1} - M_{0,2}\|_{H^{s-2}}^2 + C_R \left[\|\mathbf{u}_1 - \mathbf{u}_2\|_{L_T^2; H^{s-1}}^2 + \|\xi_1 - \xi_2\|_{L_T^2}^2 \right. \\ &\quad \left. + T \|M_1 - M_2\|_{L_T^\infty; H^{s-2}}^2 \right], \end{aligned}$$

this ends the proof since T is bounded by some arbitrary constant. \square

4.4 Estimates for Ξ

Estimates on Ξ are consequences of Gronwall's inequality:

Proposition 4.7. *Operator Ξ satisfies the following properties:*

- (i) (Stability) Let $\xi_0 \in \mathbb{R}$. Let $\mathbf{u} \in (L_T^\infty; H^s)^d$ and $M \in L_T^2; H^s$. Then $\xi := \Xi(\xi_0, \mathbf{u}, M)$ satisfies

$$\|\xi\|_\infty^2 \leq \left(|\xi_0|^2 + CT \|\mathbf{u}\|_{L_T^\infty; L^1}^2 \right) \exp(CT),$$

where $C > 0$ depends only on $\alpha, \|\nu_2\|_\infty$.

- (ii) (Contraction) For $i = 1, 2$, let $\xi_{0,i}, \mathbf{u}_i$ and M_i be as previously and let $\xi_i := \Xi(\xi_{0,i}, \mathbf{u}_i, M_i)$. Assume there exists $R > 0$ such that

$$\|(\mathbf{u}_i, M_i, \xi_i)\|_{\mathcal{E}_T^s} \leq R,$$

then we have

$$\|\xi_1 - \xi_2\|_\infty^2 \leq C_R \left(|\xi_{0,1} - \xi_{0,2}|^2 + \|\mathbf{u}_1 - \mathbf{u}_2\|_{L_T^2; L^1}^2 + \|M_1 - M_2\|_{L_T^2; L^1}^2 \right),$$

where $C_R > 0$ depends only on $\alpha, \|\nu_2\|_\infty$ and R .

Proof. Multiply by ξ the equation satisfied by ξ and apply Young's inequality:

$$\frac{1}{2} \partial_t \xi^2 \leq C \left[\left(\int_\Omega |\mathbf{u}| \right)^2 + \xi^2 \right] - \lambda \xi^2,$$

integrate over time and apply Gronwall's inequality to obtain the estimate for ξ . The estimate for $\xi_1 - \xi_2$ follows the same line. \square

5 Local existence and uniqueness for problems (3) and (4)

Let us summarize the stability estimates for the operators $\mathcal{U}, \mathcal{N}, \mathcal{V}, \mathcal{M}$ and Ξ . Thanks to Proposition 4.2 and Remark 4.1, starting from $\mathbf{u}_0 - \mathbf{s}, N_0, \mathbf{p} \cdot \mathbf{u}, \mathbf{u} - \mathbf{s}$ and N compactly supported in Ω , we observe that the solutions $\tilde{\mathbf{u}}$ and \tilde{N} defined by operators Φ or Ψ are also compactly supported in Ω and stay in the same compact. We get straightforwardly

Proposition 5.1 (Stability estimates for Φ and Ψ). *For $i = 0, 1, 2$, let Ω_i be as in Definition 4.2. Operators Φ and Ψ satisfies the following estimates:*

(i) Let $X_0 := (\mathbf{u}_0, M_0, \xi_0) \in \mathcal{E}_0^s$ and $N_0 \in H^s(\Omega)$ such that $\text{supp}(\mathbf{u}_0 - \mathbf{s}) \cup \text{supp}(N_0)$ is compactly embedded in Ω_0 .

There exist $R \geq \|X_0\|_{\mathcal{E}_0^s} + \|N_0\|_{H^s}$ and $T_1^\tau > 0$ depending only on R and the parameters of the model (such as $\gamma_1, \gamma_2, \dots$) such that for any $X := (\mathbf{u}, M, \xi) \in \mathcal{E}_{T_1^\tau}^s$ and $N \in L_{T_1^\tau}^\infty; H^s$ satisfying

- $\bigcup_{t \in [0, T]} (\text{supp}(\mathbf{p} \cdot \mathbf{u}(t, \cdot)) \cup \text{supp}(N(t, \cdot)))$ is compactly embedded in Ω_1 ,
- $\bigcup_{t \in [0, T]} \text{supp}(\mathbf{u}(t, \cdot) - \mathbf{s})$ is compactly embedded in Ω_2 ,
- $\mathbf{u}(t = 0, \cdot) = \mathbf{u}_0, N(t = 0, \cdot) = N_0, M(t = 0, \cdot) = M_0, \xi(t = 0) = \xi_0$,
- $\|X\|_{\mathcal{E}_{T_1^\tau}^s} + \|N\|_{L_{T_1^\tau}^\infty; H^s} \leq R$,

therefore $(\tilde{X}, \tilde{N}) := \Phi((X, N), (X_0, N_0), \tau)$ satisfies

- $\bigcup_{t \in [0, T]} (\text{supp}(\mathbf{p} \cdot \tilde{\mathbf{u}}(t, \cdot)) \cup \text{supp}(\tilde{N}(t, \cdot)))$ is compactly embedded in Ω_1 ,
- $\bigcup_{t \in [0, T]} \text{supp}(\tilde{\mathbf{u}}(t, \cdot) - \mathbf{s})$ is compactly embedded in Ω_2 ,
- $\|\tilde{X}\|_{\mathcal{E}_{T_1^\tau}^s} + \|\tilde{N}\|_{L_{T_1^\tau}^\infty; H^s} \leq R$.

