THE SYNERGISTIC INTERPLAY OF AMYLOID BETA AND TAU PROTEINS IN ALZHEIMER'S DISEASE: A COMPARTMENTAL MATHEMATICAL MODEL
L'INTERAZIONE SINERGICA DELLE PROTEINE BETA AMILOIDE E TAU NELLA MALATTIA DI ALZHEIMER: UN MODELLO MATEMATICO COMPARTIMENTALE

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ABSTRACT. The purpose of this Note is to present and discuss some mathematical results concerning a compartmental model for the synergistic interplay of Amyloid beta and tau proteins in the onset and progression of Alzheimer's disease. We model the possible mechanisms of interaction between the two proteins by a system of Smoluchowski equations for the Amyloid beta concentration, an evolution equation for the dynamics of misfolded tau and a kinetic-type transport equation for a function taking into accout the degree of malfunctioning of neurons. We provide a well-posedness results for our system of equations. This work extends results obtained in collaboration with M.Bertsch, B.Franchi and A.Tosin.

SUNTO. Lo scopo di questa Nota é di presentare e discutere alcuni risultati matematici riguardanti un modello compartimentale per l'interazione sinergistica delle proteine beta amiloide e tau nella nascita e progressione della malattia di Alzeimer. Modelliamo i possibili meccanismi di interazione tra le due proteine attraverso un sistema di equazioni di Smoluchowski per la concentrazione di beta amiloide, un' equazione di evoluzione per la dinamica della proteina tau ed una equazione di trasporto di tipo cinetico per una funzione che tiene conto del grado di malfunzionamento dei neuroni. Viene dato un risultato di buon posizionamento per il sistema di equazioni. Questo lavoro estende risultati ottenuti in collaborazione con M.Bertsch, B.Franchi e A.Tosin.

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease extremely diffused nowadays: it is estimated that approximately 44 million people worldwide live with AD or a related form of dementia [21]. The disease is devastating for those affected, their families and the entire society, indeed the social and economic implications in terms of direct medical and social care costs, and the costs of informal care, are substantial.

To date, not only there is no cure available, but it has not even been possible to slow down the progression of the disease in a satisfactory way, probably because the mechanisms of onset and progression of AD are still quite obscure.

Until about ten years ago, the most accepted hypothesis on the onset of AD was the so-called amyloid cascade hypothesis, see [18]. Beta-amyloid is a protein naturally produced by healthy neurons, and constantly cleared by several mechanisms. According to the amyloid cascade hypothesis, it was assumed that the progression of AD was associated with the presence of soluble toxic oligomers of beta-amyloid that, due to some failure in the clearance mechanisms or overproduction (for example by a change in the metabolism), aggregate to give rise to plaques, ultimately resulting in a large quantity of highly toxic Aβ polymers. In recent years, however, the scientific community has changed this perspective and now it is generally accepted that two proteins, beta amyloid and tau, play a key role in the onset and progression of the disease, see for example [13]. Protein τ is a microtubule-associated protein with the main function to assemble microtubules and regulate motor-driven axonal transport. In patients suffering of AD it has been observed misfolded τ in form of neurofribrillary tangles. Misfolding compromises microtubule stabilization, axonal transport and in general interferes with neuronal functions. The precise role of Aβ and τ in AD onset and progression is still not well understood, but in the literature various synergetic actions of the two proteins were suggested. For a recent exhaustive review we refer to [9]. Up to date Aβ and τ remain the major therapeutic targets for the treatment of the disease, and their interplay seems more and more crucial when developing new therapies: this is also one of the main issues behind the current debate on the perspectives of the use of aducanumab [17]). Due to these uncertainties, a lot of current biomedical

research focuses on the interactions of the two proteins also in the perspective of the production of new effective drugs. In this context, flexible mathematical models may give significant contributions, for example by testing different clinical hypotheses.

The principal purpose of this note is to present and investigate a simplified scheme of interaction between Aβ and τ in AD, as proposed for instance in [13] and in [9], by means of a compartmental model expressed in terms of integro-differential equations [4, 8].

In Section 2 we present the model. There are three principal mechanisms we consider relevant for the evolution of the disease: i) diffusion and agglomeration of soluble Amyloid beta protein, ii) effects of misfolded tau protein and iii) neuron-to-neuron prion-like transmission of the disease. We model the above mentioned processes by a system of (compartmental) Smoluchowski equations for the Amyloid beta concentration, an evolution equation for the dynamics of misfolded tau and a kinetic-type transport equation for the density function (that turns out to be a probability measure) of the degree of malfunctioning of neurons . We therefore obtain an integro-differential systems of equations, that we try to descibe in reasonable detail.

