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

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

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Abstract: In this paper we study a partial differential equations model for tumour growth taking into account drug resistance. It is well known that angiogenesis, the process of creation of new blood vessels from existing ones, is induced by tumour cells to get the amount of nutrients and oxygen needed to continue their proliferation when the tumour has reached a critical size. Angiogenesis is therefore a target for therapy. The model we study takes into account two kinds of treatments: a cytotoxic treatment and a treatment which is both cytotoxic and anti-angiogenic. It is based on mass-balance equations on cells densities coupled with a diffusion equation for the nutrients and oxygen concentration. In a first part we prove that the model is well-posed if the initial tumour is compactly supported in the domain, which is the case for tumour metastases. The proof states that the tumour remains compactly supported in a finite time. In the model, we also consider the presence of a necrotic compartment composed of dead cells. Since some tumours can present necrosis while other do not, we want a model which can reproduce these two different cases. The second part of this paper is devoted to an asymptotic analysis which proves that the absence of necrosis is the limit case of our model when the necrosis is immediately evacuated.

Key-words: Tumour growth modelling; partial differential equations; asymptotic analysis.

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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 croissance tumorale. Ce modèle prend en compte l'effet du traitement et la résistance au traitement. Lorsqu'une tumeur a atteint une taille critique, celle-ci va émettre un signal afin d'engendrer l'angiogénèse, la création de nouveaux vaisseaux sanguins à partir de la vascularisation existante, dans le but d'obtenir la quantité de nutriments et d'oxygène nécessaire à sa prolifération. Le processus d'angiogénèse étant une cible de traitement possible, nous considérons dans notre modèle deux types de traitements: un premier traitement uniquement cytotoxique et un second traitement qui a à la fois un effet cytotoxique et un effet anti-angiogénique. Le modèle est basé sur des équations de conservation de la masse sur les densités de cellules couplées à une équation de diffusion pour la concentration en nutriments et en oxygène. Dans une première partie, nous prouvons que le modèle est bien posé lorsque la condition initiale sur la tumeur est à support compact dans le domaine considéré, ce qui est le cas pour les métastases, qui présentent un contour bien net. La preuve montre que dans ces conditions la tumeur reste localisée dans un compact en temps fini. Le modèle prend également en compte un compartiment de nécrose, constitué des cellules mortes. Comme certaines tumeurs présentent de la nécrose tandis que d'autres tumeurs n'en présentent pas, nous souhaitons que le modèle puisse reproduire ces deux phénomènes. La seconde partie de cet article est consacrée à une analyse asymptotique qui montre que l'absence de nécrose est le cas limite de notre modèle lorsque la nécrose est évacuée immédiatement.

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

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1 Introduction

The impact of mathematical modelling in biology has increased dramatically during the last two decades. It is especially the case in oncology, where the amount of biological knowledge combined to the data obtained by invasive and non invasive techniques allowed the elaboration of more and more accurate models of tumour growth and the impact of treatments.

Several kinds of mathematical models for solid tumour growth have been developed (for instance discrete, ordinary differential equations (ODE) or partial differential equations (PDE) models. ODE models give a good approximation on the tumour area or mass but do not account for the spatial behaviour of the tumour neither its spatial heterogeneity. Discrete models like cellular automata and agent-based models [7] are good to reproduce the growth at the cell-scale but it is still difficult to reproduce the behaviour at the organ level. PDE models can accurately reproduce the spatial behaviour at the tumour-scale even if they are less accurate for small scales. In this work, we attend to study clinical cases in relation with medical imaging. We work therefore at the organ level and we will focus on PDE model. There exist several kinds of PDE models for tumour growth [9]. While models based on reaction-diffusion equation are used to describe the active motion of tumour cells in the case of invasive tumours (see [10] or in the case of brain gliomas see [14]), models based on mass-balance equations on cells densities are used when the growth is only a consequence of cell proliferation. Roughly speaking, the shapes of primitive tumours are more complex and primitive tumours are more invasive. It is therefore difficult to define precisely the boundary of the tumour. On the other hand, metastases are usually more regular, with sharp interfaces. These interfaces can be described using free boundary methods [12] or a multiphase mixture, considering both cell densities and extracellular matrix [13]. The model we study comes from [3] and is based on mass-balance equations. It describes spatial heterogeneity as a mixture of several cell populations. For the closure of the model, we assume that the tumour behaves like a fluid in a porous media and we consider a Darcy law for the speed of advection of the boundary [2]. Other models like visco-elastic laws

can be studied [4]. These models may account for more phenomena, but their complexity is too high for clinical applications while Darcy law is sufficient in a first approximation to address some clinical cases [6].

Our model is intended for clinical applications, using imaging data (as CT scans) to reproduce the evolution of the tumour, quantify the treatment efficiency and possibly predict relapse. We therefore also need to model drug resistance. It is well known that mutations will lead to the creation of tumour cells which are resistant to cytotoxic drugs. Since we cannot get data on such mutations which can depend on several parameters (such as treatment time, patient variability, external conditions), we will not model these mutations and will assume that tumour cells resistant to some treatment are already present and will compete with other tumour cells. Moreover, this assumption is realistic because the initial time we use in the model is the time of tumour detection, which is obviously not the initial time of the tumour. We also model the process of angiogenesis and consider the application of an antiangiogenic treatment. Angiogenesis is the process in which the tumour emits a signal to create new blood vessels from the existing vasculature to get nutrients and oxygen. This signal is a secretion of vascular endothelial growth factor (VEGF, see [8]) secreted by the hypoxic cells. For the medical prognosis, an other important factor to model is the presence or absence of necrosis. The necrosis is composed of dead cells, the cells can die because of the cytotoxic drugs or hypoxia (the lack of oxygen/nutrients). For some tumours, few necrotic tissues are visible (see first line of Fig. 1: lung metastasis on the left and meningioma on the right). For more aggressive tumours like glioblastoma (line two, on the right of Fig. 1), some parts of the tumour can contain only necrotic tissues, while for other lesions like GIST metastases to the liver (line two, on the left of Fig. 1), the necrotic cells are more diffuse inside the tumour. The basis of the model is presented in [3]. This model has already been simulated and confronted to clinical data in [11], these simulations show that we must take into account spatial heterogeneity.

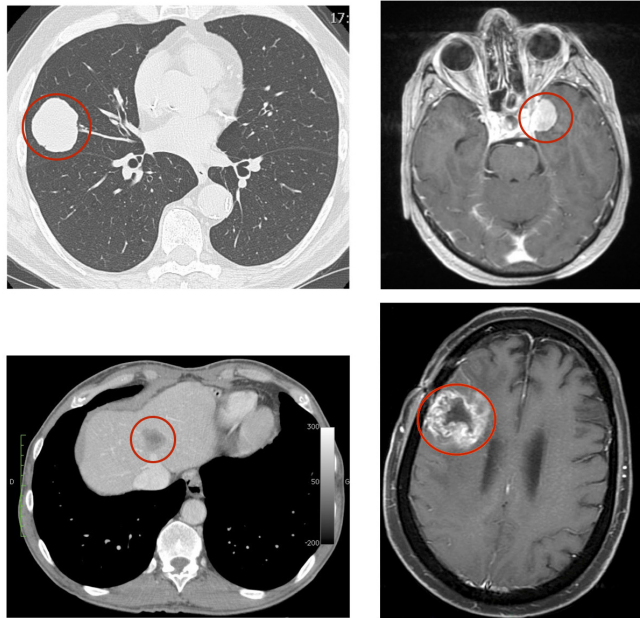


Figure 1: From the left to the right and the top to the bottom: metastasis to the lung, brain meningioma, GIST metastasis to the liver, brain glioma.

The main objective of this paper is to study mathematically this model and to prove that this model can be used to describe the three kinds of necrosis presented above in a continuous way.

The outline of the present paper is the following. In Section 2 we present briefly the model we study. We will consider the model in a bounded domain in the case of dimension 2 or 3 in space. Then we present the model without necrosis which can be seen as the limit model when the necrosis is immediately evacuated. In Section 3 we state the main results. In Section 4, we prove the well-posedness result. The proof is based on a fixed-point method and uses classical estimates for hyperbolic, elliptic and parabolic equations. Then in Section 5, we perform an asymptotic analysis. In the model we assume that the necrosis is evacuated with a characteristic time. The asymptotic analysis shows that the solution of the model converges to the solution to the model without necrosis when the evacuation time of the necrosis converges to zero.

