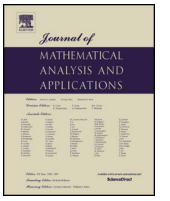
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Regular Articles

A model for the diffusion of Aβ-amyloids in the brain: existence, uniqueness, and qualitative analysis



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ABSTRACT

We introduce a PDE model for the dynamics and aggregation of Aβ-amyloids in a small neighbourhood of a few neurons, in relation to their role in the early stage of Alzheimer's disease. We analyse the well-posedness of the associated semilinear system of heat equations with nonlinear, time-dependent boundary conditions: local existence, uniqueness and global boundedness of positive $C^0_{t,x}$ solutions are established via a semigroup approach. We further perform a linear stability analysis for the monomer equilibrium $u^* = (m^*, 0, \dots, 0)$. We show that this equilibrium is stable only under very strong assumptions on the parameters b, β, γ. Several numerical simulations show how oligomers affect the nearby neurons, and tend to move from dying neurons to healthy ones.

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1. Introduction

In recent years, several different PDE models for the propagation of Aβ amyloids chains have been proposed as modelling for the development of the Alzheimer disease in the early stage [4,7]. The biochemical process that these models are aiming at describing is the aggregation of Aβ monomers and polymers, according to the amyloid cascade hypothesis [16,17]. Let us briefly sketch the biological background. The main object of study is the protein β-amyloid, which has a soluble neurotoxic isoform Aβ_{42} that it is believed to play a central role in the decline of neuronal activity of AD patients. Monomers of Aβ_{42} are regularly produced by the neurons and, in a healthy brain, there is a dynamic equilibrium among monomer production, monomer degradation, and aggregation of monomers in polymers. One of the possible causes of the on-set of AD disease is the structural transition of Aβ-monomers [29]; after misfolding, they are not easily degraded, thus creating an unbalance between production and degradation. Once a misconformed Aβ amyloid has appeared, misfolded monomers start to aggregate in proto-oligomers of increasing length. After they reach

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a critical threshold, proto-oligomers become LMW (low molecular weight) oligomers. Oligomers might then assemble in more ordered structures, that are widely accepted biological markers of the Alzheimer's disease [16,18]. Among them, we mention plaques and mature fibrils, that have been suggested to play an important role in the neuronal dysfunction [24]. In fact, there is evidence that high concentration levels of soluble Aβ oligomers are pivotal for the AD pathogenesis [26].

The purpose of this article is to introduce and analyse a novel model for the oligomerisation and diffusion of Aβ-amyloids in a small area of the brain Ω_0 containing J neurons ω_k. Let Ω_0 and $\omega_k \subset \Omega_0$, for $k = 1,..,J$, be smooth bounded domain of $\mathbb{R}^N$, with $N = 2$ or $N = 3$, and set $\Omega := \Omega_0 \setminus \left(\bigcup_{k=1}^{J} \overline{\omega_k}\right)$, so that $\partial\Omega = \partial\Omega_0 \cup \partial\omega_1 \cup \cdots \cup \partial\omega_J$. We denote by u_1 the concentration of monomers, u_l the concentration of proto-oligomers of length l, u_n the concentration of oligomers of length n. The diffusion process is modelled with a Laplacian operator with diffusion coefficient d_j. The polymerization and concatenation processes, happening with rate a_{ij}, are described by nonlinear quadratic terms, whereas the depolymerization, the fragmentation and the monomer degradation are linear terms with rates b, β and δ (see Section 2 for more details). We look for nonnegative $C^0([0,T)\times\overline{\Omega})^n$ solutions $u = (u_1,\dots,u_n)$ to the following fully-coupled system of n semilinear heat equations

$$\begin{cases} \frac{\partial u_1}{\partial t} = d_1\Delta u_1 - u_1\left(\sum_{j=2}^{n-1} a_{1,j}u_j + \delta\right) + 2\beta u_2 + \sum_{j=3}^{n-1}(\beta(j-1)+b)u_j, \\ \frac{\partial u_2}{\partial t} = d_2\Delta u_2 - a_{1,2}u_1u_2 + bu_3 - \beta u_2 + 2\beta u_3 - \sum_{j=2}^{n-1} a_{2,j}u_2u_j, \\ \frac{\partial u_l}{\partial t} = d_l\Delta u_l - a_{1,l}u_1u_l + a_{1,l-1}u_1u_{l-1} + bu_{l+1} - bu_l - \beta(l-1)u_l \\ \qquad +l\beta u_{l+1} - \sum_{j=2}^{n-1} a_{l,j}u_lu_j + \sum_{\substack{j+k=l \\ 1<j\le k<l}} a_{j,k}u_ju_k, \\ \frac{\partial u_{n-1}}{\partial t} = d_{n-1}\Delta u_{n-1} - a_{1,n-1}u_1u_{n-1} + a_{1,n-2}u_1u_{n-2} \\ \qquad -(b+\beta(n-2))u_{n-1} - \sum_{j=2}^{n-1} a_{j,n-1}u_ju_{n-1} + \sum_{\substack{j+k=n-1 \\ 1<j\le k<n-1}} a_{j,k}u_ju_k, \\ \frac{\partial u_n}{\partial t} = d_n\Delta u_n + a_{1,n-1}u_1u_{n-1} + \sum_{\substack{j+k\ge n \\ 1<j,k<n}} a_{j,k}u_ju_k, \end{cases} \tag{1.1}$$

in $\Omega_T := (0,T)\times\Omega$, where $3 \le l \le n-2$. Here $d_i, a_{i,j}, \beta, b, \gamma$ are positive constants with $a_{i,j} = a_{j,i}$ for $i,j \in \{1,\dots,n\}$. The boundary and initial conditions are given by

$$\begin{cases} d_l\frac{\partial u_l}{\partial \nu} = -\gamma u_l, & \text{on } (0,T)\times\partial\Omega_0, \\ d_1\frac{\partial u_1}{\partial \nu} = B_k(t,u_n(t)), & \text{on } (0,T)\times\partial\omega_k,\ k=1,\dots,J, \\ d_i\frac{\partial u_l}{\partial \nu} = 0, & \text{on } (0,T)\times\partial\omega_k,\ k=1,\dots,J, \\ u_i(0,x) = \varphi_i(x) \ge 0, & \text{in } \Omega,\ i=1,\dots,n \end{cases}$$

and

$$B_k(t,u_n(t)) = B_k^0 e^{-\tau\|u_n\chi_k\|_{L^1((0,t)\times\Omega)}},$$

with χ_k being the characteristic function of a small neighbourhood of the neuron ω_k and B_k^0, τ positive constants. We note that the production of monomers by the neuron ω_k is modelled only through the boundary condition B_k; this is a nonlinear, time-dependent boundary condition that models the deterioration of the neuron in presence of high concentration of neurotoxic oligomers in a neighbourhood of ω_k.

We refer to Section 2 for a more elaborate discussion on the biochemical meaning of the system. We note that the mathematical formulation of (1.1) is a refinement of previous models based on the Aβ-cascade hypothesis, that were originally deduced as variants of the Smoluchowski system. The latter is commonly used to describe the time-evolution of a system of particles that coagulate, or assemble, in structures involving a specific number of particles. The Smoluchowski system with diffusion reads as follows

$$\partial_t u_m = d_m \Delta u_m + \left[\frac{1}{2} \sum_{j=1}^{m-1} a_{j,m-j} u_j u_{m-j} - u_m \sum_{j=1}^{N} a_{m,j} u_j \right],$$

in $(0,T) \times \Omega$, $m = 1, \dots, n$, where d_m, $a_{i,j} = a_{j,i}$ are all positive real constants. We note that in the Smoluchowski system proto-oligomers of length m_1 and length m_2 are allowed to assemble to form a proto-oligomer of length $m_1 + m_2 < N$, and they are also allowed to fragment in shorter proto-oligomers of any size. Our contribution to the mathematical modelling of the Aβ-amyloid propagation and aggregation is the implementation of the concatenation terms appearing in the Smoluchowski system, adding new complex interactions between proto-oligomers that were not allowed in previous existing models such as [4].

The main difference between [5, Eq.(1)] and our model (1.1), which also makes the mathematical analysis more complicated, is the presence of the positive nonlinear terms

$$\sum_{\substack{j+k=l \\ 1<j\leq k<l}} a_{j,k} u_j u_k$$

modelling the concatenation of proto-oligomers. Note that these terms are present in the Smoluchowski system and in other models for the Aβ aggregation, see for instance [7].

We also note that nonlinear parabolic reaction-diffusion systems often appear in population dynamics; for instance, systems with spatial segregation have been analysed in [12], Lotka-Volterra systems with strong competition and fractional diffusion in [33], and competition diffusion systems with spiraling asymptotic profiles in [31].

• **Description of the results.**

Our novel contribution is the rigorous analysis of system (1.1) by means of the semigroup theory for (systems of) semilinear heat equations [10,14]. It is known that the Laplacian with mixed Robin-Neumann boundary conditions generates a C_0-semigroup of linear operators; however, system (1.1) features an inhomogeneous, nonlinear, and time-dependent Neumann boundary condition for the monomer concentration. To avoid the hurdle of dealing with this boundary condition directly, we prefer to first transform the system in a non-autonomous system with homogeneous boundary conditions, at the price of introducing positive source terms in all the equations. Once this has been achieved, the system can be written in the form

$$\partial_t u = Au + F(t,u),$$

where $A = \mathrm{diag}(d_1 \Delta_{\mathrm{NR}}, \dots, d_n \Delta_{\mathrm{NR}})$ and Δ_{NR} is the Laplacian acting in $C^0(\overline{\Omega})$ with mixed Neumann-Robin boundary conditions. In view of an argument exploiting the maximum principle, A is m-dissipative in $X := C^0(\overline{\Omega})^n$, and therefore it generates a C_0-semigroup $\mathcal{T}$ of linear operators. Thus, we can define mild solutions to system (1.1) in the usual way, by means of the Duhamel formula

$$u(t) = \mathcal{T}(t)u(0) + \int_0^t \mathcal{T}(t-s)F(s,u(s))ds.$$

Local existence and uniqueness of a mild solution immediately follows from a fixed point argument. Moreover, we show that if the initial datum φ is componentwise nonnegative, there exists a componentwise nonnegative mild solution u to system (1.1); if the initial data are more regular, the unique mild solution u has additional regularity, and it is a classical solution if the initial datum is in $C^{2,\alpha}(\overline{\Omega})^n$. Assuming that the initial data are nonnegative, we further show that there exists a componentwise nonnegative mild solution of (1.1); this is achieved via a fixed point argument in the cone of componentwise nonnegative solutions, which is

non-standard due to the presence of the nonlinear boundary condition. Finally, we show that the unique local nonnegative mild solution is in fact global and bounded for all times, that is $u \in C_b^0([0,+\infty), X)$.