In Section 3 we provide the main result: the well-posedness of our system of equations. This is obtained basically as follows: our integro-differential system is shown to be equivalent to another integro-differential system formulated in terms of characteristics. Technically the situation is a bit complicated as we are working with measures, and we have to transport a measure along the characteristics. Then we prove a local existence result for the system with the characteristics, essentially using a Banach-Caccioppoli fixed point argument, slightly adapted to the present setting. The local solution thus obtained can be extended globally, and we finally get the global solution of the original system through the equivalence of the two systems. Since several proofs are quite technical, we give here a sort of sketch by steps of some of them, and we refer to [7] for the details. Notice that in [7] the τ protein is not considered, however the technical details are very similar.

2. Description of the model

We identify a portion of the brain by a bounded set Ω in $\mathbb{R}^3$. Each point in space is denoted by x. Concerning time, we need two different time scales to describe the evolution of the disease: a rapid time scale denoted by s, with unit time coinciding with hours, for the diffusion and agglomeration of Aβ [14]; and a slow time scale denoted by t, with unit time coinciding with several months, for the progression of AD. Introducing a small constant $0 < \varepsilon << 1$, the relationship between the slow time variable t and the fast one s can be expressed as follows:

$$s := \frac{t}{\varepsilon}. \tag{1}$$

Given a point $x \in \Omega$ and a time $t > 0$, we denote with $w(x,t)$ the density of intracellular misfolded τ protein, with $u_1(x,t)$ the density of Aβ monomers, with $u_2(x,t)$ the density of Aβ soluble oligomers, which are regarded collectively as a single compartment, and with $u_3(x,t)$ the density of Aβ senile plaques (sometimes called fibrils), also regarded as a single compartment. The quantity f takes into account, in an appropriate sense that will be discussed later, the "health state" of the brain.

The compartmental model we present here is given by the following system of integro-differential equations:

$$\begin{cases} \partial_t f + \partial_a(f v[f]) = J[f] & \text{in } \Omega \times [0,1] \times (0,T] \quad \text{(2a)} \\ \varepsilon \partial_t u_1 - d_1 \Delta u_1 = -\alpha u_1 \sum_{j=1}^{3} u_j + \mathcal{F}[f] - \sigma_1 u_1 & \text{in } Q_T = \Omega \times (0,T] \quad \text{(2b)} \\ \varepsilon \partial_t u_2 - d_2 \Delta u_2 = \frac{\alpha}{2} u_1^2 - \alpha u_2 \sum_{j=1}^{3} u_j - \sigma_2 u_2 & \text{in } Q_T \quad \text{(2c)} \\ \varepsilon \partial_t u_3 = \frac{\alpha}{2} \sum_{3 \le j+k < 6} u_j u_k & \text{in } Q_T \quad \text{(2d)} \\ \partial_t w = C_w (u_2 - U_w)^+ + \int_\Omega h_w(|y-x|) w(y,t)\, dy + H(x) & \text{in } Q_T, \quad \text{(2e)} \end{cases}$$

The coefficient ε appears obviously in front of the time derivatives of the fast variables u_1, u_2 and u_3, which are coupled with the slowly changing variables f and w explicitly

(equation (2e)) and through the term $v[f]$. Such term will be described precisely below; for the moment we keep in mind that it corresponds to the velocity of spreading of the disease, and therefore contains the toxic action of both Aβ and misfolded τ proteins.

Equation (2a) is a kinetic-type equation which describes the progression of the disease. Roughly speaking, $f = f(x, a, t)$ is the probability density of the number of neurons located in $x \in \Omega$ at time $t > 0$, with degree of malfunctioning $a \in [0, 1]$, and is such that $f(x, a, t)\, da$ represents the number of neurons in x which at time t have a degree of malfunctioning comprised between a and $a + da$ (i.e. it is the local percentage of neuronal mass at time t with degree of malfunctioning between a and $a + da$). For a precise mathematical formulation of f in terms of probability measures, see [7]. In fact, in Section 3 we shall replace the absolute continuous measure $f(x, a, t)\, da$ with a generic probability measure $df_{x,t}(a)$. We assume that a close to 0 stands for "the neuron is healthy" whereas a close to 1 stands for "the neuron is dead".

Equations (2b), (2c), (2d) describe the dynamics of Aβ. Here

(1) $u_1(x, t)$ is the density of monomers in the point $x \in \Omega$ at time $t > 0$;
(2) $u_2(x, t)$ is the cumulative density of soluble oligomers, which are regarded collectively as a single compartment;
(3) $u_3(x, t)$ is the density of senile plaques, also considered as a single compartment. We include in this compartment all the combinations of monomers and oligomers producing Aβ entities other than those comprised in the compartments 1 and 2.

