A reaction-diffusion model of spatial propagation of Aβ oligomers in early stage Alzheimer's disease

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Abstract The misconformation and aggregation of the protein Amyloid-Beta (Aβ) is a key event in the propagation of Alzheimer's Disease (AD). Different types of assemblies are identified, with long fibrils and plaques deposing during the late stages of AD. In the earlier stages, the disease spread is driven by the formation and the spatial propagation of small amorphous assemblies called oligomers. We propose a model dedicated to studying those early stages, in the vicinity of a few neurons and after a polymer seed has been formed. We build a reaction-diffusion model, with a Becker-Döring-like system that includes fragmentation and size-dependent diffusion. We hereby establish the

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theoretical framework necessary for the proper use of this model, by proving the existence of solutions using a fixed point method.

Keywords Alzheimer's Disease · Reaction-diffusion · Partial differential equations

Mathematics Subject Classification (2010) 35K57 · 92B05

1 Introduction

Alzheimer's disease (AD) is the most common of neurodegenerative diseases, a group that also includes Parkinson's disease, Huntington disease, Creutzfeldt-Jakob disease, and transmissible spongiform encephalopathies. AD consists in a gradual neuron loss not consistent with habitual aging. As is the case for these other diseases, AD is associated with the misconformation, aggregation and propagation of different proteins in the neural system (Soto, 2003), in particular Amyloid-beta (Aβ) and Tau (Hardy and Higgins, 1992; Hardy, 2003). These proteins can adopt different stable conformations. Some of them, called misconformations, lead to the creation of structured assemblies that are reliable biological markers of the disease (Haass and Selkoe, 2007; Ittner and Götz, 2011; Jack Jr et al., 2013).

Aβ is formed by cleavage of the Amyloid Precursor Protein (APP), which is produced by healthy neurons and attaches to the membrane of neuron cells with an endogenous purpose that remains unclear (Hiltunen et al., 2009). The self-assembly of Aβ leads to different types of structures. Fibrils are long linear polymers, that can coalesce into large tangles called plaques. Plaques constitute the visible deposits observed in most late-stage AD patients. During the earlier stages smaller and less ordered structures are also formed, commonly named oligomers. To the best of our knowledge the interactions between the different types of structures are unclear, but it has been shown that oligomers appear early on during the onset of Alzheimer's disease (Oda et al., 1994, 1995), while fibrils and plaques become detectable much later. Oligomers are soluble and difficult to detect, but their role in AD propagation and pathology is believed to be essential (Čižas et al., 2011; Haass and Selkoe, 2007; Sengupta et al., 2016; Zhao et al., 2012).

The generally accepted mechanism for the onset of AD is the so-called *cascade hypothesis* (Yankner, 1996; Hardy and Higgins, 1992; Haass and Selkoe, 2007; Cohen et al., 2013). The first appearance of misfolded Aβ in the form of oligomers is a rare and highly stochastic event, possibly favored by mutations or co-factors. Monomers can spontaneously change conformation and assemble into small proto-oligomers. This process is termed (primary) nucleation. Once the process has started and a seed has appeared, the oligomers replicate and propagate rapidly (Morales et al., 2012; Olsson et al., 2018; Sowade and Jahn, 2017). This second step is usually referred to as secondary nucleation (Cohen et al., 2013). Although the precise phenomenon that allows oligomers to replicate is not known, it can be described as a prion-like propagation (Rasmussen

et al., 2017). Moreover, recent discoveries show the existence of a positive feedback where infected cells increase production of Aβ proteins leading to a further acceleration of the pathology (Elliott et al., 2018). The propagation of misconformed proteins in the brain is the result of multiple phenomena acting at different scales. At smaller scales diffusion drives the propagation, but for long range propagation other mechanisms come into play (*e.g.* exosomes) (Xiao et al., 2017). As the pathology progresses, stagnant fibrillar structures and plaques begin to form. These structures remain fixed or travel slowly. However, breakage of fibrils potentially produces new seeds that propagate fast and drive the spatial progression and the development of AD (Cohen et al., 2013). It is only at advanced stages of the disease and at longer-time-scales that the symptoms of dementia appear (Perrin et al., 2009). The spatial and temporal progression of biomarkers and the appearance of symptoms in AD is thus highly complex and heterogeneous (Storandt et al., 2002; Ohm et al., 1995; Smith, 2002; Perrin et al., 2009). For this reason, it is of particular interest for the biomedical community to understand the mechanisms of propagation and replication of Aβ oligomers, especially during the early latent stages of AD. Insights into this phenomenon could help develop therapeutic strategies before the first signs of dementia (Eleuteri et al., 2015; Haass and Selkoe, 2007). Having a mechanistic model of the oligomers replication coupled with spatial propagation is a first step towards identifying the key parameters in the early stage development of the disease. If this mechanistic model is validated (which is the following step in the process), hopefully some therapeutic strategies could be proposed by focusing on the events that impact propagation the most.

One approach towards this purpose is via mathematical and computational modeling. The dynamics of misfolded proteins and their role in neurodegenerative disorders have attracted considerable attention from mathematicians (Carbonell et al., 2018) with a strong increase during the last 30 years. Most influential studies have used systems of Ordinary Differential Equations (ODEs) to model and replicate the dynamics of aggregation and proliferation of prion proteins (Eigen, 1996; Harper and Lansbury Jr, 1997; Nowak et al., 1998; Greer et al., 2006). Different spatial extensions to these models have been proposed under the assumption of isotropic diffusion (Matthäus, 2006), diffusion combined with a network topology (Matthaeus, 2009; Raj et al., 2012) or lattice-like domains based on cell connectivity networks (Stumpf and Krakauer, 2000). Concerning AD, mathematical modeling has focused on analyzing microscopic processes related to prion-like replication or joint prion-Aβ dynamics. Recently, a number of multi-scale, non-spatial models have been aimed at studying the evolution of monomers, oligomers, fibrils, and plaques (Ciuperca et al., 2018; Helal et al., 2014, 2018). Some descriptions use discrete aggregate sizes, others favor continuous sizes. The two approaches are similar at large aggregate sizes but have discrepancies at the scale of small oligomers (Doumic et al., 2009; Vasseur et al., 2002; Velázquez, 1998). In the case of discrete sizes, models generally use the Becker-Döring Equations. Spatial extensions of these models have been rare with the possible exception of

(Bertsch et al., 2016, 2017) where interesting results where achieved but where potentially essential biological factors were not considered when extrapolating microscopic processes to larger-spatial scales. Integration of microscopic, mesoscopic and macroscopic scales is difficult as there are different processes intervening at each level (*e.g* spreading through exosomes, axons, or cerebrospinal fluid). Overall, few models have successfully integrated molecular and large scales (Carbonell et al., 2018).

In the present study we introduce a model based on a discrete growth-fragmentation system of oligomeric species, in which we include spatial diffusion. We focus our analysis on the early stages of the pathology, after a seed has appeared and oligomers start replicating. The resulting system of partial differential equations aims at representing the simultaneous replication and spatial diffusion of Aβ oligomers in the vicinity of a few neurons. More precisely, the considered $A\beta$ monomers can assemble first into proto-oligomers and then oligomers. Proto-oligomers are small unstable polymers that grow by addition of monomers (**polymerization**) and shrink by loosing monomers (**depolymerization**). Proto-oligomers can also fragment (**fragmentation**) into smaller pieces. Those processes are illustrated in Figure 1. The goal here is to establish a robust mathematical framework for the study of this model with theoretical results ensuring the relevance and stability of the model. This model is novel in the sense that it couples the chemical replication oligomers with their spatial-dependent toxicity. The results that we obtain here differ from the classical models of growth-fragmentation with spatial diffusion in that the oligomers have a direct impact on the production of monomers. This interplay needs to be dealt with and the mathematical study needs to be adapted. In the preliminary work (Andrade-Restrepo et al., 2020), we carried out a modeling work based on the description and the numerical simulation of this model where a simple representation of the oligomers neurotoxic effect is included. The numerical results reveal that the oligomers spatial dynamics are very sensitive to the balance between their diffusion and their replication. The paper is organized as follows. In Section 2 we describe the considered problem, Section 3 is devoted to setting up an associated regularized problem and the proof of its well-posedness. In Section 4 we prove the existence of solutions to our initial problem.