We note that system (1.1) does not have spatially homogeneous equilibria due to the boundary conditions; in fact, it does not even admit heterogeneous equilibria unless $u_5 = 0$ almost everywhere in a neighbourhood of the neurons ω_k, in view of the boundary condition $\partial_\nu u_1(t) = B_k(t, u_n(t))$ on $\partial\omega_k$. We study the linear stability of (1.1) in a neighbourhood of the heterogeneous equilibrium $u^* = (m^*, 0, \dots, 0)$, where m^* is the solution of a boundary value problem for the Laplacian with mixed Neumann-Robin boundary conditions and constant Neumann boundary datum, and only in the case of perturbations $f = (f_1, \dots, f_n)$ with $f_n = 0$. We provide sufficient conditions for the (conditional) stability of the equilibrium u^* in terms of the parameters of (1.1). We further note that as $t \to +\infty$ the time-dependent boundary condition $\partial_\nu u_1(t) = B_k(t, u_n(t))$ on $\partial\omega_k$ is behaving almost as an homogeneous Neumann boundary condition $\partial_\nu u_1 = 0$ on $\partial\omega_k$; we expect therefore the existence of asymptotic homogeneous equilibria, to which the solutions of (1.1) are expected to tend. However, the rigorous proof of this statement seems out of reach.

Finally, we complement our analysis with several numerical simulations. We depict how the dynamics of the system depends upon the concatenation parameters $a_{i,j}$; for small values of the coefficients $a_{i,j}$ there is less interaction between the different polymers of Aβ-amyloid, and therefore the dynamics is more diffusion- than reaction-driven. On the other hand, high concatenation parameters result in more nonlinear interactions between the different polymers, resulting in a reaction-driven dynamics where the maximum of the oligomer concentration shifts from dying to healthy neurons, as to maximise the neurotoxic effect.

This article is structured as follows: in Section 2 we describe the mathematical modelling of the biochemical processes that led to formulate system (1.1). In Section 3 we first introduce some well-known facts about semigroup theory, and we then recast system (1.1) in an equivalent form with homogeneous boundary conditions (3.6), at the price of adding smooth sources to all the equations. We apply semigroup theory and a fixed point argument to (3.6) to prove the existence and uniqueness of a local mild solution, for any choice of continuous initial data. Moreover, if the initial data are non-negative, the unique mild solution is componentwise non-negative, see Theorem 3.6. Finally, if the boundary $\partial\Omega$ is of class $C^{2,\alpha}$ and the initial data are $C^{2,\alpha}(\overline{\Omega})$, the solution of (1.1) is classical and lies in a suitably defined Hölder space (Proposition 3.8). In Section 4 we compute the trivial equilibrium of the system and we study the linear stability of such equilibrium via a careful eigenvalue analysis of the linearized operator, that requires an operator version of the Gershgorin theorem. In Corollary 4.3 we exploit this enclosure to show that under certain (restrictive) conditions the trivial equilibrium is linearly stable. In Section 5, we prove that there exists a unique non-negative mild solution for any choice of non-negative continuous initial data. The solution is proved to be bounded for all times. Finally, in Section 6, we produce several numerical simulations in FreeFEM++, outlining different dynamical regimes according to different choices of the concatenation parameters. In many regimes, we see a movement of the neurotoxic oligomers from ill to healthy neurons, therefore showing a possible mechanism that accelerates the loss of neuronal activity in AD patients.

2. Description of the model

The formation and spread of Aβ-amyloid peptides in the brain is central to the pathogenesis of Alzheimer's disease (AD) according to the amyloid cascade hypothesis [17,26]. Aβ-peptides, particularly the Aβ_{42} isoform, are produced through the sequential cleavage of the amyloid precursor protein (APP). In healthy brains, Aβ-monomers are cleared by enzymatic degradation, cellular uptake, or drainage via the glymphatic system. However, in AD, changes in production, aggregation kinetics, or clearance may lead to the accumulation of neurotoxic Aβ species.

It is important to underline that the biochemical mechanisms leading to AD involve very complex interactions between different molecules, among which we mention: proteins proliferation, interleukins reaction, microglia deployment, and misfolded protein agglomeration. It is therefore our choice to focus mainly on the

Aβ-amyloid diffusion and agglomeration process, while disregarding other important pathogenetic factors as the τ-protein and the microglia cells. We refer to the recent article [11] for a mathematical model taking into account the interaction between these different factors, where however the complexity of the model forces the authors to consider only a bimonomeric model, with no spatial diffusion, when performing the analytical discussion.

Aβ-monomers can undergo conformational changes and self-assemble into soluble oligomers, protofibrils, and eventually insoluble fibrils that deposit as extracellular plaques. Among these, soluble Aβ-oligomers are now widely recognized as the most neurotoxic species, disrupting synaptic function, inducing oxidative stress, and triggering inflammatory responses [16,24]. Oligomers can further aggregate into larger structures, including plaques, which serve as reservoirs of toxic species and contribute to neuronal dysfunction and death [18].

Experimental evidence indicates that Aβ-pathology spreads in a prion-like manner, where misfolded Aβ seeds can template further misfolding and aggregation in neighbouring cells and brain regions [19]. This propagation is not merely passive diffusion but involves active cellular mechanisms, including neuronal uptake, exosomal release, and trans-synaptic transfer [23]. Mathematical models of Aβ spread often combine reaction–diffusion dynamics with aggregation kinetics to capture the spatiotemporal evolution of Aβ-species [4,6].

The mathematical modelling of amyloid aggregation has been originally described by means of the classical Smoluchowski system of equations [13,28], which at least in the work by Smoluchowski did not take into account spatial diffusion effects, as it was introduced as a population balance equation in statistical physics. However, when considering the agglomeration of molecules of small size (1-5 nm), diffusion effects need to be considered [21]. We note that the original work by Smoluchowski involved an infinite number of differential equations, whereas, in the literature, systems with only a finite number of equations are often referred as Smoluchowski systems.

It is clear that depending on the scale at which we observe the events, different mathematical models need to be considered. For instance, at a macroscopic or mesoscopic level, transport effects along blood vessels or neurons and interactions between different membranes play a central role in the fast spreading of AD. Here ODE models, also supported on graphs, seem to be more efficient, as Laplacian-driven spatial diffusion can be disregarded at this scale. For this reason, we focus on the microscopic scale of the neighbourhood of a small number of adjacent neurons (approximately 50 µm).

A point could be made that linear diffusion based on the Laplacian in the space variables is not the only possibility. Indeed, there is biological evidence that neuronal activity may affect the speed of diffusion of amyloids. In our model we assume for simplicity that the spatial diffusion is uniform, whereas we implement the neuronal effect via a suitable boundary condition affecting mostly the reaction part of the equations.

Starting from the work of Murphy and Pallitto [22,25] the classical Smoluchowski coagulation–diffusion equations have been widely adapted to model Aβ-aggregation [1]; recent extensions incorporate spatial diffusion, cellular interactions, and clearance mechanisms [5,7]. However, many models assume simplified boundary conditions or neglect concatenation processes—the merging of existing polymers, which may accelerate oligomer formation in vivo [9].

From a more abstract perspective, Smoluchowski-type system has been considered in great generality in a series of articles by Amann and collaborators [2,3], by means of semigroup theory.

We give now more information on the biochemical setting described in (1.1). We denote by u_1 the concentration of monomers, u_l the concentration of proto-oligomers of length l, u_n the concentration of oligomers of length n. We assume that the following biochemical processes can arise:

(1) Polymerization: when monomers attach to a proto-oligomer of length l to produce one of length $l+1$, with rate $a_{1,l}$

(2) Depolymerization: when proto-oligomers of length l lose a monomer from the bottom or the top of the chain, with rate b.
(3) Fragmentation: when the proto-oligomer of length l loses a monomer, due to rupture of one of the bonds, with rate β.
(4) Degradation: monomers are degraded by the system and disappear with rate δ.
(5) Concatenation: when two proto-oligomers of length j and k attach to each other creating a proto-oligomer of length $j+k$, with rate $a_{j,k}$.

We further assume that when the proto-oligomers reach length n are considered oligomers. Oligomers are stable structure that do not combine with monomers nor proto-oligomers, and are not susceptible to fragmentation. In order to account for the various interactions between molecules, we must assume $n \geq 5$. This is consistent with the biological perspective, given that we are considering Aβ_{42} peptides, whose oligomers usually appear with length greater or equal than 20.