Therefore (2c) and (2d) are *compartmental* Smoluchowski-type equations with diffusion, agglomeration and clearence. A classical reference for Smoluchowski equations is [20, 10]. Originally, these equations were introduced for the study of the aerosols; applications of Smoluchowski system to the description of the agglomeration of Aβ amyloid appeared for the first time in [15], and subsequently in [1, 3, 6, 5]. Such a compartmental model (see also [4]), which in particular does not distinguish the densities of the soluble oligomers based on their length, is justified by the fact that, according to the literature, there is no clinical evidence on the maximum length of toxic Aβ oligomers [11]. Notice that equation (2d) for the concentration of fibrils u_3 does not feature a diffusion term since fibrils are assumed not to move. Finally, consistently with the compartmental nature of the model, we take

the coagulation parameters constant and equal to $\alpha > 0$, neglecting the fact that they may feature a dependence on the specific lengths of the aggregating oligomers, see [3]. Since senile plaques were also found in "healthy brains", we have chosen to take $\alpha > 0$ and introduced in (3) the modelling hypothesis that there is a positive threshold $\overline{U}$ for the density of oligomers below which toxic effects do not occur. Given the complexity of the fluid flow in the parenchima, in the present paper we have chosen to assume that the diffusion of Aβ simply isotropic, while the terms $-\sigma_1 u_1$ in (2b) and $-\sigma_2 u_2$ in (2c) are meant to keep into account several clearance phenomena, mainly due to phagocytic activity of the microglia. We are fully aware of the oversimplification of these choices, but we have preferred to focus on the possible interaction between Aβ and τ.

Equation (2e) is the equation for the density $w(x,t)$ of misfolded τ protein. The first right-hand-side term takes into account the potential triggering effect of Aβ olygomers on the misfolding process for τ. It is known that Aβ-plaques proximal to neuronal cell bodies can instigate τ-pathology [16, 18, 13]. However, there is no current evidence that τ influences Aβ-pathology in humans [18]. Due to these considerations, we propose an explicit modelling hypothesis in our model: *some minimal level of Aβ-aggregation is required to initiate τ-pathology.* This assumption is contained in the term $C_w(u_2 - U_w)^+$ in (2e), with $C_w > 0$ a proportionality constant. It is a built-in feature of our model that in equation (2e) the evolution of misfolded τ is only due to the toxic effect of Aβ. The second term describes the prion-like non-local spreading of the misfolded τ in possibly distant points of the brain according to the spatial kernel h_w. We assume that the dynamics of τ take place on the slow time scale t. In the absence of precise indications from the biomedical literature, this choice seems reasonable in view of the fact that τ is especially involved in the progression of the disease rather than in the Aβ agglomeration and the consequent formation of senile plaques. The term H represents a non-negative source term for w.

The progression of AD occurs on the slow time scale t, over decades, and is determined by the deterioration rate $v[f] = v[f](x,a,t)$, for which we assume the following form:

$$v[f](x,a,t) = C_{\mathcal{G}} \int_0^1 (b-a)^+ f(x,b,t)\, db + C_{\mathcal{S}}(1-a)\big(u_2(x,t) - \overline{U}\big)^+ + C_{\mathcal{W}}(1-a)w(x,t). \tag{3}$$

The integral term describes the propagation of AD among close neurons, while the second term models the action of toxic Aβ oligomers. The threshold $\overline{U} > 0$ indicates the minimal amount of toxic Aβ needed to damage neurons. The third term accounts for the toxicity of misfolded τ: it assumes that it is proportional to the concentration w through a proportionality constant $C_{\mathcal{W}} > 0$ and that it is modulated by the current degree of malfunctioning of the neurons. To stress the fact that the space variable x plays merely the role of a parameter, we shall also write $v_x = v_x(a,t) := v[f](x,a,t)$. Moreover, for sake of simplicity we will occasionally write (3) as

$$v_x(a,t) = \int_{[0,1]} \mathcal{G}_x(a,b)\, f(x,b,t)db + \mathcal{S}(x,a,u_2(x,t),w(x,t)). \tag{4}$$

The term $J[f] = J[f](x,a,t)$ on the right-hand side of (2a) describes the possible onset of AD in random locations of the domain Ω as a result of a microscopic stochastic jump process. The latter takes into account the possibility that the degree of malfunctioning of neurons randomly jumps to higher values due to external agents or genetic factors. The explicit expression of this term is

$$J[f](x,a,t) = \eta(t)\chi(x,t)\left(\int_0^1 P(t,x,a_* \to a) f(x,a_*,t)\, da_* - f(x,a,t)\right), \tag{5}$$

where $P(t,x,a_* \to a)$ denotes the probability that the degree of malfunctioning of neurons in the point $x \in \Omega$ jumps at time $t > 0$ from a_* to $a > a_*$. The coefficient $\eta > 0$ is the jump rate, while for an explicit form of P see [7]. It is worth stressing that (2a), together with the detailed expressions (3), (5) of the terms $v[f]$, $J[f]$, may be obtained from a mesoscopic description of a microscopic model of neuron-to-neuron interactions as shown in [6].