2 The model

We consider the following model on a bounded domain Ω in \mathbb{R}^2 or \mathbb{R}^3 , where \mathbf{n} denotes the outward normal to Ω .

$$\partial_t P_1 + \nabla \cdot (\mathbf{v}P_1) = (\gamma_1(M) - \gamma_2(M))P_1 - (\mu_1 + \mu_2)MP_1, \quad (1a)$$

$$\partial_t P_2 + \nabla \cdot (\mathbf{v}P_2) = (\gamma_1(M) - \gamma_2(M))P_2 - \mu_2MP_2, \quad (1b)$$

$$\partial_t P_3 + \nabla \cdot (\mathbf{v}P_3) = (\gamma_1(M) - \gamma_2(M))P_3, \quad (1c)$$

$$\partial_t N + \nabla \cdot (\mathbf{v}N) = (\mu_1 + \mu_2)MP_1 + \mu_2MP_2 + \gamma_2(M)P - (1/\tau)N, \quad (1d)$$

$$\partial_t S + \nabla \cdot (\mathbf{v}S) = 0, \quad (1e)$$

$$P_1 = P_2 = P_3 = N = 1 - S = 0, \quad \text{if } \mathbf{v} \cdot \mathbf{n} < 0 \text{ on } \partial\Omega, \quad (1f)$$

$$\nabla \cdot \mathbf{v} = \gamma_1(M)P - (1/\tau)N, \quad (1g)$$

$$\mathbf{v} = -k\nabla\Pi, \quad (1h)$$

$$\Pi|_{\partial\Omega} = 0, \quad (1i)$$

$$\partial_t M - \Delta M + \nabla \cdot (M\xi\nabla P) = -\eta MP + C_0 S(1 - M), \quad (1j)$$

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

$$\partial_t \xi = \alpha \int_{\Omega} \frac{\gamma_2(M)}{\max \gamma_2} [(1 - \nu_2)(P_1 + P_2) + P_3] dx - \lambda \xi, \quad (1l)$$

with initial conditions for P_1, P_2, P_3, N, S, M and ξ .

In this model we consider the application of two treatments. The first one \mathcal{T}_1 is a cytotoxic treatment and the second one \mathcal{T}_2 is both cytotoxic and antiangiogenic. We denote by P_1 the density of the proliferative cells which are assumed to be sensitive to the two treatments \mathcal{T}_1 and \mathcal{T}_2 , while P_2 denotes the density of proliferative cells which are assumed to be resistant to first treatment and sensitive to the second treatment and P_3 denotes the cells which are resistant to both treatments. We denote by $P := P_1 + P_2 + P_3$. M is a function related to the vascularization of the tumour, it is assumed to come from the health tissue. The growth rate of these two kinds of cells is assumed to be the same and is denoted by $\gamma_1(M) - \gamma_2(M)$, where γ_1 and γ_2 are positive functions, standing respectively for the proliferative rate and the death rate due to hypoxia. For example, we take for γ_1, γ_2 regularizations of the unit step:

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

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

We model the efficiency of the treatments with the parameters μ_1 and μ_2 which describe the cytotoxic effect of treatments \mathcal{T}_1 and \mathcal{T}_2 respectively. We assume that the absorption is proportional to the rate of oxygen.

We assume that the tumour is moving at speed \mathbf{v} thanks to the increase of its volume.

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.

We denote by S the density of the healthy cells. Since their metabolism is slow compared to the metabolism of proliferative cells, S is assumed to satisfy the equation (1e).

The equation (1g) on \mathbf{v} is obtained by summing the equations (1a) to (1e) and adding a saturation assumption:

$$P + N + S = 1. \quad (3)$$

ξ stands for the signal produced by the tumour cells to involve angiogenesis, it is assumed to be global at any time and proportional to the number of cells dying by hypoxia, which are the fraction $\frac{\gamma_2(M)}{\max \gamma_2}$. The parameter ν_2 stands for the antiangiogenic effect of treatment \mathcal{T}_2 and the parameter λ is the coefficient of absorption of this signal by the organism.

For further explanations on the model, see [3, 11].

Notations 2.1. For all $\alpha \in \mathbb{R}^n, \beta \in \mathbb{R}^m$ we denote

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

We define

$$\mathbf{u} := (P_1, P_2, P_3, N, S)^t,$$

We denote $\gamma(M) := \gamma_1(M) - \gamma_2(M)$. Now we define

$$A(M) := \begin{pmatrix} \gamma(M) - (\mu_1 + \mu_2)M & 0 & 0 & 0 & 0 \\ 0 & \gamma(M) - \mu_2 M & 0 & 0 & 0 \\ 0 & 0 & \gamma(M) & 0 & 0 \\ \gamma_2(M) + (\mu_1 + \mu_2)M & \gamma_2(M) + \mu_2 M & \gamma_2(M) & -1/\tau & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\mathbf{\Gamma}(M) := (\gamma_1(M), \gamma_1(M), \gamma_1(M), -1/\tau, 0)^t.$$

We rewrite (1a)-(1e) as follows

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

and (1g) is rewritten as follows

$$\nabla \cdot \mathbf{v} = \mathbf{\Gamma}(M) \cdot \mathbf{u}.$$

In the following we denote by $P := P_1 + P_2 + P_3$.

3 Main results and interpretation

In this paper we prove the local existence and uniqueness of the solution to the problem (1), under appropriate assumptions on the initial data and the boundary.

In our study, we work in a $d = 2$ or 3 dimensional domain denoted by Ω .

Definition 3.1. *For the spatial regularity, we use the Sobolev space $H^s(\Omega)$ with $s > d/2 + 2$ such that all the products in the equations are well-defined. To simplify the computations we also assume that $s \in \mathbb{N}$ so that $s \geq 4$.*

Let $\tau > 0$ be given. We assume in the following that

- the domain Ω is a bounded domain with Lipschitz-continuous boundary,
- the rates $\gamma_1(M)$ and $\gamma_2(M)$ are smooth enough to avoid any singularity (this is the case for the examples given by (2)),
- the parameters μ_1 , μ_2 and ν_2 are continuous functions of time, such as regularization of the time-characteristic functions of treatment $\mathcal{T}_1, \mathcal{T}_2$,
- $P_{1,0}, P_{2,0}, P_{3,0}, N_0, S_0 \in H^s(\Omega)$,
- $P_{1,0}, P_{2,0}, P_{3,0}, N_0$ are compactly supported in Ω ,
- $M_0 \in H^{s-1}(\Omega)$,
- $\xi_0 \in \mathbb{R}$.

We introduce the following notations

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

- $\mathbf{u} = (P_1, P_2, P_3, N, S)^t$ belongs to $\mathcal{E}_{\mathbf{u}}^s := L^\infty(0, T; H^s(\Omega))$. On this space, we use the norm:

$$\|\mathbf{u}\|_{\mathcal{E}_{\mathbf{u}}^s} := \|\mathbf{u}\|_{L_T^\infty; H^s(\Omega)}. \quad (4)$$

For the sake of clarity, $\mathbf{u} \in L^\infty(0, T; H^s(\Omega))$ means that each component of \mathbf{u} is in $L^\infty(0, T; H^s(\Omega))$.

- \mathbf{v} belongs to $\mathcal{E}_{\mathbf{v}}^s := L^\infty(0, T; H^s(\Omega)) \cap L^2(0, T; H^{s+1}(\Omega))$. On this space, we use the norm:

$$\|\mathbf{v}\|_{\mathcal{E}_{\mathbf{v}}^s} := \|\mathbf{v}\|_{L_T^\infty; H^s(\Omega)} + \|\mathbf{v}\|_{L_T^2; H^{s+1}(\Omega)}, \quad (5)$$

- M belongs to $\mathcal{E}_M^s := L^\infty(0, T; H^{s-1}(\Omega)) \cap L^2(0, T; H^s(\Omega))$. On this space, we use the norm:

$$\|M\|_{\mathcal{E}_M^s} := \|M\|_{L_T^\infty; H^{s-1}(\Omega)} + \|M\|_{L_T^2; H^s(\Omega)}, \quad (6)$$

- ξ belongs to $C^0([0, T])$ (even $C^1([0, T])$) but we do not use this property on which we use the uniform norm.

Then the result is the following

Theorem 3.1. *Let $s \geq 4$, $\tau > 0$, $\mathbf{u}_0 \in H^s(\Omega)$, $M_0 \in H^{s-1}(\Omega)$ and $\xi_0 \in \mathbb{R}$. Let us assume that $P_{1,0}, P_{2,0}, P_{3,0}, N_0$ are compactly supported in Ω and that $P_{1,0} + P_{2,0} + P_{3,0} + N_0 + S_0 = 1$ on Ω .*

Then for any $C > 1$, there exists a maximal time of existence $T^\tau > 0$ such that the problem (1) has a unique solution $(\mathbf{u}, \mathbf{v}, M, \xi)$ in $\mathcal{E}_{\mathbf{u}}^s \times \mathcal{E}_{\mathbf{v}}^s \times \mathcal{E}_M^s \times \mathcal{C}^0([0, T^\tau])$. 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 tumour does not hit the boundary).