2 Initial problem description

2.1 Domain description and variables definition

Let us describe the problem at hand and its mathematical formulation. We consider a bounded domain $\Omega \subset \mathbb{R}^n$, with $n = 2$ or $n = 3$. A number N of holes in the domain, representing the neuron cells, are defined by the boundaries $\partial\omega_k$ for $k = 1 \in \{1, \dots, N\}$. The exterior boundary of Ω is denoted Γ. The whole

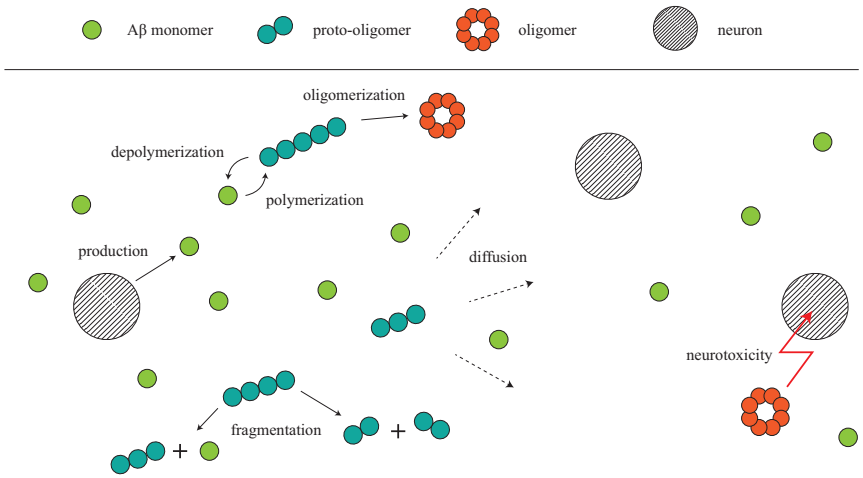

Fig. 1 Illustration of the biological species and interactions represented in the model

boundary of Ω is thus

$$\partial\Omega = \Gamma \cup \bigcup_{k=1}^{N} \partial\omega_k.$$

This geometric description of the domain is illustrated in Figure 2.

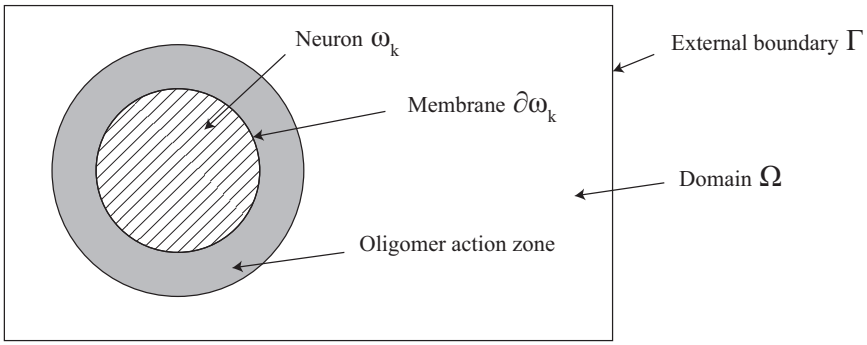

Fig. 2 Illustration of the mathematical domain used in the model

We consider a time interval $[0,T]$ with $T>0$. The unknowns of the problem are $m, \mu_2, \mu_3, \cdots, \mu_{i_0} : \Omega \times (0,T) \mapsto \mathbb{R}$ with $i_0 \in \mathbb{N}, i_0 \geq 5$. Here $m := m(x,t)$ represents the monomers concentration, $\mu_i := \mu_i(x,t)$ with $i \in \{2, \cdots, i_0 - 1\}$ represents the concentration of proto-oligomers of size i and $\mu_{i_0} := \mu_{i_0}(x,t)$ is the concentration of oligomers.

We look for solutions that are L^2 both in time and in space for generality, and that are non-negative. For this purpose, let us define the Banach space

$$X = L^2(0,T : L^2(\Omega))$$

which is identified with $L^2(\Omega \times (0,T))$.
In the following for any space $\mathcal{B}$ of functions defined on $(0,T) \times \Omega$ or on Ω only, we denote by $\mathcal{B}_+$ the subset of non negative function of $\mathcal{B}$.
Our problem will be defined on $\underbrace{X_+ \times X_+ \cdots \times X_+}_{i_0 \text{ times}}$ which is denoted by $X_+^{i_0}$.

2.2 Parameters description and assumptions

All parameters introduced in the following are assumed to be real and non-negative. Each species, from monomers to oligomers of size i_0, has its own diffusion coefficient denoted as D_i for size i. Monomers are degraded from the system with rate δ. Proto-oligomers grow by monomer addition with polymerization rate r_i for size i, and they can lose one monomer by depolymerization with rate b (constant). Proto-oligomers can also fragment with a homogeneous fragmentation kernel and a fragmentation rate $\beta \times (i-1)$ for size i. Finally γ denotes the rate of absorption of matter at the external boundaries of the domain, and B_k denotes the time-dependent rate of monomer production by neuron k. A summary of all parameters and variables is proposed in Table 1, and the biological model behind those processes is illustrated in Figure 1.

In order to simplify the equations formulation, we define the following coefficients

$$\begin{aligned}
&a_{2,2} = \beta, a_{2,3} = 2\beta + b,\\
&\text{for } j = 4, \ldots, i_0 - 1,\ a_{2,j} = 2\beta,\\
&\text{for } i = 3, \ldots, i_0 - 2,\ a_{i,i} = b + \beta(i-1), a_{i,i+1} = 2\beta + b,\\
&\text{ and for } j = i+2, i_0 - 1,\ a_{i,j} = 2\beta,\\
&a_{i_0-1,i_0-1} = b + \beta(i_0 - 2).
\end{aligned}$$

The monomer production rate B_k of neuron k, for $k \in \{1, \ldots, N\}$, satisfies the equations

$$\begin{aligned}
B_k'(t) =& -\tau \left(\int_{\mathbb{R}^N - \omega_k} \mu_{i_0}(x,t) \eta_k(x) dx \right) B_k,\\
B_k(0) =& B_k^0.
\end{aligned} \tag{1}$$

The function η_k is the indicator function of the oligomer action zone around neuron k, taking its values in $\{0, 1\}$. The oligomer action zone is a bounded domain containing the neuron ω_k, in which the oligomers of concentration μ_{i_0} have an impact on the monomer production rate, as described by (1). In practice for numerical simulations (already done in (Andrade-Restrepo et al., 2020)), the neurons are defined as circles and the oligomer action zones as larger concentric circles around the neurons, as it is illustrated in Figure 2.

Remark 1 We observe that B_k is expressed in terms of μ_{i_0} by

$$B_k(t) = B_k^0 \exp\Big(-\tau \int_0^t \int_{\mathbb{R}^n - \omega_k} \mu_{i_0}(x,s)\eta_k(x)dxds \Big). \tag{2}$$

One additional assumption is that the polymerization rate is an increasing function of the proto-oligomers size

$$\text{for } i = 2, \dots, i_0 - 2,\ r_i \leq r_{i+1}. \tag{3}$$

With all the parameters introduced and the assumptions established, we can formulate the problem at hand.