To conclude the presentation of the model, we mention that the term $\mathcal{F}[f] = \mathcal{F}[f](x,a,t)$ in (2b) describes the production of Aβ monomers by neurons, taking into account that, up to a certain extent, damaged neurons increase such a production. In view of these considerations, we choose

$$\mathcal{F}[f](x,t) = C_{\mathcal{F}} \int_0^1 (\mu_0 + a)(1-a) f(x,a,t)\, da. \tag{6}$$

Here, the small constant $\mu_0 > 0$ accounts for Aβ production by healthy neurons while the factor $1 - a$ expresses the fact that dead neurons do not produce amyloid. As usual, $C_{\mathcal{F}} > 0$ is a proportionality constant.

3. Results

3.1. **Initial and boundary conditions.** Concerning boundary conditions, we assume that $\partial\Omega$ is formed by two smooth disjoint sets, $\partial\Omega_0$ and $\partial\Omega_1$, where $\partial\Omega_0$ is the outer boundary, delimiting the considered portion of cerebral tissue, and $\partial\Omega_1$ is the inner boundary delimiting the cerebral ventricles. On $\partial\Omega_0$ we prescribe classical no-flux conditions for the concentrations of soluble Aβ oligomers. On $\partial\Omega_1$ we prescribe a Robin type condition for the concentrations of the Aβ oligomers in order to take into account their removal by the cerebrospinal fluid through the choroid plexus [12, 19]. We have then:

$$\begin{cases} \nabla u_i \cdot \mathbf{n} = 0 & \text{on } \partial\Omega_0,\ i = 1, 2 \\ \nabla u_i \cdot \mathbf{n} = -\beta u_i & \text{on } \partial\Omega_1,\ i = 1, 2, \end{cases} \tag{7}$$

where $\beta > 0$ is a proportionality parameter and $\mathbf{n}$ the outward normal unit vector to $\partial\Omega$. The choice of the right-hand side of the above Robin condition is a simple one, due to the lack of experimental data.

We complement system (2a)–(2e) with a proper set of initial conditions:

$$f(x, a, 0) = f_0(x, a), \qquad u_i(x, 0) = u_{0,i}(x)\ (i = 1, 2, 3), \qquad w(x, 0) = 0, \tag{8}$$

where the condition on w is taking into account that for $t = 0$ the brain is healthy and therefore there is no misfolded τ.

3.2. **Hypotheses on the data.**

Definition 3.1. *The space $\mathcal{P}([0, 1])$ of probability measures on $[0, 1]$ endowed with the Wasserstein distance $\mathcal{W}_1$ is denoted by $X_{[0,1]}$.*

We will use the following assumptions on the data (below ∂_a, ∇_u etc. denote distributional derivatives; C denotes a generic constant):

(H_1) $\varepsilon, C_{\mathcal{F}}, C_{\mathcal{G}}, C_{\mathcal{S}}, C_{\mathcal{W}}, C_w, \mu_0, d_i, \sigma_i, \alpha, \overline{U}$ are positive constants ($1 \le i < 3$, $1 \le j \le 3$);

(H_2) $u_{0,i} \in C(\overline{\Omega})$ is nonnegative ($i = 1, 2, 3$), and $f_0(x, a) \in X_{[0,1]}$ for a.e. $x \in \Omega$;

(H_3) χ is the characteristic function of a measurable set $Q_0 \subseteq Q_T = \Omega \times [0, T]$; the function $\eta \in C([0, T])$ is nonnegative;

(H_4) for a.e. $x \in \Omega$, $\mathcal{G}_x \in C\left([0, 1]^2\right)$, $\mathcal{G}_x(1, b) = 0$ for $b \in [0, 1]$, and

$$-C \leq \partial_a \mathcal{G}_x \leq 0, \ |\partial_b \mathcal{G}_x| \leq C \quad \text{in } [0, 1]^2; \tag{9}$$