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

$$\max(\|\mathbf{u}\|_{\mathcal{E}_{\mathbf{u}}^s}, \|M\|_{\mathcal{E}_M^s}, \|\xi\|_\infty) \leq C \max(\|\mathbf{u}_0\|_{H^s}, \|M_0\|_{H^{s-1}}, |\xi_0|). \quad (7)$$

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

- $P_1, P_2, P_3, N, S \geq 0$,
- $P + N + S = 1$.

The second result states that, if the initial data are well-prepared, the solution to the model with necrotic compartment converges to the solution to the model without necrosis when the characteristic time of evacuation of the necrosis tends to 0. The model without necrosis is given by

$$\partial_t P_1^0 + \nabla \cdot (\mathbf{v}^0 P_1^0) = (\gamma_1(M^0) - \gamma_2(M^0))P_1^0 - (\mu_1 + \mu_2)M^0 P_1^0, \quad (8a)$$

$$\partial_t P_2^0 + \nabla \cdot (\mathbf{v}^0 P_2^0) = (\gamma_1(M^0) - \gamma_2(M^0))P_2^0 - \mu_2 M^0 P_2^0, \quad (8b)$$

$$\partial_t P_3^0 + \nabla \cdot (\mathbf{v}^0 P_3^0) = (\gamma_1(M^0) - \gamma_2(M^0))P_3^0, \quad (8c)$$

$$\partial_t S^0 + \nabla \cdot (\mathbf{v}^0 S^0) = 0, \quad (8d)$$

$$P_1^0 = P_2^0 = P_3^0 = 1 - S^0 = 0, \quad \text{if } \mathbf{v}^0 \cdot \mathbf{n} < 0 \text{ on } \partial\Omega, \quad (8e)$$

$$\nabla \cdot \mathbf{v}^0 = (\gamma_1(M^0) - \gamma_2(M^0))P^0 - (\mu_1 + \mu_2)M^0 P_1^0 - \mu_2 M^0 P_2^0, \quad (8f)$$

$$\mathbf{v}^0 = -k \nabla \Pi^0, \quad (8g)$$

$$\Pi^0|_{\partial\Omega} = 0, \quad (8h)$$

$$\partial_t M^0 - \Delta M^0 + \nabla \cdot (M^0 \xi^0 \nabla P^0) = -\eta M^0 P^0 + C_0 S^0 (1 - M^0), \quad (8i)$$

$$M^0|_{\partial\Omega} = 1. \quad (8j)$$

$$\partial_t \xi^0 = \alpha \int_{\Omega} \frac{\gamma_2(M^0)}{\max \gamma_2} [(1 - \nu_2)(P_1^0 + P_2^0) + P_3^0] dx - \lambda \xi^0, \quad (8k)$$

Theorem 3.2. *For any initial data $(P_{1,0}^0, P_{2,0}^0, P_{3,0}^0, S_0^0) \in H^s(\Omega)^4$, $M_0^0 \in H^{s-1}(\Omega)$ and $\xi_0^0 \in \mathbb{R}$ such that $P_{1,0}^0, P_{2,0}^0, P_{3,0}^0$ are compactly supported in Ω and $P_{1,0}^0 + P_{2,0}^0 + P_{3,0}^0 + S_0^0 = 1$ on Ω , there exists a maximal existence time $T^0 > 0$ and a unique solution $(P_1^0, P_2^0, P_3^0, S^0, \mathbf{v}^0, M^0, \xi^0)$ of (8) with P_1^0, P_2^0, P_3^0 compactly supported in Ω for all $t < T^0$.*

If N_0^τ is such that

$$\forall \tau > 0, \quad \|N_0^\tau\|_{H^{s-1}} \leq C\sqrt{\tau},$$

for some arbitrary constant $C > 0$, then the solution to (1) with initial data satisfying the assumption of Theorem 3.1 given by

$$(P_1^\tau, P_2^\tau, P_3^\tau, N^\tau, S^\tau, M^\tau, \xi^\tau)(t=0) = (P_{1,0}^\tau, P_{2,0}^\tau, P_{3,0}^\tau, N_0^\tau, S_0^\tau, M_0^\tau, \xi_0^\tau),$$

with

$$\lim_{\tau \rightarrow 0} (P_{1,0}^\tau, P_{2,0}^\tau, P_{3,0}^\tau, N_0^\tau, S_0^\tau, M_0^\tau, \xi_0^\tau) = (P_{1,0}^0, P_{2,0}^0, P_{3,0}^0, 0, S_0^0, M_0^0, \xi_0^0) \text{ in } H^{s-1}(\Omega)^6 \times \mathbb{R},$$

satisfies

$$\liminf_{\tau \rightarrow 0} T^\tau = T^0,$$

$$\frac{1}{\sqrt{\tau}} \|N^\tau\|_{L^\infty_{T^0}; H^{s-1}} + \frac{1}{\tau} \|N^\tau\|_{L^2_{T^0}; H^{s-1}} \leq C,$$

and

$$\lim_{\tau \rightarrow 0} (P_1^\tau, P_2^\tau, P_{3,0}^\tau, N^\tau, S^\tau, \mathbf{v}^\tau, M^\tau, \xi^\tau) = (P_1^0, P_2^0, P_3^0, 0, S^0, \mathbf{v}^0, M^0, \xi^0)$$

in $(L^\infty(0, T^0; H^{s-1}))^7 \times \mathcal{C}^0([0, T^0])$.

As it can be seen on scans, some tumours present necrosis while others not. So the model studied can describe the two kinds of behaviour as well, which has a great interest for medical applications. Tumours which do not develop necrosis can be interpreted, in terms of this model, as tumours whose characteristic time of evacuation of the necrosis is too short with respect to the macroscopic scale.

4 Local existence and uniqueness for $\tau > 0$

In this section we prove the well-posedness of the solution to the problem (1). In a first step (section 4.1) we construct the application on which we apply the fixed point strategy. Then section 4.2 is devoted to the proof of *a priori* estimates that will ensure the stability of this map. In section 4.3 we prove that this mapping is a contraction in some suitable spaces.

The key argument is that if the initial data for P_1, P_2, P_3, N have compact support in Ω , then any solution to (1) 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 alinhac2007pseudo) and usual parabolic estimates for M . The strategy is therefore to construct a suitable mapping such that this property remains true.

4.1 The iterative method

For any given $(\mathbf{u}, M, \xi) \in \mathcal{E}_{\mathbf{u}}^s \times \mathcal{E}_M^s \times \mathcal{C}^0([0, T])$ we define $(\tilde{\mathbf{u}}, \tilde{M}, \tilde{\xi}) \in \mathcal{E}_{\mathbf{u}}^s \times \mathcal{E}_M^s \times \mathcal{C}^0([0, T])$ as follows

- First we define \mathbf{v} as the solution to

$$\begin{cases} \nabla \cdot \mathbf{v} = \Gamma(M) \cdot \mathbf{u} & (\text{in } \Omega), \\ \mathbf{v} = -k \nabla \Pi & (\text{in } \Omega), \\ \Pi = 0 & (\text{on } \partial\Omega), \end{cases} \quad (9)$$

- Then $\tilde{\mathbf{u}}$ is solution to

$$\begin{cases} \partial_t \tilde{\mathbf{u}} + \nabla \cdot (\tilde{\mathbf{u}} \otimes \mathbf{v}) = A(M) \tilde{\mathbf{u}} & (\text{in } \Omega), \\ \tilde{\mathbf{u}} = (0, 0, 0, 0, 1)^t & (\text{if } \mathbf{v} \cdot \mathbf{n} < 0 \text{ on } \partial\Omega), \\ \tilde{\mathbf{u}}|_{t=0} = \mathbf{u}_0 & (\text{in } \Omega), \end{cases} \quad (10)$$

- \tilde{M} is solution to

$$\begin{cases} \partial_t \tilde{M} - \Delta \tilde{M} + \nabla \cdot (\tilde{M} \xi \nabla P) = -\eta \tilde{M} P + C_0 S (1 - \tilde{M}) & (\text{on } \Omega), \\ \tilde{M}|_{\partial\Omega} = 1, \\ \tilde{M}|_{t=0} = M_0, \end{cases} \quad (11)$$

- and $\tilde{\xi}$ is solution to:

$$\begin{cases} \partial_t \tilde{\xi} &= \alpha \int_{\Omega} \frac{\gamma_2(M)}{\max \gamma_2} [(1 - \nu_2)(P_1 + P_2) + P_3] dx - \lambda \tilde{\xi}, \\ \tilde{\xi}|_{t=0} &= \xi_0. \end{cases} \quad (12)$$

Our aim is to use a fixed-point method on the operator defined by

$$\Phi : (\mathbf{u}, M, \xi) \longrightarrow (\tilde{\mathbf{u}}, \tilde{M}, \tilde{\xi}). \quad (13)$$

It is clear that function $\mathbf{v}, \tilde{\mathbf{u}}, \tilde{M}, \tilde{\xi}$ are well defined and we omit their construction. The next section is devoted to the proof of stability inequalities on Φ .