2.3 Problem formulation

The problem is defined as follows

Problem 1 **($\mathcal{P}$)** Find $(m, \mu_2, \mu_3 \dots, \mu_{i_0}) \in X_+^{i_0}$ such that

$$\frac{\partial m}{\partial t} = D_1 \Delta m - m\Big(\sum_{j=2}^{i_0-1} r_j \mu_j + \delta \Big) + \sum_{j=3}^{i_0-1} b\mu_j + 2\beta \sum_{j=2}^{i_0-1} \mu_j, \tag{4}$$

$$\frac{\partial \mu_2}{\partial t} = D_2 \Delta \mu_2 - m r_2 \mu_2 - a_{2,2}\mu_2 + \sum_{j=3}^{i_0-1} a_{2,j}\mu_j, \tag{5}$$

for $i = 3, \dots, i_0 - 2$,

$$\frac{\partial \mu_i}{\partial t} = D_i \Delta \mu_i + m r_{i-1}\mu_{i-1} - m r_i \mu_i - a_{i,i}\mu_i + \sum_{j=i+1}^{i_0-1} a_{i,j}\mu_j, \tag{6}$$

$$\frac{\partial \mu_{i_0-1}}{\partial t} = D_{i_0-1}\Delta \mu_{i_0-1} + m r_{i_0-2}\mu_{i_0-2} - m r_{i_0-1}\mu_{i_0-1} - a_{i_0-1,i_0-1}\mu_{i_0-1}, \tag{7}$$

$$\frac{\partial \mu_{i_0}}{\partial t} = D_{i_0}\Delta \mu_{i_0} + m r_{i_0-1}\mu_{i_0-1}. \tag{8}$$

We add the boundary conditions

$$D_1 \frac{\partial m}{\partial \nu} = -\gamma m \text{ on } \Gamma, \tag{9}$$

$$\text{for } k = 1, \dots, N,\ D_1 \frac{\partial m}{\partial \nu} = B_k(t) \text{ on } \partial\omega_k, \tag{10}$$

$$\text{and for } i = 2, \dots, i_0,\ D_i \frac{\partial \mu_i}{\partial \nu} = -\gamma \mu_i \text{ on } \Gamma, \tag{11}$$

$$D_i \frac{\partial \mu_i}{\partial \nu} = 0 \text{ on } \partial\omega_k. \tag{12}$$

Finally we have the initial conditions

$$\begin{aligned} \text{for almost all } x \in \Omega,\ \text{and for } i = 1, \dots, i_0, \mu_i(t=0,x) &= \mu_i^0(x), \\ \text{for almost all } x \in \Omega, m(t=0,x) &= m^0(x), \end{aligned} \tag{13}$$

with each initial concentration distribution $m^0, \mu_2^0, \mu_3^0, \dots, \mu_{i_0}^0$ taken in $L^2(\Omega)$ and non-negative.

We recall that this model is introduced in more detail and with biological interpretation of every term in (Andrade-Restrepo et al., 2020). More precisely, numerical simulations are performed and strong dependency of Alzheimer's disease progression and balance between oligomers diffusion and replication is highlighted.
Our purpose is here to establish the theoretical well-posedness of the model by proving the existence of solutions. In this prospect, we use a regularization method.

Table 1 Model variables and parameters

Symbol	Description
m (or μ_1)	Local density of Aβ monomers
μ_i, $i = 2 \dots i_0 - 1$	Local density of proto-oligomers
μ_{i_0}	Local density of oligomers
D_i	Diffusion coefficient of size i particles
δ	Degradation coefficient of monomers
γ	Boundary absorption rate
r_i	Polymerization rate of size i proto-oligomers
b	Depolymerization rate
β	Fragmentation rate
B_k	Monomer production rate on the membrane of neuron k

3 The associated regularized problem

We first define a regularized problem associated with $(\mathcal{P})$, by introducing a regularization of the monomer concentration.

3.1 Setting up a regularization

We denote by $\mathcal{D}(\mathbb{R}^{n+1})$ the set of test functions on $\mathbb{R}^{n+1}$, *i.e.* the set of infinitely smooth and compactly supported functions from $\mathbb{R}^{n+1}$ to $\mathbb{R}$. Let us consider, for $\varepsilon > 0$, a mollifier function $\theta_\varepsilon : \begin{cases} \mathbb{R}^{n+1} \to \mathbb{R} \\ (x,t) \to \theta_\varepsilon(x,t) \end{cases}$, with the following properties

$$\theta_\varepsilon \in \mathcal{D}(\mathbb{R}^{n+1}), supp(\theta_\varepsilon) \subset B_{\mathbb{R}^{n+1}}(0,\varepsilon), \theta_\varepsilon \geq 0, \int_{\mathbb{R}^{n+1}} \theta_\varepsilon(x,t)dxdt = 1,$$

where $B_{\mathbb{R}^{n+1}}(0,\varepsilon)$ is the ball centered in 0 and of radius ε in $\mathbb{R}^{n+1}$. For any function $v \in L^1(\Omega \times (0,T))$ we denote by $v * \theta_\varepsilon$ the convolution defined on $\mathbb{R}^{n+1}$ by

$$(v * \theta_\varepsilon)(x,t) = \int_{\mathbb{R}^{n+1}} v(x-y, t-s)\theta_\varepsilon(y,s)dyds$$

where v is extended by 0 outside $\Omega \times (0,T)$. The properties of θ_ε give the regularity of $(v * \theta_\varepsilon)$, more precisely

$$v * \theta_\varepsilon \in C^\infty(\bar{\Omega} \times [0,T]).$$

The first step to study the existence of solutions to the initial problem $\mathcal{P}$ is to prove the existence of solutions to the regularized problem $(\mathcal{P}_\varepsilon)$ defined below for any $\varepsilon > 0$, using a fixed point argument. After this regularization step, we study the limit $\varepsilon \to 0$ and obtain the existence of weak solutions to the problem $(\mathcal{P})$.

The problem $(\mathcal{P}_\varepsilon)$ is described as follows: find $(m_\varepsilon, \mu_{2,\varepsilon}, \dots, \mu_{i_0,\varepsilon})$ in X^{i_0} such that

$$\frac{\partial m_\varepsilon}{\partial t} = D_1 \Delta m_\varepsilon - m_\varepsilon \left(\sum_{j=2}^{i_0-1} r_j \mu_{j,\varepsilon} + \delta \right) + \sum_{j=3}^{i_0-1} b\mu_{j,\varepsilon} + 2\beta \sum_{j=2}^{i_0-1} \mu_{j,\varepsilon}, \quad (14)$$

$$\frac{\partial \mu_{2,\varepsilon}}{\partial t} = D_2 \Delta \mu_{2,\varepsilon} - (m_\varepsilon * \theta_\varepsilon) r_2 \mu_{2,\varepsilon} - a_{2,2}\mu_{2,\varepsilon} + \sum_{j=3}^{i_0-1} a_{2,j}\mu_{j,\varepsilon}, \quad (15)$$

$$\begin{aligned} \text{for } i =& 3, \dots, i_0 - 2, \\ \frac{\partial \mu_{i,\varepsilon}}{\partial t} =& D_i \Delta \mu_{i,\varepsilon} + (m_\varepsilon * \theta_\varepsilon) r_{i-1} \mu_{i-1,\varepsilon} - (m_\varepsilon * \theta_\varepsilon) r_i \mu_{i,\varepsilon} \\ & - a_{i,i}\mu_{i,\varepsilon} + \sum_{j=i+1}^{i_0-1} a_{i,j}\mu_{j,\varepsilon}, \end{aligned} \quad (16)$$

$$\begin{aligned} \frac{\partial \mu_{i_0-1,\varepsilon}}{\partial t} =& D_{i_0-1} \Delta \mu_{i_0-1,\varepsilon} + (m_\varepsilon * \theta_\varepsilon) r_{i_0-2} \mu_{i_0-2,\varepsilon} - (m_\varepsilon * \theta_\varepsilon) r_{i_0-1} \mu_{i_0-1,\varepsilon} \\ & - a_{i_0-1,i_0-1}\mu_{i_0-1,\varepsilon}, \end{aligned} \quad (17)$$

$$\frac{\partial \mu_{i_0,\varepsilon}}{\partial t} = D_{i_0} \Delta \mu_{i_0,\varepsilon} + m_\varepsilon r_{i_0-1} \mu_{i_0-1,\varepsilon}, \quad (18)$$

The boundary and initial conditions are the same as for the problem $(\mathcal{P})$.