(H_5) $\mathcal{S} \in L^\infty\left(\Omega; C\left([0, 1] \times [0, \infty)^3\right)\right)$, $\mathcal{S}(x, 1, u_1, u_2, w) = 0$ for $u_i \geq 0, w \geq 0$, and a.e. $x \in \Omega$, and for all compact sets $K \subset [0, \infty)^3$ there exists a constant $C(K)$ such that for a.e. $x \in \Omega$

$$-C(K) \leq \partial_a \mathcal{S}(x, a, u, w) \leq 0, \ |\nabla_u \mathcal{S}(x, a, u, w)| + |\nabla_w \mathcal{S}(x, a, u, w)| \leq C(K) \tag{10}$$

for $a \in [0, 1]$, $(u, w) \in K$;

(H_6) $P \in C([0, T] \times [0, 1]^2)$, P is nonnegative, for all $t \in [0, T]$

$$\int_0^1 P(t, b, a)\, da = 1 \quad \text{for } b \in [0, 1], \qquad P(t, b, a) = 0 \quad \text{if } a < b \tag{11}$$

and there exists $L > 0$ such that for all $a', a'', b', b'' \in [0, 1]$ and $t \in [0, T]$

$$\left|P(t, b', a') - P(t, b'', a'')\right| \leq L\left(\left|b' - b''\right| + \left|a' - a''\right|\right). \tag{12}$$

(H_7) $h_w \geq 0$ and $\sup_{x \in \Omega} \int_\Omega h_w(x, y)\, dy < +\infty$. Moreover, we assume that the nonnegative source term H for w belongs to $C(\overline{\Omega})$.

3.3. **Main result.** The main result of this note is a well-posedness result for the system (2), with boundary condition (7) and initial conditions (8). In order to state the main theorem, we need to define an appropriate weak solution for the model under consideration.

Definition 3.2. *A* $(3+2)$*-ple* (f, u_1, u_2, u_3, w) *is called a solution of problem* (2), (7), (8) *in* $[0, T]$ *if*

(*i*) $f \in \mathcal{L}(\Omega; C([0, T]; X_{[0,1]}))$;

(*ii*) $u_i, w \in C(\overline{Q}_T)$ *and* $u_i, w \geq 0$ *in* Q_T *for* $1 \leq i \leq 3$;

(*iii*) *the first equation in* (2) *is satisfied in a weak sense: for a.e.* $x \in \Omega$

$$\int_0^\tau \left(\int (\partial_t \phi + v_x \partial_a \phi)\, df_{x,t} + \int \phi\, dJ_{x,t} \right) dt = \int \phi(\cdot, \tau)\, df_{x,\tau} - \int \phi(\cdot, 0)\, d(f_0)_x$$

for all $\tau \in [0,T]$ *and* $\phi \in C^1([0,1] \times [0,T])$*, where the function* v *is defined by* (4) *and the signed measure* J *by* (5)*;*

(*iv*) *if* $1 \le i < 3$*,* $u_i \in L^2([0,T]; H^1(\Omega))$ *and*

$$\begin{aligned} d_i \int_0^T \left[\int_\Omega \nabla u_i(x,s) \cdot \nabla \psi(x,s) dx + \gamma_i \int_{\partial\Omega_1} u_i(x,s) \psi(x,s) d\sigma(x) \right] ds \\ = \varepsilon \iint_{Q_T} u_i \psi_t + \varepsilon \int_\Omega u_{0i} \psi(x,0)\, dx + \iint_{Q_T} R_i \psi \end{aligned} \tag{13}$$

for all $\psi \in H^1([0,\tau]; H^1(\Omega))$*,* $\psi(x,\tau) = 0$*, where* R_i *is defined as the right hand side in* (2b) *and* (2c)*;*

(*v*) $\partial_t u_3 \in C(\overline{Q}_T)$*,* $u_3(\cdot,0) = u_{0,3}$ *in* Ω*, and the equation for* u_3 *in* (2d) *is satisfied in* Q_T*;*

(*vi*) w *satisfies* (2e) *in the integral sense.*

We are now in a position to provide the following well-posedness result:

Theorem 3.1 (well-posedness)**.** *Let* $\Omega \subset \mathbb{R}^n$ *be an open and bounded set with a smooth boundary* $\partial\Omega$*, which is the disjunct union of* $\partial\Omega_0$ *and* $\partial\Omega_1$*. Let* $T > 0$*, and let hypotheses* (H_{1-7}) *be satisfied. Then problem* (2)-(7)-(8) *has a unique solution in* $[0,T]$ *in the sense of Definition 3.2.*

Below we shall reformulate problem (2)-(7)-(8) in terms of the characteristics and we will establish the equivalence between the original problem and the one in terms of characteristics. Then we will present a local (in terms of time t) existence theorem for the latter system (the one in terms of characteristics). Since this local solution can be continued in $[0,T]$, the proof of Theorem 3.1 will then follow due to the equivalence between the two systems.