4.2 A priori estimates for Φ

Proposition 4.1 (Estimates for \mathbf{v}). *Let $(\mathbf{u}, M) \in \mathcal{E}_{\mathbf{u}}^s \times \mathcal{E}_M^s$ be given. Then the solution \mathbf{v} to (9) belongs to $\mathcal{E}_{\mathbf{v}}^s$ and satisfies*

$$\|\mathbf{v}\|_{\mathcal{E}_{\mathbf{v}}^s} \leq C \|M\|_{\mathcal{E}_M^s} \|\mathbf{u}\|_{\mathcal{E}_{\mathbf{u}}^s}. \quad (14)$$

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

Remark 4.1. *Since $\Gamma(M)$ is orthogonal to $(0, 0, 0, 0, 1)^t$, we have $\nabla \cdot \mathbf{v} = 0$ where $\mathbf{u} = (0, 0, 0, 0, 1)^t$.*

Proof. The proof is a consequence of classical results on elliptic equations that can be found in [5]. Since the equations in (9) are not time dependent (time is indeed only a parameter), we can solve them at any time and then get the estimate in time by using the assumptions on \mathbf{u} and M . This leads also to the time continuity. \square

The stability estimate on $\tilde{\mathbf{u}}$ relies on the fact that $\tilde{P}_1, \tilde{P}_2, \tilde{P}_3, \tilde{N}$ have compact support in Ω on $[0, T]$ for T small enough. This property is needed to prove the *a priori* estimate. In order to satisfy this property, we use the characteristic curves of the system.

Notations 4.1. *Let us introduce notations*

- We denote by $\Omega_0 = \{x \in \Omega, \mathbf{u}_0(x) \neq (0, 0, 0, 0, 1)^t\}$ the initial domain of the tumour. We assume that $\Omega_0 \subset\subset \Omega$,
- We also use a **security domain** Ω_1 (containing Ω_0) in which the characteristic curves coming from Ω_0 stay until the time T . So the tumour remains located in Ω_1 at any time $t \leq T$.

We assume that

$$T < \frac{\frac{1}{4} \text{dist}(\Omega_0, \Omega)}{\|\mathbf{v}\|_{L_T^1; H^s}}.$$

Proposition 4.2 (Estimate for $\tilde{\mathbf{u}}$). *Let $\mathbf{u}_0 \in H^s(\Omega)$ such that $\mathbf{u}_0(x) = (0, 0, 0, 0, 1)^t$ in Ω_0 . Let $(\mathbf{v}, M) \in \mathcal{E}_{\mathbf{v}}^s \times \mathcal{E}_M^s$ be such that*

1. $\mathbf{v} \in \mathcal{C}^0([0, T]; H^{s-1}(\Omega))$.
2. $\nabla \cdot \mathbf{v} = 0$ on $\Omega \setminus \Omega_1$.

Then there exists a unique solution $\tilde{\mathbf{u}} \in \mathcal{E}_{\mathbf{u}}^s$ to (10), this solution satisfies

$$\|\tilde{\mathbf{u}}\|_{\mathcal{E}_{\mathbf{u}}^s} \leq \|\mathbf{u}_0\|_{H^s} \exp \left[C\sqrt{T}(\|M\|_{L_T^2; H^s} + \|\mathbf{v}\|_{L_T^2; H^{s+1}}) \exp \left(C\|\mathbf{v}\|_{L_T^1; H^s} \right) \right], \quad (15)$$

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

Remark 4.2.

- $\mathbf{u} = (P_1, P_2, P_3, N, S)^t$ satisfies the following properties
 - $\mathbf{u} = (0, 0, 0, 0, 1)^t$ on $[0, T] \times \Omega \setminus \Omega_1$,
 - $P_1, P_2, P_3, N, S \geq 0$ on $[0, T] \times \Omega$.
- the assumption (1) is useful to define the characteristic curves of the equation but it is not needed to prove the time continuity on $\tilde{\mathbf{u}}$.

Proof. It is worth noting that because of the equation (1g), the speed \mathbf{v} is not necessary non negative. We need to introduce two more domains to use the characteristic method.

Notations 4.2. We introduce these notations

- the domain Ω_3 (included in Ω) on which we can define the characteristic curves coming from Ω_3 by

$$\begin{cases} \partial_\sigma X(\sigma, t, x) &= \mathbf{v}(\sigma, X(\sigma, t, x)), \\ X(t, t, x) &= x. \end{cases}$$

Assumption (1) of the Proposition 4.2 ensures the existence of such characteristic curves.

- the domain Ω_2 ($\Omega_1 \subset \Omega_2 \subset \Omega_3$) such that the solution given by the characteristic method remains equal to $(0, 0, 0, 1)^t$ in $\Omega_2 \setminus \Omega_1$. This makes it possible to extend the solution out of Ω_2 by the same constant.

We use the fact that

Lemma 4.1. The jacobian $J(\sigma, t, x) = \det(D_x(X(\sigma, t, x)))$ satisfies

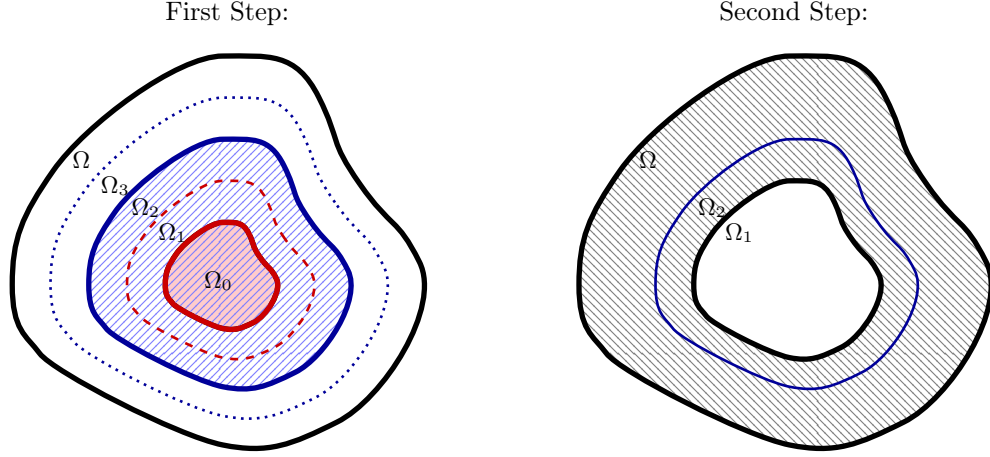
$$|J(\sigma, t, x)| \leq \exp \left(C\|\mathbf{v}\|_{L_T^1; H^s} \right) \text{ for any } (\sigma, t) \in [0, T]^2 \text{ and } x \in \Omega_3.$$

Thanks to the change of coordinates along the characteristics, we solve equation (10) in Ω_2 . The assumptions ensures that the characteristic curves coming from Ω_2 stay in Ω_3 . Consequently we can come back from Ω_3 to Ω_2 by using the characteristic curves. We use this change of coordinates to get estimates for the H^s semi-norms in Ω_2 , these semi-norms are bounded by semi-norms along the characteristics and the Jacobian of the change of coordinates. Since $\tilde{\mathbf{u}}$ along the characteristics satisfies a linear differential equation, we apply Gronwall inequality to get estimate on the norms along the characteristics. Then we get estimates on $\|\tilde{\mathbf{u}}\|_{\mathcal{E}_{\mathbf{u}}^s}$ in Ω_2 . Finally the solution on Ω_2 can be smoothly extended to the hole Ω using the assumption (2) that implies that the solution is equal to $(0, 0, 0, 1)^t$ on $\Omega \setminus \Omega_1$ (since this vector belongs to $\ker A(M)$ on this domain).

- The property that $P_1, P_2, P_3, N, S \geq 0$ follows from the expression of the solution given by the characteristic method and the assumption on the initial condition.

- To prove the time continuity, the assumptions on \mathbf{v} and M and equation (10) imply that $\partial_t \tilde{\mathbf{u}}$ belongs to $L^\infty(0, T; H^{s-1}(\Omega))$. By integrating $\partial_t \tilde{\mathbf{u}}$ 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 $\tilde{\mathbf{u}} \in C^0([0, T]; H^{s-1}(\Omega))$ (even Lipschitz continuous).