Remark 2 We would normally denote by $(m_\varepsilon, \mu_{2,\varepsilon}, \dots, \mu_{i_0,\varepsilon})$ the solution of problem $(\mathcal{P}_\varepsilon)$, but for simplicity we omit the subscript ε in the following.

We can now study the existence of solutions to the regularized problem, by using a fixed-point method.

3.2 Existence of solutions for the regularized problem

Now we define the following application $F_0 : \begin{cases} (L^\infty(0,T:L^2(\Omega)))_+ \to X^{i_0-2} \\ \tilde{m} \to (\mu_2, \dots, \mu_{i_0-1}) \end{cases}$,
where $\mu_2, \dots, \mu_{i_0-1}$ are solutions of the system

$$\begin{aligned}
\frac{\partial \mu_2}{\partial t} =& D_2 \Delta \mu_2 - \tilde{m} r_2 \mu_2 - a_{2,2}\mu_2 + \sum_{j=3}^{i_0-1} a_{2,j}\mu_j, \\
\text{for } i =& 3, \dots, i_0 - 2, \\
\frac{\partial \mu_i}{\partial t} =& D_i \Delta \mu_i + \tilde{m} r_{i-1}\mu_{i-1} - \tilde{m} r_i \mu_i - a_{i,i}\mu_i + \sum_{j=i+1}^{i_0-1} a_{i,j}\mu_j, \\
\frac{\partial \mu_{i_0-1}}{\partial t} =& D_{i_0-1} \Delta \mu_{i_0-1} + \tilde{m} r_{i_0-2}\mu_{i_0-2} - \tilde{m} r_{i_0-1}\mu_{i_0-1} - a_{i_0-1,i_0-1}\mu_{i_0-1},
\end{aligned}$$

with boundary and initial conditions as for the problem $(\mathcal{P})$.
Then we introduce the function
$F_\varepsilon : \begin{cases} X_+ \to X^{i_0-2} \\ \tilde{m} \to F_\varepsilon(\tilde{m}) = F_0(\tilde{m} * \theta_\varepsilon) \end{cases}$, for any $\tilde{m} \in X_+$.
Since $\tilde{m} * \theta_\varepsilon$ is in $(L^\infty(0,T:L^2(\Omega)))_+$ for any $\tilde{m} \in X_+$ it is clear that F_ε is well defined as long as F_0 is.

Now we consider the application $G_\varepsilon : \begin{cases} X_+^2 \to X^2 \\ (\tilde{m}, \tilde{\mu}_{i_0}) \to (m, \mu_{i_0}). \end{cases}$
In the definition of G_ε, m is a solution to the reduced problem

$$\begin{aligned}
\frac{\partial m}{\partial t} =& D_1 \Delta m - m\Big(\sum_{j=2}^{i_0-1} r_j \tilde{\mu_j} + \delta \Big) + \sum_{j=3}^{i_0-1} b\tilde{\mu_j} + 2\beta \sum_{j=2}^{i_0-1} \tilde{\mu_j}, \\
D_1 \frac{\partial m}{\partial \nu} =& -\gamma m \text{ on } \Gamma, \\
\text{for } k = 1, \dots, N,\ D_1 \frac{\partial m}{\partial \nu} =& B_k(t) \text{ on } \partial\omega_k, \\
B_k(t) =& B_k^0 \exp\Big(-\tau \int_0^t \int_{\mathbb{R}^n - \omega_k} \tilde{\mu}_{i_0}(x,s)\eta_k(x) dx ds \Big),
\end{aligned} \tag{19}$$

with $(\tilde{\mu}_2, \dots, \tilde{\mu}_{i_0-1}) = F_\varepsilon(\tilde{m})$. Then, μ_{i_0} is solution to the problem

$$\begin{aligned} \frac{\partial \mu_{i_0}}{\partial t} =& D_{i_0} \Delta \mu_{i_0} + m r_{i_0-1} \tilde{\mu}_{i_0-1}, \\ D_{i_0} \frac{\partial \mu_{i_0}}{\partial \nu} =& -\gamma \mu_{i_0} \text{ on } \Gamma, \\ \text{for } k = 1, \dots, N,\ D_{i_0} \frac{\partial \mu_{i_0}}{\partial \nu} =& 0 \text{ on } \partial\omega_k. \end{aligned} \tag{20}$$

It is clear that if we prove F_ε and G_ε are well defined (the solutions of the reduced problems do exist and are in the right sets) and if (m, μ_{i_0}) is a fixed point of G_ε, then $(m, \mu_2, \dots, \mu_{i_0})$ is a solution to the problem $(\mathcal{P}_\varepsilon)$ (with $(\mu_2, \dots, \mu_{i_0-1}) = F_\varepsilon(m)$).
So, we apply Schauder fixed point theorem for G_ε. In what follows, we denote by $V_k = (H^1(\Omega))^k$ and $U_k = (L^2(\Omega))^k$. We denote by V_k' the dual space of V_k and use the classical continuous embeddings $V_k \subset U_k \equiv U_k' \subset V_k'$.

3.2.1 Proof that F_0 is well defined

Let us fix $m_0 \in (L^\infty(0, T : L^2(\Omega))_+$ for this section. To remain consistent with the rest, we index the components of the elements of V_{i_0-2} and U_{i_0-2} by $\{2, \dots, i_0 - 1\}$. We introduce the function $A : \begin{cases} V_{i_0-2} \times V_{i_0-2} \times U_1 \to \mathbb{R} \\ (u, v, w) \to A(u, v, w), \end{cases}$ where

$$\begin{aligned} A(u, v, w) = & \sum_{i=2}^{i_0-1} \left(D_i \int_\Omega \nabla u_i \cdot \nabla v_i dx + \gamma \int_\Gamma u_i v_i d\sigma \right) \\ & + \sum_{i=2}^{i_0-1} \int_\Omega r_i u_i v_i w dx - \sum_{i=3}^{i_0-1} \int_\Omega r_{i-1} u_{i-1} v_i w dx \\ & + \sum_{i=2}^{i_0-1} \int_\Omega a_{i,i} u_i v_i dx - \sum_{i=2}^{i_0-2} \sum_{j=i+1}^{i_0-1} \int_\Omega a_{i,j} u_j v_i dx, \end{aligned}$$

For any $w \in U_1$, A is bilinear on $V_{i_0-2} \times V_{i_0-2}$. The variational formulation of the parabolic system that defines F_0 is

$$\begin{cases} \dfrac{d}{dt}(\mu(t), v)_{U_{i_0-2}} + A\big(\mu(t), v, m_0(t, \cdot)\big) = 0, \text{ for } v \in V_{i_0-2} \\ \mu(0) = \mu^0, \end{cases} \tag{21}$$

where $\mu = \begin{pmatrix} \mu_2 \\ \vdots \\ \mu_{i_0-1} \end{pmatrix}, \mu^0 = \begin{pmatrix} \mu_2^0 \\ \vdots \\ \mu_{i_0-1}^0 \end{pmatrix}$. This equation is to be interpreted as follows:

For all $\varphi \in C^1([0, T])$ s.t. $\varphi(T) = 0,$ and for all $v \in V_{i_0-2}$,

$$-\int_0^T (\mu(t), v)_{U_{i_0-2}} \varphi'(t) dt - (\mu^0, v)_{U_{i_0-2}} \varphi(0) + \int_0^T A\big(\mu(t), v, m_0(t, \cdot)\big) \varphi(t) dt = 0.$$

As a preliminary lemma we obtain the result below.