According to these hypotheses, we propose (1.1) as a suitable model for the biochemical processes described above. Focusing for instance on the first equation in (1.1) describing the diffusion and agglomeration of monomers of Aβ-amyloid

$$\frac{\partial u_1}{\partial t} = d_1 \Delta u_1 - u_1 \left(\sum_{j=2}^{n-1} a_{1,j} u_j + \delta \right) + 2\beta u_2 + \sum_{j=3}^{n-1} (\beta(j-1) + b) u_j,$$

we observe that the agglomeration of monomers to other proto-oligomers of length $2, \dots, n-1$ is modelled via the term $-u_1 \left(\sum_{j=2}^{n-1} a_{1,j} u_j \right)$ as in the usual Smoluchowski system; we further note the degradation term with rate δ, the polymerization terms with rate b and the fragmentation terms with rate β. We note that the nonlinear boundary condition

$$d_1 \frac{\partial u_1}{\partial \nu} = B_k(t, u_n(t)), \qquad \text{on } (0,T) \times \partial\omega_k,$$

has the explicit form

$$B_k(t, u_n(t)) = B_k^0 \exp\left(-\tau \int_0^t \int_\Omega |u_n(x,s)| \chi_k(x) dx ds \right), \tag{2.1}$$

where χ_k is the characteristic function of a small neighbourhood of the neuron ω_k, B_k^0 is the monomer production rate of the k-th neuron, and $\tau > 0$ is the infectivity rate. This boundary condition introduces a nonlinear feedback in the system, describing the neurotoxic effect of the oligomers, that diminish exponentially the neuron capability of producing monomers, provided they concentrate sufficiently close to the neuron, see [30], where the neurotoxic effect was observed, leading to synaptic dysfunction and neuronal damage. Differently from the model proposed in [4], the argument of the exponential in the boundary condition B_k is proportional to the L^1 norm of $u_n \chi_k$ in $(0,t) \times \Omega$. This assumption allows a better control of the nonlinearity when we study the existence of a nonnegative solution. We remark that this feedback mechanism is inspired by recent experimental evidence that oligomers disrupt neuronal APP processing and Aβ-production ([35]).

We note that while we added the concatenation terms with rate $a_{j,k}$, as in the usual Smoluchowski system, we set $a_{1,1} = 0$. The reason for this is both biological and mathematical: first, aggregation between monomers seems to have a negligible effect on the dynamics compared to concatenation between different terms; second, the presence of a non-trivial $a_{1,1}$ concatenation term forces any equilibrium of the system with at least one zero component to be identically zero, fact that does not seem to match the biological

setting (in an healthy patient, we expect the monomers to be naturally produced and degraded without creating neurotoxic oligomers).

3. A semigroup approach to local existence

We now show how we can rewrite system (1.1) in a form that can be treated by means of semigroup theory in the Banach space $X = C^0(\overline{\Omega})^n$. Let us define $w \in E_T$,

$$E_T := C^0([0,T), C^0(\overline{\Omega})) \cap C^0((0,T], H^1(\Omega)) \cap C^1((0,T), L^2(\Omega))$$

as the mild (in fact, classical) solution of the heat equation

$$\begin{cases} \partial_t w = d_1 \Delta w, & \text{in } (0,T) \times \Omega, \\ d_1 \partial_\nu w = -\gamma w, & \text{on } (0,T) \times \partial\Omega_0, \\ d_1 \partial_\nu w = B_k(t, u_n(t)), & \text{on } (0,T) \times \partial\omega_k \quad k = 1, .., J, \\ w(0,x) = 0, & x \in \Omega \end{cases} \tag{3.1}$$

where $B_k(t, u_n(t))$ is defined in (2.1) and $d_1, \gamma > 0$. The boundary condition $B_k(t, u_n(t))$ depends on the population u_n, but, as far as $u_n \in C^0([0,T], C^0(\overline{\Omega}))$, then $B_k(t, u_n(t)) \in C^0(0,T)$ and (3.1) admits a classical solution by the standard theory of parabolic linear equations. Note that $\Delta w \in C((0,T), L^2(\Omega))$ and w depends on u_n. However, since $B_k^0 \geq B_k(t, u_n(t)) > 0$ for all $t \geq 0$, the parabolic comparison principle (Theorem A.9) implies that

$$W \geq w > 0, \quad W \text{ solving (3.1) with } B_k^0 \text{ in place of } B_k(t, u_n(t)).$$

We note explicitly that W is $C_t^1 C_x^2(\Omega_T)$ for all $T > 0$. Indeed, there exists a constant $C > 0$ such that $\|W\|_{C_t^1 C_x^2(\Omega \times [0,+\infty))} \leq CT \sum_{k=1}^J B_k^0 |\omega_k|$. Moreover, we can get T-independent estimate via the following argument. Let H be the harmonic extension of the constant Neumann data B_0^k, that is, H is the solution of

$$\begin{cases} \Delta H = 0, & \text{in } \Omega, \\ d_1 \partial_\nu H = -\gamma H, & \text{on } \partial\Omega_0, \\ d_1 \partial_\nu H = B_0^k, & \text{on } \partial\omega_k,\ k = 1, \dots, J. \end{cases}$$

Note that H is $C^\infty(\overline{\Omega})$, and there exists a positive constant $C > 0$ such that $\|H\|_{C^0(\overline{\Omega})} \leq C \max_k B_0^k$. Set $\Phi = W - H$. Then Φ solves

$$\begin{cases} \partial_t \Phi - d_1 \Delta \Phi = 0, & \text{in } \Omega, \\ d_1 \partial_\nu \Phi = -\gamma \Phi, & \text{on } \partial\Omega_0, \\ d_1 \partial_\nu \Phi = 0, & \text{on } \partial\omega_k,\ k = 1, \dots, J, \\ \Phi(0,x) = -H(x) & x \in \Omega. \end{cases}$$

Thus, Φ solves the heat equation with initial datum $-H$. We can write

$$\Phi(t,x) = -\mathcal{T}(t) H(x),$$

where $\mathcal{T}$ is the semigroup generated by $d_1\Delta$ in $C^0(\overline{\Omega})$. Then,

$$\|\Phi(t,\cdot)\|_{C^0(\overline{\Omega})} \leq \|\mathcal{T}\|_{\mathcal{L}(C^0(\overline{\Omega}))} \|H\|_{C^0(\overline{\Omega})} \leq M e^{-\lambda t} \|H\|_{C^0(\overline{\Omega})},$$

where the inequality $\|\mathcal{T}\|_{\mathcal{L}(C^0(\overline{\Omega})} \leq Me^{-\lambda t}$ for $M = e^{\lambda|\Omega|}/(4\pi)$ and λ being the first eigenvalue of the Laplacian in Ω with mixed Neumann-Robin boundary data, is classical, see (3.37) in [10]. We conclude that

$$\|W\|_{C^0(\overline{\Omega})} = \|H + \Phi\|_{C^0(\overline{\Omega})} \leq C(1 + Me^{-\lambda t})\|H\|_{C^0(\overline{\Omega})}.$$

Then we have

$$0 < w \leq W \leq C \max_k B_0^k \tag{3.2}$$

for a suitable constant C.

Remark 3.1. The solution W exists for all times $t \in [0, +\infty)$, as it is the solution of the heat operator with smooth boundary datum. Note that $W(t)$ must tend (at least in $L^2(\Omega)$) as $t \to +\infty$ to the solution of the elliptic problem

$$\begin{cases} \Delta W_\infty = 0, & \text{in } \Omega, \\ d_1 \partial_\nu W_\infty = -\gamma W_\infty, & \text{on } \partial\Omega_0, \\ d_1 \partial_\nu W_\infty = B_k^0, & \text{on } \partial\omega_k, \ k = 1, .., J, \end{cases}$$

that satisfies $W_\infty \geq 0$ in Ω since $B_k^0 > 0$ and $\gamma > 0$. Regarding w, it exists for all times $t \in [0, +\infty)$, provided that u_n exists for all times $t \in [0, +\infty)$, and its asymptotic behaviour in time depends on $\lim_{t\to+\infty} e^{-\tau\|u_n\chi_k\|_{L^1((0,t)\times\Omega)}}$. For instance, if $\|u_n\chi_k\|_{L^1((0,t)\times\Omega)} \to +\infty$, as $t \to +\infty$, then $B_k(t, u_n(t)) \to 0$ as $t \to +\infty$, and therefore $w(t, x) \to 0$ as $t \to +\infty$.

Remark 3.2. Problem (3.1), can be recast in the following form

$$\begin{cases} \partial_t \psi = d_1 \Delta\psi + \partial_t U, & \text{in } (0, T) \times \Omega, \\ d_1 \partial_\nu \psi = -\gamma\psi, & \text{on } (0, T) \times \partial\Omega_0, \\ d_1 \partial_\nu \psi = 0, & \text{on } (0, T) \times \partial\omega_k, \ k = 1, .., J, \\ \psi(0, x) = U(0, x), & x \in \Omega \end{cases} \tag{3.3}$$

where $U(t, x)$ is the harmonic extension of the datum $B_k(t, u_n(t))$: let t be fixed and let $U(t, \cdot)$ be the solution of

$$\begin{cases} d_1 \Delta U = 0, & \text{in } \Omega, \\ d_1 \partial_\nu U = -\gamma U, & \text{on } \partial\Omega_0, \\ d_1 \partial_\nu U = B_k(t, u_n(t)), & \text{on } \partial\omega_k. \end{cases} \tag{3.4}$$

If $(\zeta_j)_j \subset L^2(\partial\Omega)$ are the eigenfunctions (corresponding to the eigenvalues σ_j) of the mixed Robin-Steklov problem

$$\begin{cases} d_1 \Delta\zeta_j = 0, & \text{in } \Omega, \\ d_1 \partial_\nu \zeta_j = -\gamma\zeta_j, & \text{on } \partial\Omega_0, \\ d_1 \partial_\nu \zeta_j = \sigma_j \zeta_j, & \text{on } \partial\omega_k \end{cases} \tag{3.5}$$

then, $(\mathrm{Tr}_{\omega_k}\zeta_j)_j$ can be renormalised to be an orthonormal basis of $L^2(\partial\omega_k)$. In particular, we can write, for any t fixed,

$$U(t,x) = \sum_j \sum_k (\zeta_j, B_k(t, u_n(t)))_{L^2(\partial\omega_k)} \zeta_j(x).$$

Thus,

$$\partial_t U(t,x) = -\tau \sum_k \left(\int_\Omega |u_n(t,x)| \chi_k(x) dx \right) \sum_j (\zeta_j, B_k(t, u_n(t)))_{L^2(\partial\omega_k)} \zeta_j(x),$$

so if $u_n \in C^0([0,T], C^0(\overline{\Omega}))$ and $\partial\Omega \in C^{2,\alpha}$, then $\partial_t U \in C^0([0,T], C^{2+\alpha}(\overline{\Omega}))$. Therefore, the solution $\psi = w + U$ of (3.3) is solving a heat equation problem with $C^0([0,T], C^{2+\alpha}(\overline{\Omega}))$ source term. An application of [20, Thm 5.1.19] implies that ψ is $C^1([0,T], C^{2+\alpha}(\overline{\Omega}))$. Therefore, $w = \psi - U \in C^1([0,T], C^{2+\alpha}(\overline{\Omega}))$.