□



We solve the problem in Ω_2 with the characteristic method and get H^s -estimates in Ω_2 .
 Every characteristic coming from Ω_3 at $t = 0$ remains in Ω for all $t < T$.
 The tumour remains in Ω_1 for all time $t < T$.

The solution is equal to $(0, 0, 0, 0, 1)^t$ in $\Omega \setminus \Omega_1$.
 This makes it possible to extend the solution obtained in Ω_2 .

Figure 2: Scheme of the domains defined for the characteristic method in the proof of Proposition 4.2

The stability inequality on M is strongly related to the presence of the diffusive term in Eq. (11). Indeed the term ∇P in the advective part of the Eq. (11) induces a loss of derivative: because of this term we only get that M is in $L^\infty(0, T; H^{s-1}(\Omega))$ but the diffusion helps to recover this derivative and we get that M belongs to $L^2(0, T; H^s(\Omega))$:

Proposition 4.3 (Estimates for \tilde{M}). *Let $M_0 \in H^{s-1}(\Omega)$. Let $P, S \in \mathcal{E}_u^s$ and $\xi \in C^0([0, T])$. Assume that P is compactly supported in Ω . Then the solution \tilde{M} to (11) belongs to \mathcal{E}_M^s and satisfies*

$$\|\tilde{M}\|_{\mathcal{E}_M^s}^2 \leq K \left(T, \|M_0\|_{H^{s-1}}^2, T(1 + \|\xi\|_\infty^2)(\|P\|_{L_T^\infty; H^s}^2 + \|S\|_{L_T^\infty; H^s}^2) \right), \quad (16)$$

where K is a continuous and increasing function of its parameters such that $\lim_{T \rightarrow 0} K(T, \|M_0\|_{H^{s-1}}^2, T(1 + R^2)2R^2) = \|M_0\|_{H^{s-1}}^2$ for every $R > 0$.

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

Proof.

Notations 4.3. Denote by

$$\begin{aligned} w &:= \xi \nabla P, \\ a &:= -\eta P - C_0 S, \\ b &:= \eta P, \end{aligned}$$

then replace \tilde{M} by $1 - \tilde{M}$ which is still denoted by \tilde{M} in the following, and replace M_0 by $1 - M_0$ still denoted by M_0 . This leads to consider

$$\begin{cases} \partial_t \tilde{M} - \Delta \tilde{M} + \nabla \cdot (w(\tilde{M} - 1)) &= a\tilde{M} + b, \\ \tilde{M}|_{\partial\Omega} &= 0, \\ \tilde{M}|_{t=0} &= M_0. \end{cases} \quad (17)$$

Remember that since P is compactly supported, w and b are compactly supported.

Since we build \tilde{M} by a Galerkin approximation using the eigenvalues of the operator $(-\Delta)$ endowed with the Dirichlet boundary conditions, we can assume in the next computations that for all $k \in \mathbb{N}$, $(-\Delta)^k \tilde{M} = 0$ on the boundary (we can also see this from the equation satisfied by \tilde{M}). We have also that $\int_{\Omega} \tilde{M}^2 + \int_{\Omega} |\nabla(\Delta \tilde{M})|^2$ is equivalent to the $H^3(\Omega)$ -norm of \tilde{M} .

- Multiply the equation (17) by \tilde{M} and integrate by parts:

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

Using Young's inequality leads to

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

then we use the fact that the injection $H^2(\Omega) \hookrightarrow L^\infty(\Omega)$ is continuous

$$\partial_t \|\tilde{M}\|_{L^2}^2 + \|\nabla \tilde{M}\|_{L^2}^2 \leq C \left[(1 + \|w\|_{H^2}^2 + \|a\|_{H^2}^2) \|\tilde{M}\|_{L^2}^2 + \|w\|_{L^2}^2 + \|b\|_{L^2}^2 \right]. \quad (18)$$

Integrating between 0 and time $t > 0$ and using Gronwall's inequality to the previous inequality gives

$$\begin{aligned} \|\tilde{M}\|_{L_T^\infty; L^2}^2 &\leq \left[\|M_0\|_{L^2}^2 + C\|w\|_{L_T^2; L^2}^2 + C\|b\|_{L_T^2; L^2}^2 \right] \\ &\quad \times \exp C \left(T + \|w\|_{L_T^2; H^2}^2 + \|a\|_{L_T^2; H^2}^2 \right). \end{aligned}$$

Then integrating inequality (18) on $[0, T]$ implies

$$\begin{aligned} \|\tilde{M}\|_{L_T^\infty; L^2}^2 + \|\nabla \tilde{M}\|_{L_T^2; L^2}^2 &\leq \left[\|M_0\|_{L^2}^2 + C\|w\|_{L_T^2; L^2}^2 + C\|b\|_{L_T^2; L^2}^2 \right] \\ &\quad \times \left[1 + C \left(T + \|w\|_{L_T^2; H^2}^2 + \|a\|_{L_T^2; H^2}^2 \right) \right] \\ &\quad \times \exp C \left(T + \|w\|_{L_T^2; H^2}^2 + \|a\|_{L_T^2; H^2}^2 \right) \end{aligned} \quad (19)$$

- Now go back to the equation (17), apply the operator $(-\Delta)$, multiply by \tilde{M} and integrate by parts:

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

Using Young's inequality leads to

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

Observe that

$$\|\nabla \cdot (w\tilde{M})\|_{L^2} \leq \|(\nabla \cdot w)\tilde{M}\|_{L^2} + \|w \cdot \nabla \tilde{M}\|_{L^2},$$

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

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

and we use the same idea for $\|\nabla(a\tilde{M})\|_{L^2}$.

These estimates give us

$$\partial_t \|\nabla \tilde{M}\|_{L^2}^2 + \|\Delta \tilde{M}\|_{L^2}^2 \leq C \left[(1 + \|w\|_{H^2}^2 + \|a\|_{H^2}^2) \|\nabla \tilde{M}\|_{L^2}^2 + \|w\|_{H^1}^2 + \|b\|_{H^1}^2 \right]. \quad (20)$$

Integrating between 0 and time $t > 0$ and using Gronwall's inequality to the previous inequality gives

$$\begin{aligned} \|\nabla \tilde{M}\|_{L_T^\infty; L^2}^2 &\leq \left[\|\nabla M_0\|_{L^2}^2 + C \left(\|w\|_{L_T^2; H^1}^2 + \|b\|_{L_T^2; H^1}^2 \right) \right] \\ &\quad \times \exp C \left(T + \|w\|_{L_T^2; H^2}^2 + \|a\|_{L_T^2; H^2}^2 \right). \end{aligned}$$

Using this estimate and the estimate (20) leads to

$$\|\nabla \tilde{M}\|_{L_T^\infty; L^2}^2 + \|\Delta \tilde{M}\|_{L_T^2; L^2}^2 \leq K \left(T, \|M_0\|_{H^1}^2, \|w\|_{L_T^2; H^2}^2 + \|a\|_{L_T^2; H^2}^2 + \|b\|_{L_T^2; H^1}^2 \right), \quad (21)$$

where K satisfies the assumptions of Proposition 4.3.

• To go further, we go back to equation (17), we apply $(-\Delta)$, multiply by $-\Delta \tilde{M}$ and integrate by parts. Then follows

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

Young's inequality gives

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

For $\|\Delta(w\tilde{M})\|_{L^2}$ and $\|\Delta(a\tilde{M})\|_{L^2}$ we use the fact that $H^2(\Omega)$ is an algebra (since the injection $H^2(\Omega) \hookrightarrow L^\infty(\Omega)$ is continuous) and that the H^2 -norm of \tilde{M} is equivalent to $\|\tilde{M}\|_{L^2} + \|\Delta \tilde{M}\|_{L^2}$. This leads to

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

We use the same ideas as before (integrate in time, Gronwall) and we get

$$\|\Delta \tilde{M}\|_{L_T^\infty; L^2}^2 + \|\nabla \Delta \tilde{M}\|_{L_T^2; L^2}^2 \leq K \left(T, \|M_0\|_{H^2}^2, \|w\|_{L_T^2; H^2}^2 + \|a\|_{L_T^2; H^2}^2 + \|b\|_{L_T^2; H^2}^2 \right), \quad (22)$$

where K satisfies the assumptions of Proposition 4.3.