Lemma 1 *The function A is well defined and the following estimates hold:*

a) There exists a constant $M_1 \geq 0$ such that

for all $(u,v,w) \in V_{i_0-2} \times V_{i_0-2} \times (U_1)_+$, $|A\big(u,v,w\big)| \leq M_1(1+\|w\|_{U_1})\|u\|_{V_{i_0-2}}\|v\|_{V_{i_0-2}}$.

b) There exist two constants $C_1 > 0$ and $C_2 \in \mathbb{R}$ such that

$$A\big(v,v,w\big) \geq C_1\|v\|^2_{V_{i_0-2}} - C_2\|v\|^2_{U_{i_0-2}}, \quad \text{for } v \in V_{i_0-2} \text{ and } w \in (U_1)_+.$$

Proof a) This is clear due to the continuous embedding of $H^1(\Omega)$ in $L^4(\Omega)$.
b) We have

$$\sum_{i=2}^{i_0-1}\Big(\int_\Omega D_i|\nabla v_i|^2 + \gamma\int_\Gamma v_i^2 d\sigma\Big) \geq \big(\min_{i=2,\dots,i_0-1} D_i\big)\|\nabla v\|^2_{U_{i_0-2}}. \tag{22}$$

We also have

$$\left|\sum_{i=2}^{i_0-1}\int_\Omega a_{i,i}v_i^2 - \sum_{i=2}^{i_0-2}\sum_{j=i+1}^{i_0-1}\int_\Omega a_{i,j}v_jv_i\right| \leq C_3\|v\|^2_{U_{i_0-2}} \tag{23}$$

with C_3 a constant independent of $\tilde{m}$. It remains to estimate the terms containing w. Rearranging the sums and using the hypothesis that $(r_i)_i$ is an increasing sequence, we have

$$\begin{aligned}
&\sum_{i=2}^{i_0-1}\int_\Omega r_i v_i^2 w - \sum_{i=3}^{i_0-1}\int_\Omega r_{i-1}v_{i-1}v_i w = \\
&\qquad \int_\Omega w\Big(\frac{1}{2}\sum_{i=2}^{i_0-1} r_i v_i^2 + \frac{1}{2}\sum_{i=2}^{i_0-1} r_i v_i^2 - \sum_{i=3}^{i_0-1} r_{i-1}v_{i-1}v_i\Big), \\
&\qquad \geq \int_\Omega w\Big[\frac{1}{2}r_2v_2^2 + \frac{1}{2}r_{i_0-1}v_{i_0-1}^2 \\
&\qquad\qquad + \sum_{i=3}^{i_0-1}\Big(\frac{1}{2}r_{i-1}v_{i-1}^2 + \frac{1}{2}r_{i-1}v_i^2 - r_{i-1}v_{i-1}v_i\Big)\Big], \\
&\qquad \geq \int_\Omega w\Big(\frac{1}{2}r_2v_2^2 + \frac{1}{2}r_{i_0-1}v_{i_0-1}^2 + \frac{1}{2}\sum_{i=3}^{i_0-1} r_{i-1}(v_i - v_{i-1})^2\Big) \geq 0.
\end{aligned} \tag{24}$$

Combining the inequalities (22), (23) and (24) we get the wanted result.

Using a classical result (Lions and Magenes, 2012), we have the existence and uniqueness of a solution $\mu \in V$ to (21) thanks to the fact that $m_0 \in L^\infty(0,T:L^2(\Omega))$. This is the reason why we regularize by convolution because $m_0 \in X$ alone is not enough.
Then F_0 is well defined. Moreover $\mu \in C(0,T:U_{i_0-2}) \cap L^2(0,T:V_{i_0-2})$ and $\dfrac{d\mu}{dt} \in L^2(0,T:(V_{i_0-2})')$.

3.2.2 Estimates for $F_\varepsilon(\tilde{m})$

Let us consider $\mu = F_0(\tilde{m} * \theta_\varepsilon)$, with $\tilde{m} \in X_+$ fixed. We define the application $A_\varepsilon : [0,T] \times V_{i_0-2} \longrightarrow (V_{i_0-2})'$, such that

For all $t \in [0,T], u \in V_{i_0-2}$ and $v \in V_{i_0-2}, \langle A_\varepsilon\big(t,u\big), v\rangle = A\big(u, v, (\tilde{m} * \theta_\varepsilon)(t,\cdot)\big)$

where $\langle\cdot,\cdot\rangle$ denotes the duality in $\big((V_{i_0-2})', V_{i_0-2}\big)$.
With this notation, we have the following equality in $L^2(0,T : (V_{i_0-2})')$

$$\frac{d\mu}{dt} + A_\varepsilon\big(t, \mu(t)\big) = 0. \tag{25}$$

We then claim the following estimate for μ:

Proposition 1 *There exists a constant $C_4(T)$ independent of $\tilde{m}$ and ε, such that the solution μ of* (21) *satisfies*

$$\|\mu\|_{L^\infty(0,T:U_{i_0-2})} + \|\mu\|_{L^2(0,T:V_{i_0-2})} \leq C_4(T).$$

Proof We apply (25) to μ which gives

$$\frac{1}{2}\frac{d}{dt}\|\mu(t)\|^2_{U_{i_0-2}} + A\big(\mu(t), \mu(t), (\tilde{m} * \theta_\varepsilon)(t,\cdot)\big) = 0.$$

From Lemma 1 we get

$$\frac{1}{2}\frac{d}{dt}\|\mu(t)\|^2_{U_{i_0-2}} + C_1\|\mu(t)\|^2_{V_{i_0-2}} \leq C_2\|\mu(t)\|^2_{U_{i_0-2}}.$$

The Gronwall lemma then gives us the appropriate estimate.

We now obtain the following maximum principle:

Proposition 2 *Under the hypotheses $m^0 \geq 0$ and $\mu_i^0 \geq 0$ for $i = 2, \ldots, i_0 - 1$, and with $\mu = F_\varepsilon(\tilde{m})$ we have*

$$\mu_i \geq 0 \text{ for } i = 2, \ldots, i_0 - 1.$$

In other words $F_\varepsilon : X_+ \to X_+^{i_0-2}$.

Proof We denote $\mu^- = \begin{pmatrix} \mu_2^- \\ \vdots \\ \mu_{i_0-1}^- \end{pmatrix}$, with $\mu_i^-(x,t) = -\min\{\mu_i(x,t), 0\}$ and similarly μ^+, with $\mu_i^+(x,t) = \max\{\mu_i(x,t), 0\}$ (so that we have $\mu = \mu^+ - \mu^-$). We now show that $\mu^- = 0$.

We apply (25) to μ^-, noting that $\mu^- \in L^2(0,T : V_{i_0-2})$ and that

$$\langle \frac{d\mu}{dt}, \mu^-\rangle = -\frac{1}{2}\frac{d}{dt}\|\mu^-\|^2_{U_{i_0-2}}$$

(this equality is obtained by a density argument) which gives the relation

$$\frac{1}{2}\frac{d}{dt}\|\mu^-\|^2_{U_{i_0-2}} = A\big(\mu(t), \mu^-(t), \tilde{m} * \theta_\varepsilon(t,\cdot)\big). \tag{26}$$

Now using the fact that

$$\mu_i^+ \mu_i^- = 0 \text{ and } \nabla\mu_i^+ \cdot \nabla\mu_i^- = 0,$$

we expand the expression of A

$$\begin{aligned}
A(\mu, \mu^-, &\tilde{m} * \theta_\varepsilon(t,\cdot)) = \\
&- \sum_{i=2}^{i_0-1} \int_\Omega D_i |\nabla\mu_i^-|^2 \, dx - \sum_{i=2}^{i_0-1} \gamma \sum_{k=1}^{N} \int_{\partial\omega_k} (\mu_i^-)^2 \, d\sigma \\
&- \sum_{i=2}^{i_0-1} \int_\Omega r_i (\mu_i^-)^2 \tilde{m} * \theta_\varepsilon dx - \sum_{i=2}^{i_0-1} \int_\Omega a_{i,i} (\mu_i^-)^2 \, dx \\
&- \sum_{i=3}^{i_0-1} \int_\Omega r_{i-1} \mu_{i-1}^+ \mu_i^- \tilde{m} * \theta_\varepsilon \, dx - \sum_{i=2}^{i_0-2} \sum_{j=i+1}^{i_0-1} \int_\Omega a_{i,j} \mu_j^+ \mu_i^- \, dx \\
&+ \sum_{i=3}^{i_0-1} \int_\Omega r_{i-1} \mu_{i-1}^- \mu_i^- \tilde{m} * \theta_\varepsilon \, dx + \sum_{i=2}^{i_0-2} \sum_{j=i+1}^{i_0-1} \int_\Omega a_{i,j} \mu_j^- \mu_i^- \, dx.
\end{aligned}$$