(ii) Let $X_0 := (\mathbf{u}_0, M_0, \xi_0) \in \mathcal{E}_0^s$ such that $\text{supp}(\mathbf{u}_0 - \mathbf{s})$ is compactly embedded in Ω_0 .

There exist $R \geq \|X_0\|_{\mathcal{E}_0^s}$ and $T_1 > 0$ depending only on R and the parameters of the model (such as $\gamma_1, \gamma_2, \dots$) such that for any $X := (\mathbf{u}, M, \xi) \in \mathcal{E}_{T_1}^s$ satisfying

- $\bigcup_{t \in [0, T]} \text{supp}(\mathbf{p} \cdot \mathbf{u}(t, \cdot))$ is compactly embedded in Ω_1 ,
- $\bigcup_{t \in [0, T]} \text{supp}(\mathbf{u}(t, \cdot) - \mathbf{s})$ is compactly embedded in Ω_2 ,
- $\mathbf{u}(t = 0, \cdot) = \mathbf{u}_0, M(t = 0, \cdot) = M_0, \xi(t = 0) = \xi_0$,
- $\|X\|_{\mathcal{E}_{T_1}^s} \leq R$,

we deduce that $\tilde{X} := \Psi(X, X_0)$ satisfies

- $\bigcup_{t \in [0, T]} \text{supp}(\mathbf{p} \cdot \tilde{\mathbf{u}}(t, \cdot))$ is compactly embedded in Ω_1 ,
- $\bigcup_{t \in [0, T]} \text{supp}(\tilde{\mathbf{u}}(t, \cdot) - \mathbf{s})$ is compactly embedded in Ω_2 ,
- $\|\tilde{X}\|_{\mathcal{E}_{T_1}^s} \leq R$.

Remark 5.1. The final time T_1^τ dependence on τ is due to (10) and Proposition 4.4 since the speed defined by Φ satisfies

$$\|\mathbf{v}\|_{L_T^2; H^{s+1}} \leq C \left(\|\mathbf{b}(M) \cdot \mathbf{u}\|_{L_T^2; H^s} + \frac{1}{\tau} \|N\|_{L_T^2; H^s} \right).$$

Then Proposition 4.4 requires that $C\sqrt{T}\|\mathbf{v}\|_{L_T^2; H^{s+1}}$ is small enough to obtain

$$\|\tilde{\mathbf{u}}\|_{L_{T_1^\tau}^\infty; H^s}, \|\tilde{N}\|_{L_{T_1^\tau}^\infty; H^s} \leq R.$$

Now we summarize the contraction estimates on $\mathcal{U}, \mathcal{N}, \mathcal{M}$ and Ξ :

Proposition 5.2 (Contraction estimates for Φ and Ψ). *Φ and Ψ satisfy the following contraction estimates:*

(i) For $i = 1, 2$, let $X_{0,i}, N_{0,i}, R, T_1^\tau$ and X_i, N_i as in Proposition 5.1 (i) and denote

$$(\tilde{X}_i, \tilde{N}_i) := \Phi(\Phi((X_i, N_i), (X_{0,i}, N_{0,i}), \tau), (X_{0,i}, N_{0,i}), \tau).$$

Then for all $T \leq T_1^\tau$, one has

$$\begin{aligned} \|(\tilde{X}_1, \tilde{N}_1) - (\tilde{X}_2, \tilde{N}_2)\|_{\mathcal{E}_T^{2,s-1} \times L_T^2; H^{s-1}}^2 &\leq C_R \left(\|(X_{0,1}, N_{0,1}) - (X_{0,2}, N_{0,2})\|_{\mathcal{E}_0^{s-1} \times H^{s-1}}^2 \right. \\ &\quad \left. + T \|(X_1, N_1) - (X_2, N_2)\|_{\mathcal{E}_T^{2,s-1} \times L_T^2; H^{s-1}}^2 \right). \end{aligned} \quad (22)$$

(ii) For $i = 1, 2$, let $X_{0,i}, R, T_1$ and X_i as in Proposition 5.1 (ii) and denote

$$\tilde{X}_i := \Psi(\Psi(X_i, X_{0,i}), X_{0,i}).$$

Then for all $T \leq T_1$, one has

$$\|\tilde{X}_1 - \tilde{X}_2\|_{\mathcal{E}_T^{2,s-1}}^2 \leq C_R \left(\|X_{0,1} - X_{0,2}\|_{\mathcal{E}_0^{s-1}}^2 + T \|X_1 - X_2\|_{\mathcal{E}_T^{2,s-1}}^2 \right). \quad (23)$$