• For the next step apply $(-\Delta)^2 \tilde{M}$ to equation (17), multiply by $-\Delta \tilde{M}$ and integrate by parts:

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

Young's inequality leads to

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

Then we use the fact that $H^3(\Omega)$ is an algebra and that the H^3 -norm of \tilde{M} is equivalent to $\|\tilde{M}\|_{L^2} + \|\nabla \Delta \tilde{M}\|_{L^2}$:

$$\begin{aligned} \frac{1}{2} \partial_t \|\nabla \Delta \tilde{M}\|_{L^2}^2 + \|\Delta^2 \tilde{M}\|_{L^2}^2 &\leq C \left[(1 + \|w\|_{H^3}^2 + \|a\|_{H^3}^2) \left(\|\tilde{M}\|_{L^2}^2 + \|\nabla \Delta \tilde{M}\|_{L^2}^2 \right) \right. \\ &\quad \left. + \|w\|_{H^3}^2 + \|b\|_{H^3}^2 \right]. \end{aligned}$$

The same computations as before gives

$$\|\nabla \Delta \tilde{M}\|_{L_T^\infty; L^2}^2 + \|\Delta^2 \tilde{M}\|_{L_T^2; L^2}^2 \leq K \left(T, \|M_0\|_{H^3}^2, \|w\|_{L_T^2; H^3}^2 + \|a\|_{L_T^2; H^3}^2 + \|b\|_{L_T^2; H^3}^2 \right), \quad (23)$$

where K satisfies the assumptions of Proposition 4.3.

- For the general case we proceed as follows. For each $k \in \mathbb{N}^*$
- apply $(-\Delta)^k$ to the equation (17), multiply by $(-\Delta)^k \tilde{M}$ and integrate by parts give an estimate similar to (22) on

$$\|\Delta^k \tilde{M}\|_{L_T^2; L^2}^2 + \|\nabla \Delta^k \tilde{M}\|_{L_T^2; L^2}^2,$$

and we use the fact that $\|\tilde{M}\|_{L^2} + \|\Delta^k \tilde{M}\|_{L^2}$ is equivalent to $\|\tilde{M}\|_{H^{2k}}$;

- apply $(-\Delta)^{k+1}$ to the equation (17), multiply by $(-\Delta)^k \tilde{M}$ and integrate by parts give an estimate similar to (23) on

$$\|\nabla \Delta^k \tilde{M}\|_{L_T^2; L^2}^2 + \|\Delta^{k+1} \tilde{M}\|_{L_T^2; L^2}^2,$$

and we use the fact that $\|\tilde{M}\|_{L^2} + \|\nabla \Delta^k \tilde{M}\|_{L^2}$ is equivalent to $\|\tilde{M}\|_{H^{2k+1}}$.

The conclusion follows by replacing w , a and b by their expression.

• The same arguments used to prove the time continuity for $\tilde{\mathbf{u}}$ prove that $\tilde{M} \in \mathcal{C}^0([0, T]; H^{s-2})$ since $\partial_t \tilde{M} \in L^2(0, T; H^{s-2}(\Omega))$. □

Proposition 4.4 (Estimate for $\tilde{\xi}$). *Let $(P, M) \in \mathcal{E}_{\mathbf{u}}^s \times \mathcal{E}_M^s$.*

Assume that $P, M \in \mathcal{C}^0([0, T]; H^{s-2}(\Omega))$. Then the solution $\tilde{\xi} \in \mathcal{C}^1([0, T])$ to (12) satisfies

$$\|\tilde{\xi}\|_{\infty} \leq [|\xi_0| + \alpha \text{Vol}(\Omega)T(1 + \nu_2)\|P\|_{\mathcal{E}_{\mathbf{u}}^s}] \exp(\lambda T). \quad (24)$$

Proof. Integrate (12) over time leads to

$$\tilde{\xi}(t) = \xi_0 + \alpha \int_0^t \int_{\Omega} \frac{\gamma_2(M)}{\max \gamma_2} [(1 - \nu_2)(P_1 + P_2) + P_3] dx ds - \lambda \int_0^t \tilde{\xi} ds,$$

then apply Gronwall inequality. □

We have proved the following property

Proposition 4.5. *Let $(\mathbf{u}_0, M_0, \xi_0) \in H^s(\Omega) \times H^{s-1}(\Omega) \times \mathbb{R}$ such that the components $P_{1,0}, P_{2,0}, P_{3,0}, N_0$ of \mathbf{u}_0 are compactly supported in Ω .*

Let $C > 1$ be given and denote by $R := C \max(\|\mathbf{u}_0\|_{H^s}, \|M_0\|_{H^{s-1}}, |\xi_0|)$. There exists $T_1^r > 0$ depending only on R and the parameters of the model (such as $\tau, \gamma_1, \gamma_2, \dots$) such that for any $(\mathbf{u}, M, \xi) \in \mathcal{E}_{\mathbf{u}}^s \times \mathcal{E}_M^s \times \mathcal{C}^0([0, T_1^r])$ satisfying

- P_1, P_2, P_3, N are compactly supported in Ω ,
- $\mathbf{u}(t = 0, \cdot) = \mathbf{u}_0, M(t = 0, \cdot) = M_0, \xi(t = 0) = \xi_0$,
- $\max(\|\mathbf{u}\|_{\mathcal{E}_{\mathbf{u}}^s}, \|M\|_{\mathcal{E}_M^s}, \|\xi\|_{\infty}) \leq R$,

one has

$$\max(\|\tilde{\mathbf{u}}\|_{\mathcal{E}_{\mathbf{u}}^s}, \|\tilde{M}\|_{\mathcal{E}_M^s}, \|\tilde{\xi}\|_{\infty}) \leq R,$$

where $(\tilde{\mathbf{u}}, \tilde{M}, \tilde{\xi}) = \Phi(\mathbf{u}, M, \xi)$.

4.3 Contraction estimates

The contraction estimates for Φ follows the same line that the above stability analysis. For $i = 1$ or 2, we take $(\tilde{\mathbf{u}}_i, \tilde{M}_i, \tilde{\xi}_i) = \Phi(\mathbf{u}_i, M_i, \xi_i)$ and estimate the difference $(\tilde{\mathbf{u}}_1, \tilde{M}_1, \tilde{\xi}_1) - (\tilde{\mathbf{u}}_2, \tilde{M}_2, \tilde{\xi}_2)$. For the nonlinear products on the form

$$a_1 b_1 - a_2 b_2 = a_1(b_1 - b_2) + (a_1 - a_2)b_2,$$

with a_i standing for $\tilde{\mathbf{u}}_i, \tilde{M}_i$ or $\tilde{\xi}_i$ and b_i standing for \mathbf{u}_i, M_i or ξ_i (or their derivative), we need to use uniform estimate on a_1 and b_2 . For this we use the fact that the injection $H^{s-2}(\Omega) \hookrightarrow L^\infty(\Omega)$ is continuous. It is worth noting that this assumption is needed to get contraction estimate on M . Indeed, because of Eq. (11), to get the contraction estimate on M , we need contraction estimate on ∇P . To get this estimate on ∇P , we need to get uniform estimate on ∇M . Since ∇M is only in $L^\infty(0, T; H^{s-2})$, we need that the injection $H^{s-2}(\Omega) \hookrightarrow L^\infty(\Omega)$ is continuous. Then we prove straightforwardly

Proposition 4.6. For $i = 1$ or 2 , we take $(\tilde{\mathbf{u}}_i, \tilde{M}_i, \tilde{\xi}_i) = \Phi(\mathbf{u}_i, M_i, \xi_i)$. Under the assumptions of Proposition 4.5, there exists $C_R > 0$, such that for any $0 < T \leq T_1^\tau$, we have

$$\|\tilde{\mathbf{u}}_1 - \tilde{\mathbf{u}}_2\|_{L_T^2, H^1}^2 \leq C_R T \exp(C_R T) \left(\|\mathbf{u}_1 - \mathbf{u}_2\|_{L_T^2, H^1}^2 + \|M_1 - M_2\|_{L_T^2, H^1}^2 \right), \quad (25)$$

$$\|\tilde{M}_1 - \tilde{M}_2\|_{L_T^2, H^1}^2 \leq C_R \left(\|\mathbf{u}_1 - \mathbf{u}_2\|_{L_T^2, H^1}^2 + T \|\xi_1 - \xi_2\|_\infty^2 \right), \quad (26)$$

$$\|\tilde{\xi}_1 - \tilde{\xi}_2\|_\infty^2 \leq C_R T \left(\|\mathbf{u}_1 - \mathbf{u}_2\|_{L_T^2, H^1}^2 + \|M_1 - M_2\|_{L_T^2, H^1}^2 \right). \quad (27)$$

Remark 4.3. For the estimate on $\tilde{\mathbf{u}}_1 - \tilde{\mathbf{u}}_2$ we get an estimate on $\|\tilde{\mathbf{u}}_1 - \tilde{\mathbf{u}}_2\|_{L_T^\infty, H^1}^2$ and we use the fact that $\|\tilde{\mathbf{u}}_1 - \tilde{\mathbf{u}}_2\|_{L_T^2, H^1}^2 \leq T \|\tilde{\mathbf{u}}_1 - \tilde{\mathbf{u}}_2\|_{L_T^\infty, H^1}^2$.