Proceeding as in the proof of Lemma 1, we write

$$- \sum_{i=2}^{i_0-1} \int_\Omega r_i (\mu_i^-)^2 \tilde{m} * \theta_\varepsilon \, dx + \sum_{i=3}^{i_0-1} \int_\Omega r_{i-1} \mu_{i-1}^- \mu_i^- \tilde{m} * \theta_\varepsilon \, dx \leq 0.$$

This implies

$$\begin{aligned}
A(\mu, \mu^-, \tilde{m} * \theta_\varepsilon(t,\cdot)) &\leq \sum_{i=2}^{i_0-1} \sum_{j=i+1}^{i_0-1} \int_\Omega a_{i,j} \mu_j^- \mu_i^- \, dx, \\
&\leq C \|\mu^-\|^2_{U_{i_0-2}}.
\end{aligned}$$

Combining this with (26), we get

$$\frac{d}{dt}\|\mu^-\|^2_{U_{i_0-2}} \leq 2C \|\mu^-\|^2_{U_{i_0-2}}.$$

However, our hypothesis on initial conditions imposes $\|\mu^-(t=0)\|_{U_{i_0-2}} = 0$, so the Gronwall lemma allows to conclude $\|\mu^-\|_{U_{i_0-2}} = 0$, so $\mu^- = 0$.

3.2.3 The fixed point of G_ε

For any $(\tilde{m}, \tilde{\mu}_{i_0}) \in X_+^2$, we consider the following problem with unknown m

$$\begin{aligned} &\frac{\partial m}{\partial t} - D_i \Delta m + \Big(\sum_{j=2}^{i_0-1} r_j \mu_j + \delta \Big) m = h, \\ &D_1 \frac{\partial m}{\partial \nu} = -\gamma m \text{ on } \Gamma, \\ &D_1 \frac{\partial m}{\partial \nu} = \tilde{\psi}_k(t) \text{ on } \partial\omega_k, \text{ for } k = 1, \dots, N, \end{aligned} \tag{27}$$

where we have defined

$$\begin{aligned} h(x,t) &= \sum_{j=3}^{i_0-1} b\mu_j + 2\beta \sum_{j=2}^{i_0-1} \mu_j, \\ \tilde{\psi}_k(t) &= B_k^0 \exp\Big(-\tau \int_0^t \int_{\mathbb{R}^n - \omega_k} \tilde{\mu_{i_0}}(x,s) \eta_k(x) dx ds \Big) \end{aligned}$$

and finally $(\mu_2, \dots, \mu_{i_0-1}) = F_\varepsilon(\tilde{m})$.
If we define $A_1 : \begin{cases} V_1 \times V_1 \times L^2(\Omega) \to \mathbb{R} \\ (u,v,w) \to \int_\Omega D_i \nabla u \cdot \nabla v \, dx + \int_\Gamma \gamma uv \, d\sigma + \int_\Omega wuv \, dx, \end{cases}$ the variational formulation of (27) is

$$\begin{aligned} &\frac{d}{dt}(m,v)_{L^2(\Omega)} + A_1(m, v, \sum_{j=2}^{i_0-1} r_j \mu_j + \gamma) = \\ &\qquad \int_\Omega hv \, dx + \sum_{k=1}^{N} \tilde{\psi}_k(t) \int_{\partial\omega_k} v \, d\sigma, \quad \text{for } v \in V_1. \end{aligned} \tag{28}$$

Recall that for $j = 2, \dots, i_0 - 1, \mu_j \in L^\infty(0, T : L^2(\Omega)), \mu_j \geq 0$ and $\tilde{\mu}_{i_0} \in L^2(0, T : L^2(\Omega))$. We have the following result:

Proposition 3 *a) There exists a unique solution m of (28) with $m \in L^2(0, T : V_1) \cap C(0, T : L^2(\Omega))$ and $\dfrac{\partial m}{\partial t} \in L^2(0, T : V_1')$. We also have $m \geq 0$, in other words $m \in X_+$.*
b) There exists a constant $C_5(T)$ independent of $\varepsilon, \tilde{m}, \tilde{\mu}_{i_0}$ such that

$$\|m\|_{L^\infty(0,T:L^2(\Omega))} + \|m\|_{L^2(0,T:V_1)} \leq C_5(T), \tag{29}$$

$$\left\| \frac{\partial m}{\partial t} \right\|_{L^2(0,T:V_1')} \leq C_5(T). \tag{30}$$

Proof a) Using the Sobolev inclusion $H^1(\Omega) \hookrightarrow L^6(\Omega) \subset L^4(\Omega)$ we easily obtain

$$A_1(u,v,w) \leq C \|u\|_{V_1} \|v\|_{V_1} \|w\|_{L^2(\Omega)}.$$

If $w \geq 0$, then we have

$$A_1(u,u,w) \geq \min\{D_1,\gamma\}\|u\|^2_{V_1}.$$

Finally using the fact that $h \in L^\infty(0,T:L^2(\Omega))$, we obtain the existence and uniqueness result in a classical manner.
Taking $v = m^-$ as a test function and proceeding exactly as in Proposition 2, we obtain $m \geq 0$.

b) We note that for $t \in [0,T]$ and $k \in \{1,\dots,N\}, |\tilde{\psi}_k(t)| \leq B^0_k$. Furthermore, we deduce from Proposition 1 that there exists $C_6(T)$, independent of $\tilde{m}$ and $\tilde{\mu}_{i_0}$ such that

$$\|h\|_{L^2(0,T:V_1)} \leq C_6(T).$$

Taking $v = m$ in (28), we obtain

$$\frac{1}{2}\frac{d}{dt}\|m\|^2_{L^2(\Omega)} + D_1\int_\Omega \|\nabla m\|^2 dx + \gamma\int_\Gamma |m|^2 d\sigma + \int_\Omega \Big(\sum_{j=2}^{i_0-1} r_j\mu_j + \delta\Big)m^2 dx = \int_\Omega hm\,dx + \sum_{k=1}^{N}\tilde{\psi}_k(t)\int_{\partial\omega_k} m\,d\sigma.$$

Now we use the trace inequality

$$\left|\int_{\partial\omega_k} m d\sigma\right| \leq C\|m\|_{L^1(\partial\omega_k)} \leq C\|m\|_{L^2(\partial\omega_k)} \leq C\|m\|_{H^1(\Omega)},$$

and we conclude with the first estimate on m. The second estimate is based on the estimate on A_1, the above inequalities on h and the trace inequality on m.