We then replace the variable u_1 in (1.1) with $\tilde{u}_1 := u_1 - w$. This procedure has the effect of making the boundary condition homogeneous, at the price of adding some source terms in the equations. With abuse of notation we will use the same symbol u_1 for the new variable. We obtain

$$\begin{cases} \frac{\partial u_1}{\partial t} = d_1 \Delta u_1 - (u_1 + w)\left(\sum_{j=2}^{n-1} a_{1,j} u_j + \delta \right) + 2\beta u_2 + \beta \sum_{j=3}^{n-1} (j-1) u_j + b \sum_{j=3}^{n-1} u_j, \\ \frac{\partial u_2}{\partial t} = d_2 \Delta u_2 - a_{1,2}(u_1 + w) u_2 + b u_3 - \beta u_2 + 2\beta u_3 - \sum_{j=2}^{n-1} a_{2,j} u_2 u_j, \\ \frac{\partial u_l}{\partial t} = d_l \Delta u_l - a_{1,l}(u_1 + w) u_l + a_{1,l-1}(u_1 + w) u_{l-1} + b u_{l+1} - b u_l - \beta(l-1) u_l \\ \qquad + l\beta u_{l+1} - \sum_{j=2}^{n-1} a_{l,j} u_l u_j + \sum_{\substack{j+k=l \\ 1<j\le k<l}} a_{j,k} u_j u_k, \\ \frac{\partial u_{n-1}}{\partial t} = d_{n-1} \Delta u_{n-1} - a_{1,n-1}(u_1 + w) u_{n-1} + a_{1,n-2} u_1 + w) u_{n-2} - b u_{n-1} - \beta(n-2) u_{n-1} \\ \qquad - \sum_{j=2}^{n-1} a_{j,n-1} u_j u_{n-1} + \sum_{\substack{j+k=n-1 \\ 1<j\le k<n-1}} a_{j,k} u_j u_k, \\ \frac{\partial u_n}{\partial t} = d_n \Delta u_n + a_{1,n-1}(u_1 + w) u_{n-1} + \sum_{\substack{j+k\ge n \\ 1<j,k<n}} a_{j,k} u_j u_k, \end{cases} \tag{3.6}$$

in Ω_T, endowed with the boundary and initial conditions

$$\begin{cases} d_l \frac{\partial u_l}{\partial \nu} = -\gamma u_l, & \text{on } \partial\Omega_0,\ l = 1, \dots, n, \\ d_i \frac{\partial u_l}{\partial \nu} = 0, & \text{on } \partial\omega_k,\ l = 1, \dots, n, \\ u_i(0,x) = \varphi_i(x), & x \in \Omega,\ i = 1, \dots, n. \end{cases}$$

With $X = C^0(\overline{\Omega})^n$, we note that (3.6) is in the form

$$\begin{cases} \partial_t u(t) = A u(t) + F(t, u(t)), \\ u(0) = \varphi, \end{cases}$$

where $u = (u_1, \dots, u_n)$ is understood as a map from $(0,T)$ to X,

$$A = \operatorname{diag}(d_1\Delta, \dots, d_m\Delta),$$

with Δ verifying homogeneous Robin boundary conditions on $\partial\Omega_0$ and Neumann boundary conditions on $\bigcup_k \partial\omega_k$, and F is given by

$$F^1(t,u) = -(u_1 + w)\left(\sum_{j=2}^{n-1} a_{1,j} u_j + \delta \right) + 2\beta u_2 + \beta \sum_{j=3}^{n-1} (j-1) u_j + b \sum_{j=3}^{n-1} u_j, \tag{3.7}$$

$$F^2(t,u) = -a_{1,2}(u_1+w)u_2 + bu_3 - \beta u_2 + 2\beta u_3 - \sum_{j=2}^{n-1} a_{2,j}u_2u_j,$$

$$F^l(t,u) = -a_{1,l}(u_1+w)u_l + a_{1,l-1}(u_1+w)u_{l-1} + bu_{l+1} - bu_l - \beta(l-1)u_l + l\beta u_{l+1} - \sum_{j=2}^{n-1} a_{l,j}u_lu_j + \sum_{\substack{j+k=l \\ 1<j<k<l}} a_{j,k}u_ju_k$$

$$F^{n-1}(t,u) = -a_{1,n-1}(u_1+w)u_{n-1} + a_{1,n-2}(u_1+w)u_{n-2} - bu_{n-1} - \beta(n-2)u_{n-1} - \sum_{j=2}^{n-1} a_{j,n-1}u_ju_{n-1} + \sum_{\substack{j+k=n-1 \\ 1<j<k\le n-1}} a_{j,k}u_ju_k,$$

$$F^n(t,u) = a_{1,n-1}(u_1+w)u_{n-1} + \sum_{\substack{j+k\ge n \\ 1<j,k<n}} a_{j,k}u_ju_k$$

By Example A.5, A is m-dissipative in X.

We need to check that F is Lipschitz on bounded subsets of X; equivalently, for every $M>0$, there exists $L(M)>0$, strictly increasing in M such that

$$\|F(u)-F(v)\|_X \le L(M)\|u-v\|_X$$

for every $u,v\in X$ such that $\|u\|,\|v\|\le M$.

It is clear that all the linear and quadratic terms appearing in the expression for F^j are Lipschitz on bounded subsets of X; for instance

$$\|u_lu_k - v_lv_k\|_X \le \|u_l-v_l\|_\infty\{\|u_k\|_\infty + \|v_l\|_\infty\} \le 2M\|u-v\|_X$$

for all u,v s.t. $\|u\|,\|v\|\le M$. It remains to check that the terms involving w are indeed Lipschitz functions of u. Let us check that the term $a_{1,l}w(u_n)u_l$ is Lipschitz. Due to the previous discussion it is sufficient to check that $w(u_n)$ is Lipschitz in $C^0(\overline{\Omega})$. We note that $\psi = w(u_n)-w(v_n)$ solves the parabolic problem

$$\begin{cases} \partial_t\psi = d_1\Delta\psi, & \text{in } (0,T)\times\Omega, \\ d_1\partial_\nu\psi = -\gamma\psi, & \text{on } (0,T)\times\partial\Omega_0, \\ d_1\partial_\nu\psi = B_k^0(e^{-\tau\iint_0^t|u_n|\chi_k dxdt} - e^{-\tau\iint_0^t|v_n|\chi_k dxdt}), & \text{on } (0,T)\times\partial\omega_k,\ k=1,\dots,J, \\ \psi(0,x)=0, & x\in\Omega. \end{cases}$$

In particular, we have the estimate

$$\begin{aligned} \|\psi(t,\cdot)\|_{C^0(\overline{\Omega})} &\le C\sum_k B_k^0\|e^{-\tau\iint_{\Omega_t}|u_n(t,x)|\chi_k dtdx} - e^{-\tau\iint_{\Omega_t}|v_n(t,x)|\chi_k dtdx}\|_{L^\infty(\partial\omega_k)} \\ &\le C\sum_k B_k^0\tau\|u_n(t)-v_n(t)\|_{L^\infty(\partial\omega_k)} \le C(B,\tau)\|(u-v)(t)\|_{C^0(\overline{\Omega})} \end{aligned} \tag{3.8}$$

We conclude that there exists a constant $C>0$, depending only on the coefficients a_{ij}, δ, b, β, τ, on B_k^0 and on M, such that

$$\|F(u)-F(v)\|_X \le C\|u-v\|_X,$$

for all u, v s.t. $\|u\|, \|v\| \leq M$.

As a side remark, note that $F(t,0) \neq 0$, since $F^1(t,0) = -w(t,0)\delta$, and $w(t,0) = W(t) \neq 0$. Note also that $\sup_{t\in[0,T)} \|F(t,0)\|_X < \infty$.

We search for solutions $u \in E_T^n$ to the semilinear system of parabolic equations (3.6), where E_T^n is given by

$$E_T^n := C^0([0,T]), X) \cap C^0((0,T], H^1(\Omega)^n) \cap C^1((0,T), L^2(\Omega)^n).$$

Since A is m-dissipative in X, A is the generator of a contraction semigroup $(\mathcal{T}(t))_{t\in[0,T]}$ by the Hille-Yosida Theorem. Therefore, any solution to (3.6) can be expressed by the Duhamel's formula

$$u(t) = \mathcal{T}(t)u(0) + \int_0^t \mathcal{T}(t-s)F(s,u(s))ds, \tag{3.9}$$

and conversely, every regular u given by (3.9) solves (3.6). We will say that u is a *mild solution* to (3.6) if $u \in C([0,T], X)$ and u is given by (3.9).

An immediate consequence of (3.9) is that every mild solution is unique.

Theorem 3.3. *If $u, v \in C([0,T], X)$ are mild solutions to (3.6), then $u = v$.*

Proof. Set $M = \sup_{t\in[0,T]} \max\{\|u(t)\|_X, \|v(t)\|_X\}$, and let $\psi(t) = \int_0^t \|u(s) - v(s)\|_X ds$. Then

$$\psi'(t) = \|u(t) - v(t)\|_X \leq \int_0^t \|\mathcal{T}(t-s)\|_{\mathcal{L}(X)} \|F(s,u(s)) - F(s,v(s))\|_X ds \leq L(M)\psi(t),$$

where $L(M)$ is the Lipschitz constant of F for u, v s.t. $\|u\|, \|v\| \leq M$, for all $0 \leq t \leq T$, where in the last inequality we used that $(\mathcal{T}(t))_t$ is a contraction semigroup and F is Lipschitz on bounded subsets of X. An immediate application of Gronwall's integral inequality implies that $\psi = 0$. □

It is rather standard to check that there exist local mild solutions to (3.6) for all the initial data φ with bounded X-norm.