Therefore, taking $X_{0,1} = X_{0,2} = X_0$ and $N_{0,1} = N_{0,2} = N_0$ in the previous Proposition leads to the following result:

Corollary 5.1. *Operators Φ and Ψ satisfy*

(i) Under the assumptions of Proposition 5.1 (i), there exists $0 < T_2^\tau \leq T_1^\tau$ such that

$$\Lambda_\Phi : (X, N) \longmapsto \Phi((X, N), (X_0, N_0), \tau),$$

is such that Λ_Φ^2 is a contraction in the set

$$\mathcal{E}_{\Lambda_\Phi} := \left\{ (X, N) \in \mathcal{E}_{T_2^\tau}^s \times L_{T_2^\tau}^\infty; H^s \text{ such that } \|X\|_{\mathcal{E}_{T_2^\tau}^s} + \|N\|_{L_{T_2^\tau}^\infty; H^s} \leq R \right\}$$

endowed with the usual norm on $\mathcal{E}_{T_2^\tau}^{2,s-1} \times L_{T_2^\tau}^2; H^{s-1}$.

(ii) Under the assumptions of Proposition 5.1 (ii), there exists $0 < T_2 \leq T_1$ such that

$$\Lambda_\Psi : X \longmapsto \Psi(X, X_0),$$

is such that Λ_Ψ^2 is a contraction in the set

$$\mathcal{E}_{\Lambda_\Psi} := \left\{ (\mathbf{u}, M, \xi) \in \mathcal{E}_{T_2}^s \text{ such that } \|X\|_{\mathcal{E}_{T_2}^s} \leq R \right\}$$

endowed with the usual norm on $\mathcal{E}_{T_2}^{2,s-1}$.

Remark 5.2. *The dependence of the final time T_2^τ on τ is the same as in Proposition 5.1.*

Thanks to Proposition 5.1 and Corollary 5.1, we can prove Theorem 3.2.

Proof of Theorem 3.2. We consider $T = T_2^T$ and the set $\mathcal{E}_{\Lambda_\Phi}$ endowed with the usual norm on the Banach space $(L_T^2; H^{s-1})^4 \times L_T^2; H^{s-1} \times L^2(0, T) \times L_T^2; H^{s-1}$. Since the closed unit ball in $L_T^2; H^s$ is compact in the weak topology and the closed unit balls in $L_T^\infty; H^{s-1}$ and in $L_T^\infty; H^s$ are compact in the weak* topology [6], we get that $\mathcal{E}_{\Lambda_\Phi}$ is a closed subspace of $(L_T^2; H^{s-1})^4 \times L_T^2; H^{s-1} \times L^2(0, T) \times L_T^2; H^{s-1}$. Then we apply the contraction mapping theorem in $\mathcal{E}_{\Lambda_\Phi}$ to obtain the existence and uniqueness of the fixed point $(X^\Phi, N^\Phi) \in \mathcal{E}_{\Lambda_\Phi}$ to Λ_Φ^2 . Then applying Λ_Φ to $\Lambda_\Phi^2(X^\Phi, N^\Phi) = (X^\Phi, N^\Phi)$ leads to the existence and uniqueness of the fixed point (X^Φ, N^Φ) to Λ_Φ .

Propositions 4.4 and 4.6 lead to the time continuity of \mathbf{u} and M stated in Theorem 3.2 (i)b. Then from Propositions 4.1 and 4.7 we infer the time continuity of \mathbf{v} and ξ .

By construction of the solution, we get

$$P_1, P_2, P_3, N, S \geq 0, \quad \text{where } (P_1, P_2, P_3, S)^t := \mathbf{u}.$$

In conclusion, the saturation $P_1 + P_2 + P_3 + N + S = 1$ is a consequence of equation satisfied by $P_1 + P_2 + P_3 + N + S$ obtained by summing the equations on P_1, P_2, P_3, N and S and Gronwall's inequality.

The exact same reasoning holds for Λ_Ψ . □

Remark 5.3. Remark 3.2 is a consequence of Theorem 3.2 and Proposition 5.2, assuming that $C_R T \leq \frac{1}{2}$ in Proposition 5.2.

6 Limit when $\tau \rightarrow 0$

The goal of this section is to prove Theorem 3.3, which is the asymptotic behavior of model (3) for $\tau \rightarrow 0^+$ towards model (4).

In the previous section, the time of existence $T > 0$ depends *a priori* on the norm of \mathbf{v} , which depends itself on τ thanks to (3e). More precisely, if we look at the proof of existence, we can see that this time depends only on $\|\mathbf{v}\|_{L_T^2; H^{s+1}}$. Note that according to Remark 5.1, this norm could blow up when $\tau \rightarrow 0^+$. Our first goal consists in finding a bound to ensure that the time of existence does not depend on τ . In the last subsection, we perform the asymptotic analysis to get the convergence of model (3) to model (4).