Therefore we begin by introducing the characteristics: let $f \in \mathcal{L}(\Omega; C([0,T]; X_{[0,1]}))$ and $u_i \in C(\overline{Q}_T)$, and let $v[f]$ be defined by (4). By the Lipschitz continuity of $a \mapsto v_x(a,t)$,

for a.e. $x \in \Omega$ the problem for the characteristic issued from $y \in [0,1]$, given by:

$$\begin{cases} \partial_t A_x(y,t) = v_x(A_x(y,t),t) & \text{for } 0 < t \le T \\ A_x(y,0) = y \end{cases} \tag{14}$$

has a unique solution which satisfies

$$\begin{cases} 0 \le A_x(y_1,t) < A_x(y_2,t) \le A_x(1,t) = 1 & \text{if } 0 \le y_1 < y_2 \le 1,\ 0 \le t \le T \\ A_x(y,t_1) \le A_x(y,t_2) & \text{if } y \in [0,1],\ 0 \le t_1 \le t_2 \le T\,. \end{cases} \tag{15}$$

Observe that, for a.e. $x \in \Omega$, the function $y \mapsto A_x(y,t)$ is continuous and

$$\partial_y A_x(y,t) = \exp\left(\int_0^t \partial_a v_x(A_x(y,s),s)\,ds\right) > 0 \quad \text{for all } t \in [0,T]. \tag{16}$$

In particular for a.e. $x \in \Omega$ the function $y \mapsto A_x(y,t)$ is injective for all $t \in [0,T]$.

We now reformulate the original problem in terms of the characteristics. Specifically, we shall see below that the measure f can be obtained by transporting along the characteristics a suitable measure g (i.e., f is the push forward of g through A) which satisfies:

$$\begin{cases} \partial_t A_x(y,t) = \displaystyle\int \mathcal{G}_x(A_x(y,t),A_x(\xi,t))\,dg_{x,t}(\xi) + \mathcal{S}(x,A_x(y,t),u_2,w) \\ \partial_t g_{x,t}(y) = \eta\chi\left[\partial_y A_x(y,t)\displaystyle\int P(t,A_x(\xi,t),A_x(y,t))\,dg_{x,t}(\xi) - g_{x,t}(y)\right] \\ \varepsilon\partial_t u_1 - d_1\Delta u_1 = -u_1\displaystyle\sum_{j=1}^{3} a_{1,j}u_j - \sigma_1 u_1 \\ \qquad\qquad + C_{\mathcal{F}}\displaystyle\int(\mu_0 + A_x(\xi,t))(1 - A_x(\xi,t))\,dg_{x,t}(\xi) \\ \varepsilon\partial_t u_2 - d_2\Delta u_2 = \frac{1}{2}a_{1,1}u_1^2 - u_2\displaystyle\sum_{j=1}^{3} a_{2,j}u_j - \sigma_2 u_2 \\ \varepsilon\partial_t u_3 = \frac{1}{2}\displaystyle\sum_{\substack{j+k\ge 3 \\ k,\,j<3}} a_{j,k}u_j u_k, \\ \partial_t w = C_w(u_2 - U_w)^+ + \int_\Omega h_w(|y-x|)w(y,t)\,dy + H(x), \end{cases} \tag{17}$$

where $x \in \Omega$, $y \in [0,1]$, $t \in (0,T]$, with initial-boundary conditions

$$
\begin{cases}
g_{x,0}(y) = f_0(x,y),\ A_x(y,0) = y & \text{if } x \in \Omega,\ 0 \le y \le 1 \\
u_i(x,0) = u_{0,i}(x) & \text{if } x \in \Omega,\ 1 \le i \le 3 \\
\partial_n u_i(x,t) = 0 & \text{if } x \in \partial\Omega_0,\ t \in (0,T],\ 1 \le i < 3 \\
\partial_n u_i(x,t) = -\gamma_i u_i(x,t) & \text{if } x \in \partial\Omega_1,\ t \in (0,T],\ 1 \le i < 3 \\
w(x,0) = 0, & \text{if } x \in \Omega.
\end{cases} \tag{18}
$$

The appropriate notion of weak solution of system (17)-(18) can be derived from that of solution of the original system (see definition (3.2)) through a change of variables.

We now state a local (in time) existence theorem for system (17)-(18) and give a sketch of the proof proceeding by steps (for a detailed proof, but without τ, see [7]).