Theorem 3.4. *Let $M > 0$, set $K = 2M + \|F(0)\|_X$ and choose an initial datum $\varphi \in X$, $\|\varphi\|_X \leq M$. Set $T_M = \frac{1}{2(L(2M+\|F(0)\|_X)+2}$, where $L(K)$ is the Lipschitz constant of F for u, v s.t. $\|u\|, \|v\| \leq K$. Then there exists a mild solution u to (3.6) with initial datum φ in $[0, T_M)$.*

Proof. Let $K = 2M + \|F(0)\|_X$. Define

$$E = \{u \in C([0,T_M], X), \sup_{0\leq t\leq T_M} \|u(t)\|_X \leq K\}$$

$$d_E(u,v) = \max_{t\in[0,T_M]} \|u(t) - v(t)\|_X, \qquad u, v \in E.$$

Then (E, d_E) is a complete metric space. Set

$$\Phi_u(t) = \mathcal{T}(t)\varphi + \int_0^t \mathcal{T}(t-s)F(s,u(s))ds, \qquad t \in [0, T_M].$$

Since $\|F(s,u(s))\|_X \le \|F(0)\|_X + L(K)K \le \frac{M+\|F(0)\|_X}{T_M}$ for all $0 \le s \le T_M$, it is not difficult to check that $\|\Phi_u(t)\|_X \le K$, and therefore Φ maps E into itself. A similar computation also shows that

$$\|\Phi_u(t) - \Phi_v(t)\|_X \le L(K) \int_0^t \|v(s) - u(s)\|_X ds \le T_M L(K) d_E(u,v) \le \frac{d_E(u,v)}{2},$$

hence $\Phi : E \to E$ is a contraction in the complete metric space (E, d_E) with constant $\frac{1}{2}$. We conclude by the Banach fixed point theorem. □

Corollary 3.5. *For all $u_0 \in X$ there exists a maximal existence time $\hat{T}(u_0)$ verifying $2L(2\|u_0\|_X + \|F(0)\|_X) \ge \frac{1}{\hat{T}(u_0)-t}$ for all $0 \le t < \hat{T}(u_0)$. Therefore: either $\hat{T}(u_0) < +\infty$, and then $\lim_{t\uparrow\hat{T}(u_0)} \|u(t)\|_X = +\infty$; or, $\hat{T}(u_0) = +\infty$.*

In our model the solution $(u_1, .., u_n)$ represents the concentration of Aβ-amyloid in a portion of the brain, and therefore it is essential that each component u_i remain non-negative. For this reason we prove the following result.

Theorem 3.6. *Given an initial datum $\varphi \in C^0(\overline{\Omega})^n$ such that $\varphi_j \ge 0$ for all $j = 1, \dots, n$, there exists a positive time $T(\varphi) > 0$ such that (1.1) admits a unique mild solution $u \in (C_t^0 C_x^0([0, T(\varphi)) \times \overline{\Omega}))^n$ with $u_j \ge 0$ for all $j = 1, \dots, n$.*

Proof. Let us first introduce some notation. Define the cone of *componentwise nonnegative* solutions

$$X_+ = \{u \in X : u_j(x) \ge 0 \text{ for all } x \in \overline{\Omega},\ j = 1, .., n\}.$$

Let M such that $\|\varphi\|_X \le M$, $K \ge 2M$. For $T > 0$ define

$$E_+ = E_+(T) = \{u \in C([0,T], X_+),\ \sup_{0\le t\le T} \|u(t)\|_X \le K\},$$
$$d_E(u,v) = \max_{t\in[0,T]} \|u(t) - v(t)\|_X, \qquad u, v \in E.$$

Then (E_+, d_E) is a complete metric space. Define a map Φ that maps $u \in E_+$ to the solution v of the *linear* system of heat equations

$$\begin{cases} \frac{\partial v_1}{\partial t} = d_1 \Delta v_1 - v_1 \left(\sum_{j=2}^{n-1} a_{1,j} u_j + \delta \right) + 2\beta u_2 + \sum_{j=3}^{n-1} (\beta(j-1) + b) u_j, \\ \frac{\partial v_2}{\partial t} = d_2 \Delta v_2 - a_{1,2} u_1 v_2 + b u_3 - \beta v_2 + 2\beta u_3 - \sum_{j=2}^{n-1} a_{2,j} v_2 u_j, \\ \frac{\partial v_l}{\partial t} = d_l \Delta v_l - a_{1,l} u_1 v_l + a_{1,l-1} u_1 u_{l-1} + b u_{l+1} - b v_l - \beta(l-1) v_l \\ \qquad + l\beta u_{l+1} - \sum_{j=2}^{n-1} a_{l,j} v_l u_j + \sum_{\substack{j+k=l \\ 1<j\le k<l}} a_{j,k} u_j u_k, \\ \frac{\partial v_{n-1}}{\partial t} = d_{n-1} \Delta v_{n-1} - a_{1,n-1} u_1 v_{n-1} + a_{1,n-2} u_1 u_{n-2} \\ \qquad - (b + \beta(n-2)) v_{n-1} - \sum_{j=2}^{n-1} a_{j,n-1} u_j v_{n-1} + \sum_{\substack{j+k=n-1 \\ 1<j\le k<n-1}} a_{j,k} u_j u_k, \\ \frac{\partial v_n}{\partial t} = d_n \Delta v_n + a_{1,n-1} u_1 u_{n-1} + \sum_{\substack{j+k\ge n \\ 1<j,k<n}} a_{j,k} u_j u_k, \end{cases} \tag{3.10}$$

in Ω_T, $3 \le l \le n-2$, endowed with the boundary and initial conditions

$$\begin{cases} d_l \frac{\partial v_l}{\partial \nu} = -\gamma v_l, & \text{on } (0,T)\times\partial\Omega_0, \\ d_1 \frac{\partial v_1}{\partial \nu} = B(t,u_n(t)), & \text{on } (0,T)\times\partial\omega_k, \\ d_l \frac{\partial v_l}{\partial \nu} = 0, & \text{on } (0,T)\times\partial\omega_k, \\ v_i(0,x) = \varphi_i(x), & \text{in } \Omega,\ i=1,\dots,n. \end{cases}$$

Let us rewrite (3.10) in the abstract form

$$\partial_t v - d\Delta v + c(u)v = F(u),$$

where $v=(v_1,\dots,v_n)$ and $u=(u_1,\dots,u_n)$ and, in the first component we have $c_1(u)=\sum_{j=2}^{n-1} a_{1,j}u_j+\delta$ and $F^1(u)=2\beta u_2+\sum_{j=3}^{n-1}(\beta(j-1)+b)u_j$; the expressions for the other components are derived in the same way from system (3.10).

We first note that we can recast (3.10) as a linear system with homogeneous boundary conditions by introducing a function w as done in (3.6). Namely w solves

$$\begin{cases} \partial_t w = d_1\Delta w, & \text{in } (0,T)\times\Omega, \\ d_1\partial_\nu w = -\gamma w, & \text{on } (0,T)\times\partial\Omega_0, \\ d_1\partial_\nu w = B_k(t,u_n), & \text{on } (0,T)\times\partial\omega_k \quad k=1,..,M, \\ w(0,x)=0, & x\in\Omega. \end{cases} \tag{3.11}$$

Next letting $\tilde v_1 = v_1 - w$ we have that $(\tilde v_1,..,v_n)$ solves

$$\begin{cases} \frac{\partial \tilde v_1}{\partial t} = d_1\Delta\tilde v_1 - (\tilde v_1+w)\left(\sum_{j=2}^{n-1} a_{1,j}u_j+\delta\right) + 2\beta u_2 + \sum_{j=3}^{n-1}(\beta(j-1)+b)u_j, \\ \frac{\partial v_2}{\partial t} = d_2\Delta v_2 - a_{1,2}u_1v_2 + bu_3 - \beta v_2 + 2\beta u_3 - \sum_{j=2}^{n-1} a_{2,j}v_2u_j, \\ \frac{\partial v_l}{\partial t} = d_l\Delta v_l - a_{1,l}u_1v_l + a_{1,l-1}u_1u_{l-1} + bu_{l+1} - bv_l - \beta(l-1)v_l \\ \qquad +l\beta u_{l+1} - \sum_{j=2}^{n-1} a_{l,j}v_lu_j + \sum_{\substack{j+k=l \\ 1<j\le k<l}} a_{j,k}u_ju_k, \\ \frac{\partial v_{n-1}}{\partial t} = d_{n-1}\Delta v_{n-1} - a_{1,n-1}u_1v_{n-1} + a_{1,n-2}u_1u_{n-2} \\ \qquad -(b+\beta(n-2))v_{n-1} - \sum_{j=2}^{n-1} a_{j,n-1}u_jv_{n-1} + \sum_{\substack{j+k=n-1 \\ 1<j\le k<n-1}} a_{j,k}u_ju_k, \\ \frac{\partial v_n}{\partial t} = d_n\Delta v_n + a_{1,n-1}u_1u_{n-1} + \sum_{\substack{j+k\ge n \\ 1<j,k<n}} a_{j,k}u_ju_k, \end{cases} \tag{3.12}$$

in Ω_T, endowed with the boundary and initial conditions

$$\begin{cases} d_l \frac{\partial v_l}{\partial \nu} = -\gamma v_l, & \text{on } (0,T)\times\partial\Omega_0, \\ d_l \frac{\partial v_l}{\partial \nu} = 0, & \text{on } (0,T)\times\partial\omega_k, \\ v_i(0,x) = \varphi_i(x), & \text{in } \Omega,\ i=1,\dots,n. \end{cases}$$

Then, there exists a weak solution $v\in L^2((0,T),H^1(\Omega)^n)\cap C^0([0,T),L^2(\Omega)^n)$ with $\partial_t v\in L^2((0,T),(H^1(\Omega)^n)')$ of (3.12), and hence also of (3.10), for all initial data $\varphi\in C^0(\overline{\Omega})^n$ and for all sources $u\in E_+$. This can be proved via Galerkin approximation, as in the classical proof for the heat equation (see e.g., [15, Theorem 2, p. 354]). We now divide the proof in several steps.