6.1 Uniform bound on the final time of existence

Let $\tau > 0$ be given. Let \mathbf{u} , M , \mathbf{v} and N as in Theorem 3.2 (i). According to Remark 5.1, \mathbf{v} satisfies

$$\|\mathbf{v}\|_{L_T^2; H^{s+1}} \leq C \left(\|\mathbf{b}(M) \cdot \mathbf{u}\|_{L_T^2; H^s} + \frac{1}{\tau} \|N\|_{L_T^2; H^s} \right). \quad (24)$$

The right-hand side blows up as $\tau \rightarrow 0^+$. The goal of the following results is to prove more precise estimates. First let us prove the next Lemma:

Lemma 6.1. *Under the assumptions of Theorem 3.2 (i), N satisfies the following inequality:*

$$\begin{aligned} \left(\frac{1}{\sqrt{\tau}} \|N\|_{L_T^\infty; H^s} \right)^2 + \left(\frac{1}{\tau} \|N\|_{L_T^2; H^s} \right)^2 &\leq C\sqrt{T} \left(\|\mathbf{b}(M) \cdot \mathbf{u}\|_{L_T^2; H^s} + \frac{1}{\tau} \|N\|_{L_T^2; H^s} \right) \\ &\quad \times \left(\frac{1}{\sqrt{\tau}} \|N\|_{L_T^\infty; H^s} \right)^2 \\ &\quad + C\|\mathbf{d}(M) \cdot \mathbf{u}\|_{L_T^2; H^s}^2 + \left(\frac{1}{\sqrt{\tau}} \|N_0\|_{H^s} \right)^2. \end{aligned} \quad (25)$$

where C does not depend on τ .

Proof. We consider the equation satisfied by $\frac{N}{\sqrt{\tau}}$:

$$\partial_t \left(\frac{N}{\sqrt{\tau}} \right) + \nabla \cdot \left(\mathbf{v} \frac{N}{\sqrt{\tau}} \right) = \frac{\mathbf{d}(M) \cdot \mathbf{u}}{\sqrt{\tau}} - \frac{1}{\tau} \left(\frac{N}{\sqrt{\tau}} \right), \quad (26)$$

Let $m \in \mathbb{N}$ such that $m \leq s$. Apply ∂_x^m to (26), multiply by $\partial_x^m(1/\sqrt{\tau})N$ and apply Lemma 4.1 to $\partial_x^m \nabla \cdot (\mathbf{v}(1/\sqrt{\tau})N) \partial_x^m(1/\sqrt{\tau})N$, sum over $m \leq s$ and use (24). This leads to

$$\begin{aligned} \frac{1}{2} \partial_t \left(\frac{1}{\sqrt{\tau}} \|N\|_{H^s} \right)^2 &\leq C \left(\|\mathbf{b}(M) \cdot \mathbf{u}\|_{H^s} + \left(\frac{1}{\tau} \|N\|_{H^s} \right) \right) \left(\frac{1}{\sqrt{\tau}} \|N\|_{H^s} \right)^2 \\ &\quad + C\|\mathbf{d}(M) \cdot \mathbf{u}\|_{H^s} \left(\frac{1}{\tau} \|N\|_{H^s} \right) - \frac{1}{\tau} \left(\frac{1}{\sqrt{\tau}} \|N\|_{H^s} \right)^2. \end{aligned}$$

Applying Young's inequality, we obtain for almost any time $t \in [0, T]$:

$$\begin{aligned} \frac{1}{2} \partial_t \left(\frac{1}{\sqrt{\tau}} \|N\|_{H^s} \right)^2 &\leq C \left(\|\mathbf{b}(M) \cdot \mathbf{u}\|_{H^s} + \left(\frac{1}{\tau} \|N\|_{H^s} \right) \right) \left(\frac{1}{\sqrt{\tau}} \|N\|_{H^s} \right)^2 \\ &\quad + \frac{1}{2} \left(C^2 \|\mathbf{d}(M) \cdot \mathbf{u}\|_{H^s}^2 + \frac{1}{\tau} \left(\frac{1}{\sqrt{\tau}} \|N\|_{H^s} \right)^2 \right) - \frac{1}{\tau} \left(\frac{1}{\sqrt{\tau}} \|N\|_{H^s} \right)^2, \end{aligned}$$

then integrate between time 0 and t and take the supremum for $t \in [0, T]$ to obtain

$$\begin{aligned} \left(\frac{1}{\sqrt{\tau}} \|N\|_{L_T^\infty; H^s} \right)^2 + \left(\frac{1}{\tau} \|N\|_{L_T^2; H^s} \right)^2 &\leq C \left(\|\mathbf{b}(M) \cdot \mathbf{u}\|_{L_T^1; H^s} + \frac{1}{\tau} \|N\|_{L_T^1; H^s} \right) \\ &\quad \times \left(\frac{1}{\sqrt{\tau}} \|N\|_{L_T^\infty; H^s} \right)^2 \\ &\quad + C\|\mathbf{d}(M) \cdot \mathbf{u}\|_{L_T^2; H^s}^2 + \left(\frac{1}{\sqrt{\tau}} \|N_0\|_{H^s} \right)^2, \end{aligned}$$

and estimate the L_T^1 -norm by the L_T^2 -norm to conclude the proof. \square

The previous Lemma makes it possible to prove the following result:

Lemma 6.2. *Assume the assumptions of Theorem 3.2 (i) hold. Denote by*

$$\begin{aligned} Y_1 &:= \|\mathbf{u}\|_{L_T^\infty; H^s}, \\ Y_2 &:= \sqrt{\|M\|_{L_T^\infty; H^{s-1}}^2 + \|M\|_{L_T^2; H^s}^2}, \\ Y_3 &:= \|\xi\|_\infty, \\ Y_4 &:= \sqrt{((1/\sqrt{\tau})\|N\|_{L_T^\infty; H^s})^2 + ((1/\tau)\|N\|_{L_T^2; H^s})^2}. \end{aligned}$$

Then $\mathbf{Y} := (Y_1, Y_2, Y_3, Y_4)$ satisfies the following estimates

$$Y_i^2 \leq F(T, \mathbf{Y}), \quad i = 1, \dots, 4, \quad (27)$$

where

$$\begin{aligned} F_1(T, \mathbf{Y}) &= \left(\|\mathbf{u}_0\|_{H^s}^2 + C\sqrt{T}(Y_1Y_2 + Y_4) \right) \exp\left(C\sqrt{T}(Y_1Y_2 + Y_4) \right), \\ F_2(T, \mathbf{Y}) &= \left[1 + (\|M_0\|_{H^{s-1}}^2 + CT(Y_1^2 + Y_3^2)) \exp(CT(1 + Y_1^2 + Y_3^2)) \right] \\ &\quad \times \left[1 + CT(1 + Y_1^2 + Y_3^2) \right] + 1 + \|M_0\|_{H^{s-1}}^2 + CT(Y_1^2 + Y_3^2), \\ F_3(T, \mathbf{Y}) &= |\xi_0|^2 + CTY_1^2 \exp(CT), \\ F_4(T, \mathbf{Y}) &= C \left[\sqrt{T}Y_4^2(Y_1Y_2 + Y_4) + F_1(T, \mathbf{Y})^2 F_2(T, \mathbf{Y})^2 \right] + \left(\frac{1}{\sqrt{\tau}} \|N_0\|_{H^s} \right)^2. \end{aligned}$$

Proof. The estimates on Y_1^2, Y_2^2 and Y_3^2 are simply consequence of stability estimates on \mathcal{U}, \mathcal{M} and Ξ given by Proposition 4.4, 4.6 and 4.7. For the estimates on Y_4^2 , the estimate (25) leads to

$$Y_4^2 \leq C \left[\sqrt{T}Y_4^2(Y_1Y_2 + Y_4) + Y_1^2Y_2^2 \right] + \left(\frac{1}{\sqrt{\tau}} \|N_0\|_{H^s} \right)^2,$$

and we use (27) to bound $Y_1^2Y_2^2$ by $F_1(T, \mathbf{Y})^2 F_2(T, \mathbf{Y})^2$. □

Now we can prove that, for T small enough, \mathbf{Y} is uniformly bounded with respect to τ . For any $R > 0$ one has

$$\lim_{T \rightarrow 0^+} F_i(T, (R, R, R, R)) = \begin{cases} \|\mathbf{u}_0\|_{H^s}^2, & \text{if } i = 1, \\ 2(1 + \|M_0\|_{H^{s-1}}^2), & \text{if } i = 2, \\ |\xi_0|^2, & \text{if } i = 3, \\ \left(2C\|\mathbf{u}_0\|_{H^s}^2(1 + \|M_0\|_{H^{s-1}}^2) + \frac{1}{\sqrt{\tau}} \|N_0\|_{H^s} \right)^2, & \text{if } i = 4. \end{cases}$$

Assume there exists $C > 0$ such that

$$\forall \tau > 0, \quad \left(\frac{1}{\sqrt{\tau}} \|N_0\|_{H^s} \right)^2 \leq C,$$

then we take $R = \sqrt{2 \max(\|\mathbf{u}_0\|_{H^s}^2, 2(1 + \|M_0\|_{H^{s-1}}^2), |\xi_0|^2, 2C\|\mathbf{u}_0\|_{H^s}^2(1 + \|M_0\|_{H^{s-1}}^2) + C)}$ and we obtain that there exists $T > 0$, which depends only on R , such that $Y_i^2 \leq R^2$ for $1 \leq i \leq 4$. We thus have proved the following result