Because of Eq. (26), we do not have that Φ is a contraction but we get by composition

Proposition 4.7. Under the assumptions of Proposition 4.5, there exists $0 < T_2^\tau \leq T_1^\tau$ such that Φ^2 is a contraction in the set

$$\mathcal{E}_\Phi := \{(\mathbf{u}, M, \xi) \in \mathcal{E}_\mathbf{u}^s \times \mathcal{E}_M^s \times \mathcal{C}^0([0, T_2^\tau]) \mid \max(\|u\|_{\mathcal{E}_\mathbf{u}^s}, \|M\|_{\mathcal{E}_M^s}, \|\xi\|_\infty) \leq R\}$$

endowed with the usual norm on $L^2(0, T_2^\tau; H^1(\Omega)) \times L^2(0, T_2^\tau; H^1(\Omega)) \times \mathcal{C}^0([0, T_2^\tau])$.

4.4 End of the proof of Theorem 3.1

- Consider the Propositions 4.5 and 4.7 and choose $T^\tau = T_2^\tau$. We consider the set \mathcal{E}_Φ endowed with the usual norm on the Banach space $L^2(0, T^\tau; H^1(\Omega)) \times L^2(0, T^\tau; H^1(\Omega)) \times \mathcal{C}^0([0, T^\tau])$. Since the closed unit balls in $L^2(0, T^\tau; H^s(\Omega))$ and in $L^2(0, T^\tau; H^{s+1}(\Omega))$ are compact in the weak topology and the closed unit balls in $L^\infty(0, T^\tau; H^{s-1}(\Omega))$ and in $L^\infty(0, T^\tau; H^s(\Omega))$ are compact in the weak* topology [5], we get that \mathcal{E}_Φ is a closed subspace of $L^2(0, T^\tau; H^1(\Omega)) \times L^2(0, T^\tau; H^1(\Omega)) \times \mathcal{C}^0([0, T^\tau])$.

Then we apply the contraction mapping theorem in this set. This leads to the existence and uniqueness of the solution to the model (1).

- The proof of the time continuity in the Propositions 4.2 and 4.3 leads to the time continuity of \mathbf{u} and M . Then follows the time continuity of \mathbf{v} and ξ by using the results of the Propositions 4.1 and 4.4.

- Thanks to the construction of the solution, we have immediately that

$$P_1, P_2, P_3, N, S \geq 0.$$

- Then the saturation (3) 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.

5 Limit when $\tau \rightarrow 0$

Since tumours develop necrotic compartment while others not, we want to see if our model can simulate this two kinds of tumours, by passing to the limit when $\tau \rightarrow 0$ to model tumours without necrosis. The aim is to use the same model to simulate these two cases.

The goal of this section is to prove the Theorem 3.2 which is that for τ going to 0 the solution to the model with necrosis given by (1) converges towards the solution to the model without necrosis given by (8).

In the previous section, the time of existence $T > 0$ depended on the norm of \mathbf{v} , which depends itself on τ . More precisely, if we look at the proof of existence, we can see that this time depends only on $\|\mathbf{v}\|_{L_T^1; H^s}$. Our work will consist in finding a bound on this norm to ensure that there exists a time of existence which does not depend on τ . Then the limit passing gives us the attempted result.

While looking at equation (1g), we see that we only need to find a bound on $\frac{1}{\tau}N$ to obtain a bound on $\|\mathbf{v}\|_{L_T^1; H^s}$.

Notations 5.1. Denote by $g := \gamma_2(M)(P_1 + P_2) + (\mu_1 + \mu_2)MP_1 + \mu_2MP_2$ and $f := \gamma_1(M)(P_1 + P_2)$. Because of Theorem 3.1, we have $f, g \in L^\infty(0, T; H^{s-1}(\Omega))$ and Eq. (7) implies that f, g are bounded by a constant depending only on the initial conditions.

Denote by $\tilde{N} := \frac{N}{\tau}$, then \tilde{N} satisfies

$$\partial_t \tilde{N} + \nabla \cdot (\mathbf{v} \tilde{N}) = \frac{g}{\tau} - \frac{1}{\tau} \tilde{N}, \quad (28)$$

and \mathbf{v} is bounded in H^s -norm:

$$\|\mathbf{v}\|_{H^s} \leq C \left(\|f\|_{H^{s-1}} + \|\tilde{N}\|_{H^{s-1}} \right). \quad (29)$$

To bound $\|\tilde{N}\|_{H^{s-1}}$, we need to prove a previous result. The objective of following section is to prove that $\|\tilde{N}(t, \cdot)\|_{H^{s-1}}$ satisfies a differential inequality. The next section will use this inequality to conclude.

5.1 The inequality satisfied by $\|\tilde{N}(t, \cdot)\|_{H^{s-1}}$

In this section we prove the following result:

Proposition 5.1. Denote by $y(t) := \|\tilde{N}(t, \cdot)\|_{H^{s-1}}^2$, then y satisfies the following differential inequality

$$y' + \frac{1}{2\tau}y \leq \frac{C}{\tau} + \left(C - \frac{1}{2\tau} \right) y + Cy^{3/2}, \quad (30)$$

where C does not depend on τ .

The proof is structured into two steps:

- we prove the inequality for $|\tilde{N}(t, \cdot)|_{H^m}$, for $m \leq 1$;
- then we prove it in the general case $m \leq s - 1$.

In the following we will use the Gagliardo-Nirenberg interpolation inequality that can be found in [1].

5.1.1 Proof of the inequality for $m \leq 1$

Case $m = 0$.

Multiply the equation (28) by \tilde{N} and integrate by parts over Ω :

$$\frac{1}{2}\partial_t \int_{\Omega} \tilde{N}^2 + \frac{1}{2} \int_{\Omega} (\nabla \cdot \mathbf{v}) \tilde{N}^2 = \frac{1}{\tau} \int_{\Omega} g \tilde{N} - \frac{1}{\tau} \int_{\Omega} \tilde{N}^2,$$

hence we infer

$$\frac{1}{2}\partial_t |\tilde{N}|_{L^2}^2 + \frac{1}{\tau} |\tilde{N}|_{L^2}^2 \leq \frac{1}{2} \left[\frac{1}{\tau} |g|_{L^2}^2 + \left(|\nabla \cdot \mathbf{v}|_{L^\infty} + \frac{1}{\tau} \right) |\tilde{N}|_{L^2}^2 \right],$$

from which we deduce

$$\partial_t |\tilde{N}|_{L^2}^2 + \frac{2}{\tau} |\tilde{N}|_{L^2}^2 \leq \frac{1}{\tau} |g|_{L^2}^2 + \left(C \|\mathbf{v}\|_{H^s} + \frac{1}{\tau} \right) |\tilde{N}|_{L^2}^2.$$

Case $m = 1$.

Denote by ∂_x a one order partial differential operator. Multiply Eq. (28) by $\partial_x \tilde{N}$ and integrate:

$$\frac{1}{2}\partial_t \int_{\Omega} (\partial_x \tilde{N})^2 + \int_{\Omega} \partial_x (\nabla \cdot (\mathbf{v} \tilde{N})) \partial_x \tilde{N} = \frac{1}{\tau} \int_{\Omega} \partial_x g \partial_x \tilde{N} - \frac{1}{\tau} \int_{\Omega} (\partial_x \tilde{N})^2.$$

Focus on the following term:

$$\begin{aligned} \int_{\Omega} \partial_x (\nabla \cdot (\mathbf{v} \tilde{N})) \partial_x \tilde{N} &= \int_{\Omega} \nabla \cdot (\partial_x \mathbf{v} \tilde{N} + \mathbf{v} \partial_x \tilde{N}) \partial_x \tilde{N}, \\ &= \int_{\Omega} \partial_x (\nabla \cdot \mathbf{v}) \tilde{N} \partial_x \tilde{N} + \int_{\Omega} \partial_x \mathbf{v} \cdot \nabla \tilde{N} \partial_x \tilde{N} - \int_{\Omega} \mathbf{v} \cdot \frac{1}{2} \nabla (\partial_x \tilde{N})^2, \end{aligned}$$

then

$$\begin{aligned} \left| \int_{\Omega} \partial_x (\nabla \cdot (\mathbf{v} \tilde{N})) \partial_x \tilde{N} \right| &\leq |\partial_x (\nabla \cdot \mathbf{v})|_{L^4} |\tilde{N}|_{L^4} |\partial_x \tilde{N}|_{L^2} + |\partial_x \mathbf{v}|_{L^\infty} |\nabla \tilde{N}|_{L^2} |\partial_x \tilde{N}|_{L^2} \\ &\quad + \frac{1}{2} |\nabla \cdot \mathbf{v}|_{L^\infty} |\partial_x \tilde{N}|_{L^2}^2, \end{aligned}$$

Thanks to the Gagliardo-Nirenberg inequality, we infer:

$$\left| \int_{\Omega} \partial_x (\nabla \cdot (\mathbf{v} \tilde{N})) \partial_x \tilde{N} \right| \leq C \|\mathbf{v}\|_{H^s} |\tilde{N}|_{H^1}^2.$$

Hence

$$\partial_t |\tilde{N}|_{H^1}^2 + \frac{2}{\tau} |\tilde{N}|_{H^1}^2 \leq \frac{1}{\tau} |g|_{H^1}^2 + \left(C \|\mathbf{v}\|_{H^s} + \frac{1}{\tau} \right) |\tilde{N}|_{H^1}^2.$$

5.1.2 The general case: $m \leq s - 1$

Let $m \leq s - 1$ be given. For each $k \leq m$, denote by ∂_x^k a k -order partial differential operator.