Step 1. Here we prove that $v_j\ge 0$ in Ω for every j.

Let us consider for simplicity only the first equation of (3.10), which is more complicated due to the non-homogeneous boundary condition. Since $u\in E_+$, there exists a weak solution v of (3.10) for all $t\in(0,T)$.

Define $f(t) = \int_\Omega (v_1^-(t))^2 dx$. Since we are assuming that $v_1(0,x) = \varphi_1(x) \geq 0$ for $x \in \Omega$, $f(0) = 0$. Multiplying times v_1^- and recalling that $v_1(t,x) = -v_1^-(t,x)$ at all x such that $v_1(t,x) < 0$, we deduce that

$$-\frac{1}{2}f'(t) = d_1 \int_\Omega |\nabla v_1^-|^2 dx + \sum_{k=1}^{J} \int_{\partial\omega_k} B_k(t, u_n(t)) v_1^- d\sigma$$
$$+ \gamma \int_{\partial\Omega_0} (v_1^-)^2 d\sigma + \int_\Omega c_1(u) |v_1^-|^2 \, dx + \int_\Omega F^1(u) v_1^- dx \geq \frac{\min\{d_1, \gamma\}}{C_p} f(t) \geq 0$$

where C_p is the best constant in the Poincaré inequality

$$\int_\Omega \varphi^2 \, dx \leq C_p \left(\int_\Omega |\nabla \varphi|^2 \, dx + \int_{\partial\Omega_0} \varphi^2 d\sigma \right) \qquad \varphi \in H^1(\Omega).$$

We conclude that $f'(t) \leq -Cf(t)$ for all $t \in (0,T)$ and therefore $f(t) \leq 0$ for all $t \in (0,T)$, which implies $f(t) = 0$ for all $t \in (0,T)$. Thus $v_1 \geq 0$ in $(0,T)$. With a similar argument, also $v_j \geq 0$ for all $j = 1, \dots, n$ in $(0,T)$. This concludes the proof of Step 1.

Step 2. We will establish now *explicit* $L^\infty_t L^2_x$ a priori estimates for the solution v of (3.10), in terms of the $L^\infty_{t,x}$ norm of u.

Assume that $u \in E_+$. We rewrite system (3.10) in the abstract form

$$\partial_t v - d \cdot \Delta v + c(u) v = F(u), \tag{3.13}$$

and we consider this as a system with $C^0_t C^0_x(\Omega_T)$ coefficients and sources, but with a nonlinear and time-dependent Neumann boundary conditions on the first components of v. We claim that the standard regularity estimate for the heat equation (see e.g., [15, Theorem 2, p. 354])

$$\|v^j\|_{L^\infty_t L^2_x(\Omega_T)} + \|v^j\|_{L^2_t H^1_x(\Omega_T)} + \|\partial_t v^j\|_{L^2_t (H^1)'_x(\Omega_T)}$$
$$\leq CTe^T (\|c(u)\|_{L^\infty_{t,x}(\Omega_T)} + \|F(u)\|_{L^\infty_{t,x}(\Omega_T)} + \max_k \|B_k(t,u_n)\|^2_{L^2(\partial\omega_k)}) \tag{3.14}$$

holds for all $j \in 1, \dots, n$. The proof is standard for the equations for v^j, $j \geq 2$, whereas is a bit more involved for v^1, due to the nonlinear boundary term. Let us then establish (3.14) for the first equation only.

Multiplying times v^1 and integrating by parts we obtain

$$\frac{1}{2}\frac{d}{dt}\|v^1\|^2_{L^2(\Omega)} + d_1 \int_\Omega |\nabla v^1|^2 + \gamma \int_{\Omega_0} |v|^2 d\sigma - \sum_{k=1}^{J} \int_{\partial\omega_k} B_k(t,u_n) v^1 d\sigma + \int_\Omega c_1(u) v_1^2 = \int_\Omega F^1(u) v^1$$

Applying Cauchy-Schwarz and the weighted trace inequality with ε, we have that

$$\int_{\partial\omega_k} B_k(t,u_n) v^1 d\sigma \leq C_{\rm tr} \big(\varepsilon \int_\Omega |\nabla v^1|^2 + C(\varepsilon) \int_\Omega |v^1|^2 \big)^{\frac{1}{2}} \|B_k(t,u_n)\|_{L^2(\partial\omega_k)}$$
$$\leq C_{\rm tr} \big(\varepsilon \int_\Omega |\nabla v^1|^2 + C(\varepsilon) \int_\Omega |v^1|^2 \big) + C_{\rm tr} \|B_k(t,u_n)\|^2_{L^2(\partial\omega_k)}$$

Thus, up to choosing ε sufficiently small, we conclude that there exists a positive constant $C > 0$ such that

$$\frac{1}{2}\frac{d}{dt}\|v^1\|^2_{L^2(\Omega)} \leq C\big(\|F(u)\|^2_{L^2(\Omega)} + \max_k \|B_k(t,u_n)\|^2_{L^2(\partial\omega_k)}\big) + C\|v^1\|^2_{L^2(\Omega)}$$

An easy application of Grönwall inequality now yields the estimate for $\|v^1\|_{L^\infty_t L^2_x(\Omega_T)}$. The estimate for the remaining terms in (3.14) follows now as in the classical case, see [15, Theorem 2, p. 354]. This proves (3.14) and concludes Step 2.

Step 3. We claim that the map $\Phi(E_+) \subseteq E_+$ if T is small enough.

We need now an *explicit* $L^\infty_t L^\infty_x$ a priori estimates for the solution v of (3.10), in terms of the $L^\infty_{t,x}$ norm of u.

Let us first assume that the boundary term $B_k(t,u_n(t)) = 0$. Then we can write

$$\partial_t v(t,x) - d\cdot\Delta v(t,x) = G(t,x,v)$$

where $G(t,x,v) = -c(u(t,x))v(t,x) + F(u(t,x))$, with homogeneous boundary conditions and initial datum φ. Then we can write

$$v(t,x) = \mathcal{T}(t)\varphi + \int_0^t \mathcal{T}(t-s)G(t,x,v)ds,$$

where $\mathcal{T}$ is the semigroup generated by $d\Delta$ in C^0. Fix $p > \min\{2; \frac{N}{2}\}$. In the following computations, to shorten the notation, we will write $L^p(\Omega_T)$ in place of $L^p(\Omega_T)^n$ to indicate the norm of the vector-valued functions u and v. We have

$$\|v(t)\|_{L^\infty(\Omega)} \leq \left(\int_0^t \|\mathcal{T}(t-s)\|_{\mathcal{L}(L^p(\Omega),L^\infty(\Omega))}\right)\left(\|\varphi\|_{L^p(\Omega)} + \sup_{s\in(0,t)}\|G(t,x,v)\|_{L^p(\Omega)}\right) \tag{3.15}$$

and since

$$\|\mathcal{T}(t)\|_{\mathcal{L}(L^p(\Omega),L^\infty(\Omega))} \leq Ct^{-\frac{N}{2p}},$$

the integral in $(0,T)$ of the right-hand side of (3.15) is finite for every $T>0$. We now note that

$$\sup_{s\in(0,T)}\|G(t,\cdot,v)\|_{L^p(\Omega)} \leq |\Omega|^{\frac{1}{p}}\sup_{s\in(0,T)}\|F(u(s,\cdot)\|_{L^\infty(\Omega)} + \sup_{s\in(0,T)}\|c(u)\|_{L^\infty(\Omega)}\|v\|_{L^p(\Omega)},$$

and by applying the interpolation and the Young inequality, for any $\varepsilon>0$,

$$\|v\|_{L^p(\Omega)} \leq \|v\|^{1-\frac{2}{p}}_{L^\infty(\Omega)}\|v\|^{\frac{2}{p}}_{L^2(\Omega)} \leq \varepsilon\|v\|_{L^\infty(\Omega)} + C(\varepsilon)\|v\|_{L^2(\Omega)}$$

with $C(\varepsilon) = \frac{2}{p}(1-\frac{2}{p})^{1-\frac{p}{2}}\varepsilon^{1-\frac{p}{2}}$. Choose $\varepsilon < \frac{1}{2CT^{1-\frac{N}{2p}}\|c(u)\|_{L^\infty(\Omega_T)}}$, and note that $\|c(u)\|_{L^\infty(\Omega_T)} \geq \delta$ since the minimum is achieved when $u=0$; we conclude that

$$\frac{1}{2}\sup_{t\in(0,T)}\|v(t)\|_{L^\infty(\Omega)} \leq C\frac{T^{1-\frac{N}{2p}}}{1-\frac{N}{2p}}\Big[|\Omega|^{\frac{1}{p}}\|\varphi\|_{L^\infty(\Omega)} + |\Omega|^{\frac{1}{p}}\sup_{s\in(0,T)}\|F(u(s,\cdot)\|_{L^\infty(\Omega)}$$
$$+ C(\varepsilon)\sup_{s\in(0,T)}\|c(u)\|_{L^\infty(\Omega)}\|v\|_{L^2(\Omega)}\Big].$$

But F and c are locally Lipschitz functions (with Lipschitz constant bounded above by $L(K)$), so we conclude that

$$\sup_{t\in(0,T)} \|v(t)\|_{L^\infty(\Omega)} \leq C'T^{1-\frac{N}{2p}}[\|\varphi\|_\infty + L(K)\|u\|_{L^\infty(\Omega_T)} + C(\varepsilon)L(K)\|u\|_{L^\infty(\Omega_T)}\|v\|_{L^\infty_t L^2_x(\Omega_T)}] \tag{3.16}$$

Recalling (3.14), the right-hand side can be further estimated as follows

$$\begin{aligned}
&\sup_{t\in(0,T)} \|v(t)\|_{L^\infty(\Omega)} \leq C'T^{1-\frac{N}{2p}}[\|\varphi\|_\infty + L(K)\|u\|_{L^\infty(\Omega_T)} \\
&+ C(\varepsilon)L(K)\|u\|_{L^\infty(\Omega_T)}CTe^T(\|c(u)\|_{L^\infty_{t,x}(\Omega_T)} + \|F(u)\|_{L^\infty_{t,x}(\Omega_T)} + \max_k \|B_k(t,u_n)\|^2_{L^2(\partial\omega_k)})] \\
&\leq C'T^{1-\frac{N}{2p}}[\|\varphi\|_\infty + L(K)\|u\|_{L^\infty(\Omega_T)}(1 + C(\varepsilon)CTe^T(2L(K)\|u\|_{L^\infty(\Omega_T)} + \max_k |B^0_k|))]
\end{aligned}$$

Since $\|\varphi\|_X \leq K$ and $u \in E_+$ we have

$$\sup_{t\in(0,T)} \|v(t)\|_{L^\infty(\Omega)} \leq C'T^{1-\frac{N}{2p}}[K + L(K)K(1 + C(\varepsilon)CTe^T(2L(K)K + \max_k |B^0_k|))]$$

We note here that for sufficiently small T the right-hand side is less or equal than K, so that Φ maps E_+ in E_+ if T is small enough.