Proposition 6.1. *Assume the assumptions of Theorem 3.2 (i) hold. If there exists $C > 0$ such that*

$$\forall \tau > 0, \quad \|\mathbf{u}_0\|_{H^s}^2 + \|M_0\|_{H^{s-1}}^2 + |\xi_0|^2 + \left(\frac{1}{\sqrt{\tau}} \|N_0\|_{H^s} \right)^2 \leq C,$$

then there exists $R > 0$ and $T > 0$ such that

$$\begin{aligned} \forall \tau > 0, \quad & \left(\frac{1}{\sqrt{\tau}} \|N\|_{L_T^\infty; H^s} \right)^2 + \left(\frac{1}{\tau} \|N\|_{L_T^2; H^s} \right)^2 \leq R^2, \\ & \|\mathbf{u}\|_{L_T^\infty; H^s}^2 \leq R^2, \\ & \|M\|_{L_T^\infty; H^{s-1}}^2 + \|M\|_{L_T^2; H^s}^2 \leq R^2, \\ & \|\xi\|_\infty^2 \leq R^2. \end{aligned}$$

Therefore the time of existence of the solution to (3) is independent of τ .

In order to finish the asymptotic analysis, we also need estimates on the time derivative of \mathbf{u} , M , ξ and N :

Corollary 6.1. *Under the assumptions of Proposition 6.1, there exists $C_R > 0$, such that for any $\tau > 0$ small enough*

- (i) $\|\partial_t \mathbf{u}\|_{L_T^2; H^{s-1}}^2 \leq C_R$,
- (ii) $\|\partial_t M\|_{L_T^2; H^{s-1}}^2 \leq C_R$,
- (iii) $\|\partial_t \xi\|_\infty^2 \leq C_R$,
- (iv) $\|\partial_t N\|_{L_T^2; H^{s-1}}^2 \leq C_R \left(\tau + \left(\frac{1}{\sqrt{\tau}} \|N_0\|_{H^s} \right)^2 \right)$.

Proof. (i) and (iii) are consequences of equations (3a), (3j) and Proposition 6.1.

To prove (ii), differentiate in time equation (3h) and apply Proposition 4.5 with $s' = s - 1$ and

$$\begin{aligned} \tilde{M} &:= \partial_t M, \\ \tilde{M}_0 &:= 0, \\ \mathbf{w}_1 &:= \xi \nabla(\mathbf{p} \cdot \mathbf{u}), \\ \mathbf{w}_2 &:= M \partial_t \mathbf{w}_1, \\ a &:= -(\eta \mathbf{p} + C_0 \mathbf{s}) \cdot \mathbf{u}, \\ b &:= \partial_t(\eta \mathbf{p} \cdot \mathbf{u}) + M \partial_t a. \end{aligned}$$

Then Proposition 6.1 and previous estimates on $\partial_t \mathbf{u}$ and $\partial_t \xi$ leads to (ii).

To prove (iv), we denote by $\tilde{N} := \partial_t N$, then \tilde{N} satisfies

$$\partial_t \tilde{N} + \nabla \cdot (\mathbf{v} \tilde{N}) = -\nabla \cdot (\partial_t \mathbf{v} N) + \partial_t (\mathbf{d}(M) \cdot \mathbf{u}) - \frac{1}{\tau} \tilde{N}.$$

Applying Lemma 4.1 leads to

$$\frac{1}{2}\|\tilde{N}\|_{H^{s-1}}^2 \leq \left[C\|\mathbf{v}\|_{H^s} - \frac{1}{\tau} \right] \|\tilde{N}\|_{H^{s-1}}^2 + C(\|\partial_t \mathbf{v}\|_{H^s} \|N\|_{H^s} + \|\partial_t (\mathbf{d}(M) \cdot \mathbf{u})\|_{H^{s-1}}) \|\tilde{N}\|_{H^{s-1}},$$

Thanks to equation (3e) and Proposition 6.1, we have the following estimates

$$\|\mathbf{v}\|_{L_T^\infty; H^s} \leq C_R \left(1 + \frac{1}{\sqrt{\tau}} \right), \quad (28)$$

and for almost any $t \in [0, T]$:

$$\|\partial_t \mathbf{v}\|_{H^s} \|N\|_{H^s} \leq C_R \left(\|\partial_t (\mathbf{b}(M) \cdot \mathbf{u})\|_{H^{s-1}} + \frac{1}{\sqrt{\tau}} \|\tilde{N}\|_{H^{s-1}} \right),$$

these estimates lead to

$$\begin{aligned} \frac{1}{2}\|\tilde{N}\|_{H^{s-1}}^2 &\leq \left[C_R \left(1 + \frac{1}{\sqrt{\tau}} \right) - \frac{1}{\tau} \right] \|\tilde{N}\|_{H^{s-1}}^2 \\ &\quad + C_R (\|\partial_t (\mathbf{b}(M) \cdot \mathbf{u})\|_{H^{s-1}} + \|\partial_t (\mathbf{d}(M) \cdot \mathbf{u})\|_{H^{s-1}}) \|\tilde{N}\|_{H^{s-1}}. \end{aligned}$$