Theorem 3.2 (local existence)**.** *Let $\Omega \subset \mathbb{R}^n$ be an open and bounded set with a smooth boundary $\partial\Omega$, which is the disjunct union of smooth manifolds $\partial\Omega_0$ and $\partial\Omega_1$. Let $T > 0$ and $N \in \mathbb{N}$, and let hypotheses (H_{1-7}) be satisfied. Then there exists $\tau \in (0,T]$ such that problem* (17)-(18) *has a unique solution in $[0,\tau]$.*

The proof relies on a suitable contraction argument. To this purpose we introduce the following metric space:

Definition 3.3. *Let $\tau \in (0,T]$ be given. We denote by $(\mathcal{X}_\tau, d)$ the complete metric space*

$$\mathcal{X}_\tau := L^\infty(\Omega; C([0,1]\times[0,\tau];[0,1]))\times\mathcal{L}(\Omega; C([0,T];X_{[0,1]}))\times C(\overline{\Omega}\times[0,\tau];\mathbb{R}^3)\times C(\overline{\Omega}\times[0,\tau];\mathbb{R}),$$

where $L^\infty(\Omega; C([0,1]\times[0,\tau];[0,1]))$, $C(\overline{\Omega}\times[0,\tau];\mathbb{R}^3)$, and $C(\overline{\Omega}\times[0,\tau];\mathbb{R})$ are endowed with their natural metrics as normed spaces. Finally $\mathcal{L}(\Omega; C([0,T];X_{[0,1]}))$ is endowed with the Wasserstein metric

$$\sup_{x\in\Omega}\max_{t\in[0,T]} \mathcal{W}_1(f_{x,t}, g_{x,t}).$$

We denote by $\mathcal{X}_{\tau,\rho}$ the closed ball in $\mathcal{X}_\tau$ of radius $\rho > 0$ centered at $(y, f_0, u_0, 0)$.

Lemma 3.1 (Step 1)**.** *Let $(\hat{A}, g, u, w) \in \mathcal{X}_T$ and set, for a.e. $x \in \Omega$,*

$$\hat{v}_x(a,t) := \int \mathcal{G}_x(a, \hat{A}_x(\xi,t))\, dg_{x,t}(\xi) + \mathcal{S}(x,a,u_2,w) \ge 0. \tag{19}$$

Then, for a.e. $x \in \Omega$, the Cauchy problem

$$\begin{cases} \partial_t \underline{A}_x(y,t) = \hat{v}_x(\underline{A}_x(y,t),t) \quad \text{for } t>0 \\ \underline{A}_x(y,0) = y \in [0,1] \end{cases} \tag{20}$$

has a unique solution defined for all $t \in (0,T]$. Thus $(\hat{A},g,u,w) \in \mathcal{X}_T$ defines a new point $(\underline{A},g,u,w) \in \mathcal{X}_T$.

Lemma 3.2 (Step 2)**.** *Let $(\hat{A},g,u,w) \in \mathcal{X}_T$. Let, for a.e. $x \in \Omega$, $\underline{A}$ be defined as in Lemma 3.1 and $(F[g])_{x,t}$ be the signed measure on $[0,1]$ defined by*

$$d(F[g])_{x,t} = \eta(t)\chi(x,t)\left[\partial_y \underline{A}_x(y,t)\int P(t,\underline{A}_x(\xi,t),\underline{A}_x(y,t))dg_{x,t}(\xi)\,dy - dg_{x,t}(y)\right]$$

for $0<t\le T$. Then, for a.e. $x \in \Omega$,

(i) the integral equation

$$\underline{g}_{x,t} = (f_0)_x + \int_0^t (F[\underline{g}])_{x,s}\,ds \tag{21}$$

has a unique solution $t \mapsto \underline{g}_{x,t}$ which belongs to $C([0,T],X_{[0,1]})$; (ii) the measure $\underline{g}_{x,t}$ is a weak solution of the system

$$\begin{cases} \partial_t \underline{g}_{x,t}(y) = \eta\chi\left[\partial_y \underline{A}_x(y,t)\int P(t,\underline{A}_x(\xi,t),\underline{A}_x(y,t))d\underline{g}_{x,t}(\xi) - \underline{g}_{x,t}(y)\right] \\ \underline{g}_{x,0} = (f_0)_x. \end{cases}$$

Thus $(\underline{A},g,u,w) \in \mathcal{X}_T$ (and hence $(\hat{A},g,u,w)$) defines a new point $(\underline{A},\underline{g},u,w) \in \mathcal{X}_T$.

Denote by F_1,F_2,F_3 the right hand sides of (2b), (2c), (2d), respectively.