Finally, we consider problem (20) and its variational formulation

$$\frac{d}{dt}(\mu_{i_0},v)_{L^2(\Omega)} + A_{i_0}(\mu_{i_0},v) = \int_\Omega r_{i_0-1}m\mu_{i_0-1}v\,dx, \text{ for } v \in V_1, \tag{31}$$

where

$$A_{i_0}(\mu_{i_0},v) = D_{i_0}\int_\Omega \nabla\mu_{i_0}\cdot\nabla v\,dx + \gamma\int_\Gamma \mu_{i_0}v\,d\sigma,$$

and m is the solution of (27) and $\mu_{i_0-1} = \big(F_\varepsilon(\tilde{m})\big)_{i_0-1}$. We have the following result:

Proposition 4 *a) There exists a unique solution μ_{i_0} to (31), with $\mu_{i_0} \in L^2(0,T:V_1)\cap C(0,T:L^2(\Omega))$ and $\dfrac{d\mu_{i_0}}{dt} \in L^2(0,T:V_1')$. Furthermore, $\mu_{i_0} \geq 0$.*

b) The following estimates hold

$$\|\mu_{i_0}\|_{L^\infty(0,T:L^2(\Omega))} + \|\mu_{i_0}\|_{L^2(0,T:V_1)} \leq C_6(T),$$
$$\left\|\frac{d\mu_{i_0}}{dt}\right\|_{L^2(0,T:V_1')} \leq C_6(T).$$

Proof a) We have for almost all $t \in [0,T]$

$$\left|\int_\Omega r_{i_0-1} m \mu_{i_0-1} v dx\right| \leq C\|m\|_{L^2(\Omega)}\|\mu_{i_0-1}\|_{L^4(\Omega)}\|v\|_{L^4(\Omega)},$$
$$\leq C\|m\|_{L^2(\Omega)}\|\mu_{i_0-1}\|_{V_1}\|v\|_{V_1}.$$

We deduce that $(r_{i_0-1} m \mu_{i_0-1}) \in V_1'$ and

$$\|r_{i_0-1} m \mu_{i_0-1}\|_{V_1'} \leq C\|m\|_{L^2(\Omega)}\|\mu_{i_0-1}\|_{V_1},$$

which gives $(r_{i_0-1} m \mu_{i_0-1}) \in L^2(0,T:V_1')$. We also have

$$\|r_{i_0-1} m \mu_{i_0-1}\|_{L^2(0,T:V_1')} \leq C\|m\|_{L^\infty(0,T:L^2(\Omega))}\|\mu_{i_0-1}\|_{L^2(0,T:V_1)}.$$

In a classical manner, we get the expected existence and uniqueness results. The positivity results from $m \geq 0, \mu_{i_0-1} \geq 0, \mu_{i_0}^0 \geq 0$.

b) Taking $v = \mu_{i_0}$ in (31), we obtain on one hand

$$\frac{1}{2}\frac{d}{dt}\|\mu_{i_0}\|^2_{L^2(\Omega)} + D_{i_0}\int_\Omega \|\nabla \mu_{i_0}\|^2_{L^2(\Omega)} dx + \gamma \int_\Gamma \mu_{i_0}^2 d\sigma + D_{i_0}\int_\Omega \mu_{i_0}^2 dx =$$
$$D_{i_0}\int_\Omega \mu_{i_0}^2 dx + \int_\Omega r_{i_0-1} m \mu_{i_0-1}\mu_{i_0} dx.$$

On the other hand, proceeding as in the previous property we have

$$\left|\int_\Omega r_{i_0-1} m \mu_{i_0-1}\mu_{i_0}\right| \leq C\|m\|_{L^2(\Omega)}\|\mu_{i_0-1}\|_{V_1}\|\mu_{i_0}\|_{V_1},$$
$$\leq \frac{D_{i_0}}{2}\|\mu_{i_0}\|^2_{V_1} + \frac{C}{2D_{i_0}}\|m\|^2_{L^2(\Omega)}\|\mu_{i_0-1}\|^2_{V_1}.$$

Using these two previous relations and the estimates from Proposition 3 and Proposition 1, we obtain the desired result.

3.3 Existence and estimates on the solution of the regularized problem

Let us define the Banach space

$$Y = \left\{u \in L^2(0,T:V_1) : \frac{\partial u}{\partial t} \in L^2(0,T:V_1')\right\},$$

with the norm $\|u\|_Y = \|u\|_{L^2(0,T:V_1)} + \left\|\frac{\partial u}{\partial t}\right\|_{L^2(0,T:V_1')}$. Note that we have the compact embedding of Y in X from compactness embedding of V_1 in $L^2(\Omega)$ (since Ω is bounded).

The above results prove that there exists $R = R(T)$ independent of ε such that

$$G_\varepsilon(X_+^2) \subset \bar{B}_{Y^2}(0,R) \cap X_+^2, \tag{32}$$

where $\bar{B}_{Y^2}(0,R)$ is the closed ball centered on 0 of radius R in Y^2.
Due to the continuous embedding of Y in X there exists $R_1 > 0$ such that $G_\varepsilon(X_+^2) \subset \Sigma$ where we denote $\Sigma = \{u \in X_+^2 : \|u\|_{X^2} \leq R_1\}$ which is a bounded closed convex subset of X^2.
We can restrict G_ε to Σ and say that G_ε send Σ to itself.
Also from (32) G_ε is a precompact set in X^2; so it remains to prove the continuity of G_ε in order to apply Schauder fixed point theorem.
For this let us fix $(\tilde{m}, \tilde{\mu}_{i_0}) \in X_+^2$ and choose a sequence $(\tilde{m}_p, \tilde{\mu}_{i_0,p})_{p\in\mathbb{N}}$ in X_+^2 such that

$$(\tilde{m}_p, \tilde{\mu}_{i_0,p}) \to (\tilde{m}, \tilde{\mu}_{i_0}) \text{ in } X_+^2.$$

We denote $(\mu_{2,p}, \ldots, \mu_{i_0-1,p}) = F_\varepsilon(\tilde{m}_p)$ and $(m_p, \mu_{i_0,p}) = G_\varepsilon(\tilde{m}_p, \tilde{\mu}_{i_0,p})$. As above, we obtain bounds independently of p for $|\mu_{2,p}, \ldots, \mu_{i_0-1,p}|$ and $(m_p, \mu_{i_0,p})$ in $L^2(0,T : H^1(\Omega)) \cap L^2(0,T : (H^1)')$. By compactness and taking the limit ε tends to 0 we prove that

$$(m_p, \mu_{i_0,p}) \to G_\varepsilon(\tilde{m}, \tilde{\mu}_{i_0}) \text{ in } X^2 \text{ strongly},$$

which proves the continuity of G_ε.

Finally by the Schauder Theorem, we obtain the existence of a solution to the problem $(\mathcal{P}_\varepsilon)$. We denote this solution by $(m_\varepsilon, \mu_{2,\varepsilon}, \ldots, \mu_{i_0,\varepsilon})$. We have the existence of $R \equiv R(T) > 0$, independent of ε, such that

$$\|m_\varepsilon\|_{L^2(0,T:V_1)} + \left\|\frac{\partial m_\varepsilon}{\partial t}\right\|_{L^2(0,T:(V_1)')} \leq R, \tag{33}$$

$$\|\mu_{i,\varepsilon}\|_{L^2(0,T:V_1)} + \left\|\frac{\partial \mu_{i,\varepsilon}}{\partial t}\right\|_{L^2(0,T:(V_1)')} \leq R, \text{ for } i = 2, \cdots i_0. \tag{34}$$

4 Stating and proof of the main result

By using the results for the regularized problem and the estimates on its solutions, we now study the original problem $\mathcal{P}$. Note that $m_\varepsilon \in Y$, $\mu_\varepsilon = (\mu_{2,\varepsilon}, \ldots, \mu_{i_0-1,\varepsilon}) \in Y^{i_0-2}$ and $\mu_{i_0,\varepsilon} \in Y$. They are a solution to the problem $(\mathcal{P}_\varepsilon)$ in the following variational sense

$$\begin{aligned} &\text{For all } (v_1, v2, \ldots, v_i) \in V_i \\ &\text{and for } \varphi \in C^1([0,T]) \text{ such that } \varphi(T) = 0, \end{aligned}$$

$$
\begin{aligned}
&-\int_0^T (m_\varepsilon, v_1)_{H_0}\varphi'(t)dt - (m^0, v_1)_{H_0}\varphi(0)\\
&+\int_0^T A_1(m_\varepsilon(t), v_1, \textstyle\sum_{j=2}^{i_0-1} r_j\mu_{j,\varepsilon} + \delta)\varphi(t)dt\\
&-\int_0^T (\mu_\varepsilon, v)_H\varphi'(t)dt - (\mu^0, v)_H\varphi(0)\\
&+\int_0^T A(\mu_\varepsilon(t), v, m_\varepsilon * \theta_\varepsilon(t,\cdot))\varphi(t)dt\\
&-\int_0^T (\mu_{i_0,\varepsilon}, v_{i_0})_{H_0}\varphi'(t)dt - (\mu_{i_0}^0, v_{i_0})_{H_0}\varphi(0)\\
&+\int_0^T A_{i_0}(\mu_{i_0,\varepsilon(t)}, v_{i_0})\varphi(t)dt\\
&\quad=\int_0^T\int_\Omega \Big(\sum_{j=3}^{i_0-1} b\mu_{j,\varepsilon} + 2\beta\sum_{j=2}^{i_0-1}\mu_{j,\varepsilon}\Big)v_1 dx\varphi(t)dt\\
&\qquad+\int_0^T\int_\Omega r_{i_0-1}m_\varepsilon\mu_{i_0-1,\varepsilon}v_{i_0}dx\varphi(t)dt\\
&\qquad+\sum_{k=1}^N\int_0^T\int_{\partial\omega_k} B_k^0\exp\Big(-\tau\int_0^t\int_{\mathbb{R}-\omega_k}\mu_{i_0,\varepsilon}\eta(x)dxds\Big)v_{i_0}d\sigma\varphi(t)dt.
\end{aligned}
\tag{35}
$$