Apply Young's formula to $C_R (\|\partial_t (\mathbf{b}(M) \cdot \mathbf{u})\|_{H^{s-1}} + \|\partial_t (\mathbf{d}(M) \cdot \mathbf{u})\|_{H^{s-1}}) \|\tilde{N}\|_{H^{s-1}}$, then for τ small enough, \tilde{N} satisfies the following estimate:

$$\|\tilde{N}\|_{H^{s-1}}^2 + \frac{1}{\tau} \|\tilde{N}\|_{H^{s-1}}^2 \leq C_R (\|\partial_t (\mathbf{b}(M) \cdot \mathbf{u})\|_{H^{s-1}}^2 + \|\partial_t (\mathbf{d}(M) \cdot \mathbf{u})\|_{H^{s-1}}^2).$$

Integrate the previous estimate between time 0 and time t and take the supremum for $t \in [0, T]$ to obtain

$$\begin{aligned} \|\tilde{N}\|_{L_T^\infty; H^{s-1}}^2 + \frac{1}{\tau} \|\tilde{N}\|_{L_T^2; H^{s-1}}^2 &\leq \|\tilde{N}(0, \cdot)\|_{H^{s-1}}^2 \\ &\quad + C_R \left(\|\partial_t (\mathbf{b}(M) \cdot \mathbf{u})\|_{L_T^2; H^{s-1}}^2 + \|\partial_t (\mathbf{d}(M) \cdot \mathbf{u})\|_{L_T^2; H^{s-1}}^2 \right). \end{aligned}$$

Thanks to Proposition 6.1 and previous estimates on $\partial_t \mathbf{u}$ and $\partial_t M$, there exists $C_R > 0$ such that for any $\tau > 0$ small enough

$$\|\tilde{N}\|_{L_T^\infty; H^{s-1}}^2 + \frac{1}{\tau} \|\tilde{N}\|_{L_T^2; H^{s-1}}^2 \leq \|\tilde{N}(0, \cdot)\|_{H^{s-1}}^2 + C_R. \quad (29)$$

We focus on the term $\|\tilde{N}(0, \cdot)\|_{H^{s-1}}^2$. Thanks to (3c), $\tilde{N}(0, \cdot)$ satisfies

$$\tilde{N}(0, \cdot) + \nabla \cdot (\mathbf{v}(0, \cdot) N_0) = \mathbf{d}(M_0) \cdot \mathbf{u}_0 - \frac{1}{\tau} N_0,$$

then we have the following estimate

$$\|\tilde{N}(0, \cdot)\|_{H^{s-1}} \leq C\|\mathbf{v}(0, \cdot)\|_{H^s} \|N_0\|_{H^s} + C\|M_0\|_{H^{s-1}} \|\mathbf{u}_0\|_{H^{s-1}} + \frac{1}{\tau} \|N_0\|_{H^{s-1}}.$$

Thanks to (28), we have

$$\|\tilde{N}(0, \cdot)\|_{H^{s-1}}^2 \leq C_R \left(1 + \frac{1}{\tau^2} \|N_0\|_{H^s}^2 \right),$$

then multiply (29) by τ and omit the non-negative term $\|\tilde{N}\|_{L_T^\infty; H^{s-1}}^2$ to obtain

$$\|\tilde{N}\|_{L_T^2; H^{s-1}}^2 \leq C_R \left(\tau + \frac{1}{\tau} \|N_0\|_{H^s}^2 \right). \quad (30)$$

□

6.2 The limit case τ tends to 0

Proposition 6.1 makes it possible to pass to the limit when $\tau \rightarrow 0^+$ and implies also that N converges to 0 in $L_T^\infty; H^s$. However the assumption that $(1/\sqrt{\tau})\|N_0\|_{H^s} \leq C$ is not sufficient to prove the convergence of the whole solution $((\mathbf{u}^\tau, M^\tau, \xi^\tau), \mathbf{v}^\tau, N^\tau)$. We need to suppose that $(1/\sqrt{\tau})\|N_0\|_{H^s} \rightarrow 0$ when $\tau \rightarrow 0^+$ to get Theorem 3.3. Actually the following Lemma ends the proof of Theorem 3.3:

Lemma 6.3. *For any $\tau > 0$, let X_0^τ, N_0^τ, X_0 be as in Theorem 3.2 and Theorem 3.3 and denote by*

- (X^τ, N^τ) the solution to $(X^\tau, N^\tau) = \Phi((X^\tau, N^\tau), (X_0^\tau, N_0^\tau), \tau)$,
- X the solution to $X = \Psi(X, X_0)$.

Then $\lim_{\tau \rightarrow 0^+} \|X^\tau - X\|_{\mathcal{E}_T^{2,s-1}}^2 = 0$.

Proof. Assumptions and Proposition 6.1 ensures that there exists $R > 0$ (depending only on X_0^τ, N_0^τ and X_0) such that for any $\tau > 0$, X^τ , $(1/\tau)N^\tau$ and X are bounded by R .