In the general case when $B(t,u_n) > 0$, one repeat the previous argument on the modified system (3.12), upon introducing the auxiliary smooth source term w in (3.11). This has the effect of modifying the first component of the function G appearing in the previous computations, but since w depends in a Lipschitz way on u_n, the exact same computations can be carried out. We conclude that, upon possibly enlarging the constant $C' > 0$, the estimate (3.16) holds (with the same dependence upon T and $\|u\|$). This concludes Step 3.

Step 4. We claim that Φ is a contraction for small enough $T > 0$.

From Steps 1-3 we conclude that the map $\Phi : E_+ \to E_+$ is continuous. Let $u, \tilde{u} \in E_+$, and assume $\|u\|_X, \|\tilde{u}\|_X \leq K$. Let v, $\tilde{v}$ the corresponding solutions of (3.10). By (3.13), we have that $\phi = v - \tilde{v}$ solves

$$\partial_t\phi - d\Delta\phi + \big(c(u)v - c(\tilde{u})\tilde{v} - F(u) + F(\tilde{u})\big) = 0 \tag{3.17}$$

with homogeneous Neumann-Robin boundary conditions for the entries ϕ^j, $j = 2,\dots,n$ and zero initial datum, whereas we have the non-homogeneous Neumann boundary conditions

$$\partial_\nu\phi^1 = B_k(t,u_n) - B_k(t,\tilde{u}_n)$$

on $\partial\omega_k$, $k = 1,\dots,J$. We note that

$$|c(u)v - c(\tilde{u})\tilde{v} - F(u) + F(\tilde{u})| \leq |c(u) - c(\tilde{u})||\tilde{v}| + |c(\tilde{u})||v - \tilde{v}| + |F(u) - F(\tilde{u})|$$

and since both c and F are locally Lipschitz on bounded sets of X, we conclude that there exists a constant $L(K) > 0$ depending only on K and the coefficients of the system (3.10) such that

$$\|c(u)v - c(\tilde{u})\tilde{v} - F(u) + F(\tilde{u})\|_X \leq L(K)(\|u - \tilde{u}\|_X\|\tilde{v}\|_X + \|v - \tilde{v}\|_X + \|u - \tilde{u}\|_X)$$

but

$$\|\tilde{v}\|_{L^\infty_t L^\infty_x(\Omega_T)} \leq C'T^{1-\frac{N}{2p}}L(K)\|u\|_{L^\infty(\Omega_T)}[1 + C(\varepsilon)CTe^T 2L(K)\|u\|_{L^\infty(\Omega_T)}]$$

so

$$\|c(u)v - c(\tilde{u})\tilde{v} - F(u) + F(\tilde{u})\|_X \leq L(K)(\|u-\tilde{u}\|_X C' T^{1-\frac{N}{2p}} L(K) K[1 + C(\varepsilon) C T e^T 2L(K)K] + \|\phi\|_X + \|u-\tilde{u}\|_X) \quad (3.18)$$

We then go back to (3.17). We want to first establish an estimate like (3.14). The only difficulty is in the first equation in ϕ^1, because of the non-homogeneous boundary term, whereas the other equations can be treated exactly as in (3.14). We multiply times ϕ^1 and we integrate in Ω (integrating by parts where possible), to obtain

$$\begin{aligned}\frac{1}{2}\|\partial_t \phi^1\|^2 + d_1 \int_\Omega |\nabla \phi^1|^2 + \gamma \int_{\partial\Omega_0} |\phi^1|^2 - \sum_{k=1}^M \int_{\partial\omega_k} (B_k(t,u_n) - B_k(t,\tilde{u}_n)\phi^1 \, d\sigma \\ + \int_\Omega \big(c(u)v - c(\tilde{u})\tilde{v} - F(u) + F(\tilde{u})\big)\phi^1 = 0.\end{aligned} \quad (3.19)$$

Now note that $B_k(t,\cdot)$ is locally Lipschitz in X, and it holds $|B_k(t,u_n) - B_k(t,\tilde{u}_n)| \leq B_k^0 |u_n - \tilde{u}_n|$, $k = 1,\dots,M$, for all $t, x \in \Omega_T$, and therefore we have that

$$\begin{aligned}&\Big|\sum_{k=1}^M \int_{\partial\omega_k} \big(B_k(t,u_n) - B_k(t,\tilde{u}_n)\big)\phi^1 \, d\sigma\Big| \leq \sum_{k=1}^J B_k^0 \|u_n - \tilde{u}_n\|_{L^2(\partial\omega_k)} \|\phi^1\|_{L^2(\omega_k)} \\ &\leq \frac{\Big(\sum_{k=1}^J B_k^0 |\partial\omega_k|^{1/2} \|u_n - \tilde{u}_n\|_{L^\infty(\partial\omega_k)}\Big)^2}{2} + \frac{\|\phi^1\|^2_{L^2(\partial\omega_k)}}{2} \\ &\leq \frac{\Big(\sum_{k=1}^J B_k^0 |\partial\omega_k|^{1/2} \|u_n - \tilde{u}_n\|_{C^0(\overline{\Omega})}\Big)^2}{2} + C_{\rm tr}\big(\varepsilon \|\nabla\phi^1\|^2_{L^2(\Omega)} + C(\varepsilon)\|\phi^1\|^2_{L^2(\Omega)}\big)\end{aligned}$$

where $\varepsilon > 0$ is a positive constant that we take to be less than $\frac{d_1 C_{\rm tr}}{2}$. Taking into account (3.18), equation (3.19) implies that there exists a (universal) constant $C > 0$ such that

$$\begin{aligned}\frac{1}{2}\|\partial_t\phi^1\|^2 \leq C\Big[&L(K)(\|u-\tilde{u}\|_X C' T^{1-\frac{N}{2p}} L(K) K[1 + C(\varepsilon) C T e^T 2L(K)K] + L(K)\|u-\tilde{u}\|_X) \\ &+ K\Big(\sum_{k=1}^J B_k^0 |\partial\omega_k|^{1/2}\Big)^2 \|u_n - \tilde{u}_n\|_X\Big] + C C_{\rm tr} C(\varepsilon)\|\phi^1\|^2_{L^2(\Omega)}\end{aligned}$$

and then estimating via Grönwall as in the proof of (3.14) we arrive at

$$\|\phi^j\|_{L^\infty_t L^2_x(\Omega_T)} + \|\phi^j\|_{L^2_t H^1_x(\Omega_T)} + \|\partial_t\phi^j\|_{L^2_t (H^1)'_x(\Omega_T)} \leq C T e^T \sup_{t\in(0,T)} \|u-\tilde{u}\|_X \Theta$$

where

$$\Theta = C\Big[L(K)(C' T^{1-\frac{N}{2p}} L(K) K(1 + C(\varepsilon) C T e^T 2L(K)K) + L(K)) + K\Big(\sum_{k=1}^J B_k^0 |\partial\omega_k|^{1/2}\Big)^2\Big]$$

for all $j = 1,\dots,n$.

Applying (3.16) to ϕ, we then conclude that there exists a possibly different constant C'' such that

$$\|\phi^j\|_{L^\infty_t L^\infty_x(\Omega_T)} \leq C'' T^{1-\frac{N}{2p}} L(K)\big(1 + C(\varepsilon)CTe^T L(K)K\Theta\big)\|u - \tilde{u}\|_{E_+} \tag{3.20}$$

for all $j = 1, \dots, n$. Therefore, we can choose T small, such that the map Φ is a contraction in E_+, concluding Step 4.