Then applying ∂_x^m on (28) and multiplying by $\partial_x^m \tilde{N}$ leads to

$$\partial_t \int_{\Omega} (\partial_x^m \tilde{N})^2 + \int_{\Omega} \partial_x^m (\nabla \cdot (\mathbf{v} \tilde{N})) \partial_x^m \tilde{N} = \frac{1}{\tau} \int_{\Omega} \partial_x^m g \partial_x^m \tilde{N} - \frac{1}{\tau} \int_{\Omega} (\partial_x^m \tilde{N})^2,$$

applying the Leibniz formula gives

$$\int_{\Omega} \partial_x^m (\nabla \cdot (\mathbf{v} \tilde{N})) \partial_x^m \tilde{N} = \sum_{k=0}^m C_m^k \int_{\Omega} \nabla \cdot (\partial_x^k \mathbf{v} \partial_x^{m-k} \tilde{N}) \partial_x^m \tilde{N}. \quad (31)$$

Now let's focus on each term of the previous sum.

- if $k = 0$, we integrate by parts:

$$\begin{aligned} \int_{\Omega} \nabla \cdot (\mathbf{v} \partial_x^m \tilde{N}) \partial_x^m \tilde{N} &= - \int_{\Omega} \mathbf{v} \cdot \frac{1}{2} \nabla \left((\partial_x^m \tilde{N})^2 \right), \\ &= \frac{1}{2} \int_{\Omega} (\nabla \cdot \mathbf{v}) (\partial_x^m \tilde{N})^2. \end{aligned}$$

then we have

$$\left| \int_{\Omega} \nabla \cdot (\mathbf{v} \partial_x^m \tilde{N}) \partial_x^m \tilde{N} \right| \leq \frac{1}{2} \|\nabla \cdot \mathbf{v}\|_{\infty} |\partial_x^m \tilde{N}|_{L^2}^2.$$

- if $1 \leq k \leq m$, we rewrite the integral:

$$\begin{aligned} \int_{\Omega} \nabla \cdot (\partial_x^k \mathbf{v} \partial_x^{m-k} \tilde{N}) \partial_x^m \tilde{N} &= \int_{\Omega} (\nabla \cdot \partial_x^k \mathbf{v}) \partial_x^{m-k} \tilde{N} \partial_x^m \tilde{N} \\ &\quad + \int_{\Omega} \partial_x^k \mathbf{v} \cdot \nabla (\partial_x^{m-k} \tilde{N}) \partial_x^m \tilde{N}. \end{aligned}$$

Denote by I_1 the first integral of previous equation and by I_2 the second one.

For the first one we have

- if $k \leq m - 1$:

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

then apply the Gagliardo-Nirenberg inequality.

- if $k = m$:

$$|I_1| \leq \|\nabla \cdot \partial_x^m \mathbf{v}\|_{L^2} \|\tilde{N}\|_{L^{\infty}} |\partial_x^m \tilde{N}|_{L^2}.$$

Let's go to the second integral:

- if $k = 1$:

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

– if $k \geq 2$:

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

then apply the Gagliardo-Nirenberg inequality.

Making a summarize of all the estimates and using the inequality (29) leads to

$$y' + \frac{2}{\tau} y \leq \frac{1}{\tau} \|g\|_{H^{s-1}}^2 + \left(C \|f\|_{H^{s-1}} + \frac{1}{\tau} \right) y + C y^{3/2}.$$

Then, Eq. (7) ensures that $\|f\|_{H^{s-1}} \leq \|f\|_{L_T^\infty; H^{s-1}}$ and $\|g\|_{H^{s-1}} \leq \|g\|_{L_T^\infty; H^{s-1}}$ are bounded for T small enough and this bound depends only on the initial data. This leads to Eq. (30).

5.2 The limit case τ tends to 0

Here we keep denote by $y(t) = \|\tilde{N}(t, \cdot)\|_{H^{s-1}}^2$. We have shown in the previous section that y satisfies the inequality (30) (page 18). Now we study the inequality (30).

We prove now the last estimate which makes it possible to pass to the limit for $\tau \rightarrow 0$.

Proposition 5.2. *Keep denote by C the constant in (30). Then if $\|N_0\|_{H^{s-1}} \leq \frac{1}{6C}$ and $\tau > 0$ is small enough we have*

$$\frac{1}{\tau} \|N\|_{L_T^\infty; H^{s-1}}^2 + \frac{1}{2\tau^2} \|N\|_{L_T^2; H^{s-1}}^2 \leq CT + \frac{1}{\tau} \|N_0\|_{H^{s-1}}^2. \quad (32)$$

Proof. Denote by $f_\tau(y) := \frac{C}{\tau} + \left(C - \frac{1}{2\tau} \right) y + C y^{3/2}$.

Denote by $y_{\tau,1} := \left(\frac{1}{3C\tau} \right)^2 (1 - 2C\tau)^2$. The function f_τ is strictly decreasing on $(0, y_{\tau,1})$ and strictly increasing on $(y_{\tau,1}, +\infty)$. Moreover for $\tau > 0$ small enough, we get that $y_{\tau,2} := \left(\frac{1}{6C\tau} \right)^2 \leq y_{\tau,1}$ satisfies $f_\tau(y_{\tau,2}) < 0$.

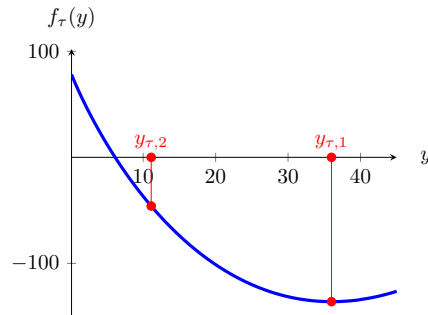


Figure 3: Plot of f_τ for $\tau = 0.025$ and $C = 2$

Then if $y(0) \leq y_{\tau,2}$ then for all $t > 0$ one have $y(t) \leq y_{\tau,2}$ so $f_\tau(y(t)) \leq f_\tau(0) = \frac{C}{\tau}$.

Hence we can rewrite (30) as follows:

$$y' + \frac{1}{2\tau}y \leq \frac{C}{\tau}.$$

Integrating between 0 and t gives

$$\begin{aligned} y(t) + \frac{1}{2\tau} \int_0^t y &\leq \frac{C}{\tau}t + y(0), \\ &\leq \frac{C}{\tau}T + y(0). \end{aligned}$$

The conclusion follows by replacing y by $\| \frac{N}{\tau} \|_{H^{s-1}}^2$.

□

Now the previous Proposition leads to the Theorem 3.2, assuming that $\|N_0\|_{H^{s-1}} \leq C\sqrt{\tau}$ for some arbitrary constant $C > 0$.

The inequality (29) implies that $\|\mathbf{v}\|_{L_T^1; H^s}$ is independently bounded with respect to τ . Then the time T found in the previous construction of the solution can be chosen independently with respect to τ . Moreover the previous inequality implies also that N converges to 0 in $L^\infty(0, T; H^{s-1}(\Omega))$ and that the solution to the model with necrosis converges to the solution to the model without necrosis when $\tau \rightarrow 0$.

6 Conclusion

A constructive proof of a solution to our model has been made. The fixed-point method we used gives an iterative procedure to build a solution by using the initial data (which can be obtained by scans segmentation for example). The main idea of this proof was that the tumour remains compactly supported for a given time until it reaches the boundary. We proved that the minimum time it reaches the boundary can be bounded such that it does not depend on the characteristic time of evacuation of the necrosis. This made it possible to prove that our model is consistent with the model without necrosis phase that we presented, which means that a solution of the model without necrosis is given as the limit of solutions of our model when the characteristic time of evacuation of the necrosis tends to zero. This result ensures that our model can describe the situation where the tumour presents a necrotic compartment and the situation where there is not a necrosis as well. This has a great interest for a clinical point of view, since it makes it possible to use the same model for both cases.

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