Denote by $(\mathbf{u}^\tau, M^\tau, \xi^\tau) := X^\tau$ and by $(\mathbf{u}, M, \xi) := X$. Remind the contraction estimates on \mathcal{U}, \mathcal{M} and Ξ :

$$\begin{aligned} \|\mathbf{u}^\tau - \mathbf{u}\|_{L_T^2; H^{s-1}} &\leq C_R T \left(\|\mathbf{u}_0^\tau - \mathbf{u}_0\|_{H^{s-1}}^2 + \|\mathbf{v}^\tau - \mathbf{v}\|_{L_T^2; H^s}^2 + \|M^\tau - M\|_{L_T^2; H^{s-1}}^2 \right), \\ \|M^\tau - M\|_{L_T^2; H^{s-1}} &\leq C_R \left(\|M_0^\tau - M_0\|_{H^{s-2}}^2 + \|\mathbf{u}^\tau - \mathbf{u}\|_{L_T^2; H^{s-1}}^2 + \|\xi^\tau - \xi\|_{L_T^2}^2 \right), \\ \|\xi^\tau - \xi\|_{L_T^2} &\leq C_R T \left(|\xi_0^\tau - \xi_0|^2 + \|\mathbf{u}^\tau - \mathbf{u}\|_{L_T^2; L^1}^2 + \|M^\tau - M\|_{L_T^2; L^1}^2 \right). \end{aligned}$$

We need to find an estimate on $\mathbf{v}^\tau - \mathbf{v}$. Observe that

$$\begin{aligned} \mathbf{v}^\tau - \mathbf{v} &= \mathcal{V}(\mathbf{b}(M^\tau) \cdot \mathbf{u}^\tau - (1/\tau)N^\tau) - \mathcal{V}((\mathbf{b}(M) - \mathbf{d}(M)) \cdot \mathbf{u}), \\ &= \mathcal{V}((\mathbf{b}(M^\tau) - \mathbf{d}(M^\tau)) \cdot \mathbf{u}^\tau - (\mathbf{b}(M) - \mathbf{d}(M)) \cdot \mathbf{u}) + \mathcal{V}(\mathbf{d}(M^\tau) \cdot \mathbf{u}^\tau - (1/\tau)N^\tau), \end{aligned}$$

then we obtain the following estimate:

$$\|\mathbf{v}^\tau - \mathbf{v}\|_{L_T^2; H^s}^2 \leq C_R \left(\|\mathbf{u}^\tau - \mathbf{u}\|_{L_T^2; H^{s-1}}^2 + \|M^\tau - M\|_{L_T^2; H^{s-1}}^2 + \varepsilon^\tau \right),$$

where $\varepsilon^\tau = \|\mathbf{d}(M^\tau) \cdot \mathbf{u}^\tau - (1/\tau)N^\tau\|_{L_T^2; H^{s-1}}^2$. Thanks to Proposition 6.1 and Corollary 6.1 and using the fact that $(1/\sqrt{\tau})\|N_0\|_{H^s} \rightarrow 0$, we obtain

$$\lim_{\tau \rightarrow 0^+} \|\partial_t N^\tau\|_{L_T^2; H^{s-1}}^2 + \|\nabla \cdot (\mathbf{v}^\tau N^\tau)\|_{L_T^2; H^{s-1}}^2 = 0,$$

then equation (3c) ensures that $\lim_{\tau \rightarrow 0^+} \varepsilon^\tau = 0$.

Making a summary of previous estimates (for $M^\tau - M$, use the estimates on $\mathbf{u}^\tau - \mathbf{u}$ and $\xi^\tau - \xi$ to obtain the T term) leads to

$$\|X^\tau - X\|_{\mathcal{E}_T^{2,s-1}}^2 \leq C_R \left(\|X_0^\tau - X_0\|_{\mathcal{E}_0^{s-1}}^2 + T \|X^\tau - X\|_{\mathcal{E}_T^{2,s-1}}^2 + \varepsilon^\tau \right),$$

then we assume that $C_R T \leq \frac{1}{2}$ to get

$$\|X^\tau - X\|_{\mathcal{E}_T^{2,s-1}}^2 \leq C_R \left(\|X_0^\tau - X_0\|_{\mathcal{E}_0^{s-1}}^2 + \varepsilon^\tau \right),$$

this conclude the proof of the Lemma. □

7 Conclusion

A constructive proof of the solution to our model has been derived. The main idea of the proof was that the tumor remains compactly supported in the domain of interest up to a given time. We proved that the minimum time for well-posedness can be bounded independently of the characteristic time τ of necrosis evacuation. This made it possible to prove that our model is consistent with the model without necrosis, which means that the solution to the model without necrosis is given as the limit of solutions for τ goes to 0. This result ensures that our model can describe continuously both situation with or without necrosis.

Acknowledgments

The authors wish to acknowledge Frédéric Lagoutière who started this study. This study has been carried out with financial support from the French State, managed by the French National Research Agency (ANR) in the frame of the "Investments for the future" Programme IdEx Bordeaux - CPU (ANR-10-IDEX-03-02).

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ISSN 0249-6399