In this section, we prove the existence of a variational solution of $(\mathcal{P})$, that is an element $(m, \mu_2, \mu_3, \cdots, \mu_i) \in Y^i$ such that for any $\varphi \in C^1([0,T])$ with $\varphi(T) = 0$ we have

$$
\begin{aligned}
&-\int_0^T (m, v_1)_{L^2(\Omega)}\varphi'(t)dt - (m^0, v_1)_{L^2(\Omega)}\varphi(0)\\
&+\int_0^T A_1(m, v_1, \textstyle\sum_{j=2}^{i_0-1} r_j\mu_j + \gamma)\varphi(t)dt\\
&-\int_0^T (\mu, v)_{U_{i_0-2}}\varphi'(t)dt - (\mu^0, v)_{U_{i_0-2}}\varphi(0)\\
&+\int_0^T A(\mu, v, m(t,\cdot))\varphi(t)dt\\
&-\int_0^T (\mu_{i_0}, v_{i_0})_{L^2(\Omega)}\varphi'(t)dt - (\mu^0_{i_0}, v_{i_0})_{L^2(\Omega)}\varphi(0)\\
&+\int_0^T A_{i_0}(\mu_{i_0}, v_{i_0})\varphi(t)dt\\
&\quad=\int_0^T\int_\Omega \Big(\sum_{j=3}^{i_0-1} b\mu_j + 2\beta\sum_{j=2}^{i_0-1}\mu_j\Big)v_1 dx\varphi(t)dt\\
&\qquad+\int_0^T\int_\Omega r_{i_0-1}m\mu_{i_0-1}v_{i_0}dx\varphi(t)dt\\
&\qquad+\sum_{k=1}^N\int_0^T\int_{\partial\omega_k} B_k^0\exp\Big(-\tau\int_0^t\int_{\mathbb{R}-\omega_k}\mu_{i_0}\eta(x)dxds\Big)v_{i_0}d\sigma\varphi(t)dt.
\end{aligned}
\tag{36}
$$

The main result is

Theorem 1 *There exists at least a solution* $(m, \mu_2, \cdots, \mu_i) \in Y^i$ *of* (36).

Proof From the above section we have a solution $(m_\varepsilon, \mu_{2,\varepsilon}, \cdots, \mu_{i_0,\varepsilon}) \in Y^i$ of the regularized problem $(\mathcal{P}_\varepsilon)$ in a variational form (35).
Due to the inequalities (33),(34) and the compact embedding of Y in $L^2(\Omega \times (0,T))$, there exists a subsequence of ε (that we also denote ε for simplicity), as well as $(m, \mu_2, \ldots, \mu_{i_0}) \in Y^{i_0}$ such that

$$
\begin{aligned}
&m_\varepsilon \rightharpoonup m \text{ in } L^2(0,T:V_1) \text{ weakly},\\
&m_\varepsilon \to m \text{ in } L^2(0,T:L^2(\Omega)) \text{ strongly},
\end{aligned}
\tag{37}
$$

and for $i = 2, \ldots, i_0$,

$$
\begin{aligned}
&\mu_{i,\varepsilon} \rightharpoonup \mu_i \text{ in } L^2(0,T:V_1) \text{ weakly},\\
&\mu_{i,\varepsilon} \to \mu_i \text{ in } L^2(0,T:L^2(\Omega) \text{ strongly}.
\end{aligned}
\tag{38}
$$

Let us now prove that

$$
m_\varepsilon * \theta_\varepsilon \to m \text{ in } L^2(\Omega \times (0,T)) \text{ strongly}. \tag{39}
$$

Indeed we have

$$m_\varepsilon * \theta_\varepsilon - m = (m_\varepsilon - m) * \theta_\varepsilon + m * \theta_\varepsilon - m.$$

We also have

$$\|(m_\varepsilon - m) * \theta_\varepsilon\|_{L^2} \leq \|\theta_\varepsilon\|_{L^1} \|m_\varepsilon - m\|_{L^2} \leq \|m_\varepsilon - m\|_{L^2},$$

so $(m_\varepsilon - m) * \theta_\varepsilon \to 0$ in $L^2(\Omega \times (0,T))$. We also know that $m * \theta_\varepsilon \to m$ in L^2, and we can conclude with the convergence of $m_\varepsilon * \theta_\varepsilon$.

Finally we use the previous convergence results to take the limit $\varepsilon \to 0$ in (35), and obtain the expected result. Here we only deal with the most delicate term which is

$$\int_0^T \int_\Omega r_i \mu_{i,\varepsilon}(t,x)(m_\varepsilon * \theta_\varepsilon)(t,x) v_i(x) \varphi(t) dx dt.$$

Since $v_i \in V_1$ then $v_i \in L^6(\Omega)$ and $v_i \varphi \in L^\infty(0,T : L^6(\Omega))$. Using the fact that if $a \in L^2$ and $b \in L^6$ then $ab \in L^{3/2}$, we have

$$(m_\varepsilon * \theta_\varepsilon)(t,x) v_i(x) \varphi(t) \to m(x,t) v_i(x) \varphi(t) \text{ in } L^2(0,T : L^{3/2}(\Omega)) \text{ strongly.}$$

On the other hand, from the weak convergence of $\mu_{i,\varepsilon}$ to μ_i in $L^2(0,T : H^1(\Omega))$, we deduce

$$\mu_{i,\varepsilon} \rightharpoonup \mu_i \text{ in } L^2(0,T : L^6(\Omega)) \text{ weakly.}$$

From those two convergence results we deduce

$$\int_0^T \int_\Omega r_i \mu_{i,\varepsilon}(m_\varepsilon * \theta_\varepsilon) v_i \varphi dx dt \underset{\varepsilon \to 0}{\to} \int_0^T \int_\Omega r_i \mu_i m v_i \varphi dx dt.$$

This achieves the proof of the theorem.

5 Conclusion

We have introduced a model combining chemical prion-like replication of oligomers and spatial diffusion, as well as neurotoxicity. Those processes are essential for the early stage development of Alzheimer's disease, and it is of great interest to understand their relative impact on the later stages of the disease. To the best of our knowledge, this work is the first use of reaction-diffusion equations to describe the secondary nucleation process leading to the formation of Aβ oligomers on the one hand, and the pathological effects of Aβ oligomers on the neuronal activity on the other hand. The results proved here establish a strong mathematical framework for this model, and allow us to go further with the use of this model in a quantitative context. The mathematical proofs are obtained using classical methods, but they were adapted in order to deal with the specificities of our model. In particular in our model the formation of oligomers directly impacts the production of monomers by

neurons, and the system had to be split into two parts in order to get existence results. Future work will be dedicated to the practical use of the model to interpret the relative importance of the different parameters. The goal is to include this local model in a multi-scale model so as to be able to carry out a quantitative comparison with data. Another important development aspect will be to validate and improve the model if need be, in collaboration with biologists.

Conflict of interest

The authors declare that they have no conflict of interest.

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