Step 3: let $\underline{u} := (\underline{u}_1\underline{u}_2,\underline{u}_3)$ be the weak solution of the problem

$$\begin{cases} \varepsilon\partial_t \underline{u}_m - d_m\Delta\underline{u}_m = F_m(\underline{A},\underline{g},u,w) & (m=1,2) \\ \varepsilon\partial_t \underline{u}_3 = F_3(\underline{A},\underline{g},u,w), \qquad \text{in } Q_\tau = \Omega\times(0,\tau] \\ \partial_t w = C_w(u_2-U_w)^+ + \int_\Omega h_w(|y-x|)w(y,t)\,dy + H(x) & \text{in } Q_\tau. \end{cases} \tag{22}$$

with initial-boundary conditions

$$\begin{cases} \underline{u}_i(x,0) = u_{0,i}(x) & \text{if } x \in \Omega \\ \partial_n \underline{u}_i(x,t) = 0 & \text{if } x \in \partial\Omega_0,\ t > 0 \\ \partial_n \underline{u}_i(x,t) = -\gamma_i \underline{u}_i(x,t) & \text{if } x \in \partial\Omega_1 \times (0,\tau] \end{cases} \qquad (1 \le i \le 3). \tag{23}$$

Such a solution exists by standard arguments and $(\underline{A}, \underline{g}, \underline{u}, w) \in \mathcal{X}_{\tau,\rho}$, provided τ is small enough. Thus, eventually, $(\hat{A}, g, u, w) \in \mathcal{X}_{\tau,\rho}$ defines a new point $(\underline{A}, \underline{g}, \underline{u}, w) \in \mathcal{X}_{\tau,\rho}$.

Finally (Step 4), Banach-Caccioppoli fixed point theorem, togheter with classical *a priori* estimates for the solutions of system (22), yields the existence of a solution of the Cauchy problem in Q_τ

$$\partial_t \underline{w} = C_w(\underline{u}_2 - U_w)^+ + \int_\Omega h_w(|y-x|)\underline{w}(y,t)\,dy + H(x)$$

with $\underline{w}(x,0) = 0$. Thus, combining Steps 1–4, we are now ready to define the map to which we shall apply a contraction argument. Let $\rho > 0$ be fixed. We set

$$\mathcal{H}(\hat{A}, g, u, w) := (\underline{A}, \underline{g}, \underline{u}, \underline{w}) \quad \text{for } (\hat{A}, g, u, w) \in \mathcal{X}_{\tau,\rho}. \tag{24}$$

Let $\mathcal{T}_d$ denote the metric topology of $X_{\tau,\rho}$ and $\mathcal{T}$ the weaker topology on $\mathcal{X}_{\tau,\rho}$ which is obtained by endowing $L^\infty(\Omega; C([0,1]\times[0,\tau];[0,1]))$ with the L^1-topology on $\Omega \times [0,1] \times [0,\tau]$.

Proposition 3.1. *Let $\rho > 0$ be fixed and let $\mathcal{H}(\hat{A}, g, u, w)$ be defined by (24). If $\tau > 0$ is sufficiently small, then $\mathcal{H} : \mathcal{X}_{\tau,\rho} \to \mathcal{X}_{\tau,\rho}$, $(\underline{A}_n, \underline{g}_n, \underline{u}_n, \underline{w}_n) \to (\underline{A}, \underline{g}, \underline{u}, \underline{w})$ in $\mathcal{T}$ if $(\hat{A}_n, g_n, u_n, w_n) \to (\hat{A}, g, u, w)$ in $\mathcal{T}_d$, and $\mathcal{H}$ is a contraction on $\mathcal{H}(X_{\tau,\rho})$.*

The proof of theorem 3.2 will then follow by means of the following fixed point theorem (see [7]):

Proposition 3.2 (Fixed Point Theorem)**.** *Let (X,d) be a complete metric space and let $\mathcal{T}_d$ be the topology induced by d. Let $\mathcal{T}$ be a Hausdorff topology on X which is weaker than $\mathcal{T}_d$. If $\mathcal{H} : X \to X$ is a contraction on $\mathcal{H}(X)$ which is $(\mathcal{T}_d, \mathcal{T})$-sequentially continuous, then $\mathcal{H}$ has a unique fixed point.*

It has been shown in [7], Section 5, that the local solution of the system (17)-(18) can be continued in $[0, T]$. Moreover, in Theorems 3.3 and 3.4 in the same paper it has been shown that system (2)-(7)-(8) and system (17)-(18) are equivalent. Therefore, the proof of Theorem 3.1 is accomplished.

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