By the Banach fixed point theorem we conclude that there exists a unique $u \in E_+$ such that $u = \Phi(u)$, that is, u is the unique componentwise nonnegative mild solution of the original system (1.1). □

Corollary 3.7. *For all $\varphi \in X_+$ there exists a maximal existence time $\hat{T}(\varphi)$ such that either $\hat{T}(\varphi) < +\infty$, and then $\lim_{t\uparrow\hat{T}(\varphi)}\|u(t)\|_X = +\infty$; or, $\hat{T}(\varphi) = +\infty$.*

Proof. In view of Corollary 3.5, we just need to check that it is not possible for the componentwise nonnegative solution $u \in E_+$ to become negative in finite time. Assume therefore that at the maximal existence time $\hat{T}(\varphi) < +\infty$ at least one of the components u_j of the solution is such that $u_j(\hat{T}(\varphi), x_0) = 0$ for some $x_0 \in \Omega$, while $\|u(t)\|_X$ remains bounded as $t \to \hat{T}(\varphi)^-$. By the proof of Theorem 3.6, there exists a positive time τ for which we can find a solution of system (1.1) in the time interval $[\hat{T}(\varphi), \hat{T}(\varphi) + \tau]$ with initial data $u_j(\hat{T}(\varphi), x) \geq 0$, for all $x \in \Omega$. Note that this solution extends the solution u in the time interval $[0, \hat{T}(\varphi))$ by continuity of u. But this contradicts the maximality of $\hat{T}(\varphi)$; we conclude that either $\lim_{t\uparrow\hat{T}(\varphi)}\|u(t)\|_X = +\infty$; or, $\hat{T}(\varphi) = +\infty$. □

Proposition 3.8. *Let $\varphi = (\varphi_1, \cdots, \varphi_n) \in X \cap H^1(\Omega)^n$, and let $T(\varphi)$ be the maximal existence time for the local mild solution of (3.6) as in Theorem 3.4. Then $u_j \in C([0, T(\varphi)), H^1(\Omega))$. If $\Delta\varphi \in L^2(\Omega)$, then $u_j \in C([0, T(\varphi)), \mathrm{dom}(\Delta)) \cap C^1([0, T(\varphi)), L^2(\Omega))$ for all $j = 1, \dots, n$.*

Proof. The proof is an easy adaptation of [10, Proposition 5.2.3] in the case of time-independent boundary conditions. Therefore we first transform system (1.1)in (3.6); this can be done at the price of introducing the source terms w. Despite the fact that (3.6) has time-dependent sources, the regularity of w (see Remark 3.2) allows us to conclude. □

Remark 3.9. As a consequence of the smoothing properties of the heat kernel, for any $\varphi \in X$ we have that

$$\|\nabla u_j(t)\|_{L^2(\Omega)} \leq C|\Omega|^{\frac{1}{2}} t^{-\frac{1}{2}}$$
$$\|\Delta u_j(t)\|_{L^2(\Omega)} \leq C|\Omega|^{\frac{1}{2}} t^{-1}$$

for all $j = 1, \dots, n$, so $u(t) \in H^1(\Omega)^n$ and $\Delta u(t) \in L^2(\Omega)^n$ for all $t > 0$. See also [10, Remark 5.1.2]. If in addition $\varphi \in X \cap \mathrm{dom}(A)$, then Proposition 3.8 applies and $u(t) \in H^1(\Omega)^n$, $\Delta u(t) \in L^2(\Omega)^n$ for all $t \geq 0$.

Proposition 3.10. *If $\partial\Omega \in C^{2,\alpha}$, and $\varphi \in C^{2,\alpha}(\overline{\Omega})^n$, and further assume the compatibility conditions $\varphi_1|_{\partial\omega_k} = B_k^0$, $\partial_\nu\varphi_1|_{\partial\omega_k} = -\gamma B_k^0$ and $\partial_\nu\varphi_j = -\gamma\varphi_j$ on $\partial\Omega_0$, $\partial_\nu\varphi_j = 0$ on $\partial\omega_k$ for $j = 2, \dots, n$. Then $u \in C^{1+\theta}([0, T], C^{2,2\theta}(\overline{\Omega}))^n$, for some $\theta \in (0, 1/2)$.*

Proof. Remark 3.2 implies that $w \in C^1([0, T(\varphi)), C^{2,\alpha}(\overline{\Omega}))$. By Proposition 3.8, each u_j belongs to $C([0, T(\varphi)), \mathrm{dom}(\Delta))$. But $\mathrm{dom}(\Delta) = \{u \in X : \Delta u \in X\}$, therefore implying that $\Delta u_j(t, \cdot) \in C^0(\overline{\Omega})$, $t \in [0, T)$, $j = 1, \dots, n$. Moreover, $u_j \in C^0([0, T], H^2(\Omega))$, and therefore $u_j \in C^0([0, T], C^{0,\gamma}(\overline{\Omega}))$ by the Sobolev embedding theorem, for some $\gamma \in (0, 1/2]$. We then look at the first equation of (3.6), that is

$$\frac{\partial u_1}{\partial t} = d_1\Delta u_1 - (u_1 + w)\left(\sum_{j=2}^{n-1} a_{1,j}u_j + \delta\right) + 2\beta u_2 + \beta\sum_{j=3}^{n-1}(j-1)u_j + b\sum_{j=3}^{n-1} u_j \tag{3.21}$$

with homogeneous boundary conditions on $\partial\Omega$ and $u_1(0,x)=\varphi_1(x)$. The right-hand side of this equation is continuous in both the time and space variable. Therefore, we conclude that also $\partial_t u_1$ must be continuous in both time and space variable, and then $u_1 \in C^1([0,T],C^0(\overline{\Omega}))\cap C^0([0,T],\mathrm{dom}(\Delta))$. Moreover, a similar argument works for all the equations so $u_j \in C^1([0,T],C^0(\overline{\Omega}))\cap C^0([0,T],\mathrm{dom}(\Delta))$ for all j. Coming back to equation (3.21) we see that we are in the assumptions of Theorem 7.3.3(iii) in [20], with $m=1$ and $\theta=\min\{\gamma/2,\alpha/2\}$. For this note that, if

$$f(t,x,u_1)=-(u_1+w)(t,x)\left(\sum_{j=2}^{n-1}a_{1,j}u_j(t,x)+\delta\right)+2\beta u_2(t,x)$$
$$+\beta\sum_{j=3}^{n-1}(j-1)u_j(t,x)+b\sum_{j=3}^{n-1}u_j(t,x),$$

then the function f is Lipschitz in time since the functions w and u_j, $j\geq 2$ are C^1 in time, and it is Hölder continuous in x due to the Sobolev Embedding Theorem. We conclude that $u_1\in C^{1+\theta}([0,T],C^{2+2\theta}(\overline{\Omega}))$.

By finite induction, one can then repeat the same argument in the m-th equation, and conclude that $u_m\in C^{1+\theta}([0,T],C^{2,2\theta}(\overline{\Omega}))$. Finally, $u\in C^{1+\theta}([0,T],C^{2,2\theta}(\overline{\Omega}))^n$. □

4. Analysis of the equilibria

Since the boundary condition $\partial_\nu u_1(t,x)=B_k(t,u_n(t))\chi_k$ for $x\in\partial\omega_k$, $k=1,\dots,J$ is time-dependent, system (1.1) does not usually admit stationary states. However, if $B_k(t,u_n(t))$, is constant for all $k=1,\dots,J$, then stationary solutions do exist. We remark that $B_k(t,u_n(t))$ is constant if

$$\frac{\mathrm{d}}{\mathrm{d}t}B_k(t,u_n)=-\tau B_k^0\left(\int_\Omega |u_n(x,t)|\chi_k(x)dx\right)e^{-\tau\int_0^t\int_\Omega|u_n(x,s)|\chi_k(x)ds}=0,$$

for all $t\in(0,T)$; it must then be $u_n(x,t)=0$ for all $t\in[0,T)$, for all x in a neighbourhood of ω_k. In this scenario, $B_k(t,u_n(t))=B_k^0$ for all $t\in[0,T)$.

In particular, the point $(m_*,0,\dots,0)$ is a stationary solution of (1.1), where $m_*\in C^{2,\alpha}(\overline{\Omega})$ is the solution of

$$\begin{cases}-d_1\Delta m_*+m_*\delta=0, & \text{in } \Omega,\\ d_1\frac{\partial m_*}{\partial\nu}=-\gamma m_*, & \text{on } \partial\Omega_0,\\ d_1\frac{\partial m_*}{\partial\nu}=B_k^0, & \text{on } \partial\omega_k,\ k=1,\dots,J.\end{cases}\tag{4.1}$$

This system always admits a solution by the Fredholm Alternative Theorem, since $-\delta$ is not in the spectrum of $-d_1\Delta$. Moreover, since B_0^k is constant (hence regular), the solution m^* will be $C^\infty(\overline{\Omega})$. A priori we know that m_* satisfies the following bound:

$$0<m_*\leq C\sum_k B_k^0|\omega_k|^{1/2}.$$

Example. We consider here a simple toy model to explicitly compute the eigenvalues (4.1). Let $\Omega_0=B(0,R_0)\subset\mathbb{R}^3$ and let $\omega=B(0,R)$ with $0<R<R_0$. We assume that the annulus $\Omega:=\Omega_0\setminus\overline{\omega}$ is the neighbourhood of a single spherical neuron ω, and we proceed to compute the stationary state m_*. For $r\in(0,R_0]$ and $\xi\in S^2$, the ansatz for m_* is

$$m_*(r,\xi)=\sum_{l,m}(Aj_l(\mathrm{i}\sqrt{\delta/d_1}r)+By_l(\mathrm{i}\sqrt{\delta/d_1}r))Y_{lm}(\xi)\tag{4.2}$$

where j_l, y_l are spherical Bessel functions, A, B are positive constants and Y_{lm} is the spherical harmonics of indices l, m. Now we impose the boundary conditions. On the inner sphere, the boundary condition $-d_1\frac{\partial m_*}{\partial r} + \gamma m_*|_{r=R} = 0$ yields

$$-d_1\mathrm{i}\sqrt{\delta/d_1}(Aj_l'(\mathrm{i}\sqrt{\delta/d_1}R) + By_l'(\mathrm{i}\sqrt{\delta/d_1}R)) + \gamma(Aj_l(\mathrm{i}\sqrt{\delta/d_1}R) + By_l(\mathrm{i}\sqrt{\delta/d_1}R)) = 0$$

while the condition $d_1\frac{\partial m_*}{\partial r}|_{r=R_0} = B_k^0$ on the outer sphere yields

$$\sum_{l,m} d_1\mathrm{i}\sqrt{\delta/d_1}(Aj_l'(\mathrm{i}\sqrt{\delta/d_1}R_0) + By_l'(\mathrm{i}\sqrt{\delta/d_1}R_0))Y_{lm}(\xi) = B_k^0.$$

Since the only constant spherical harmonics is the one corresponding to $l, m = 0$, $Y_{00} = \frac{1}{2\sqrt{\pi}}$, we further get

$$d_1\mathrm{i}\sqrt{\delta/d_1}(Aj_0'(\mathrm{i}\sqrt{\delta/d_1}R_0) + By_0'(\mathrm{i}\sqrt{\delta/d_1}R_0))\frac{1}{2\sqrt{\pi}} = B_k^0,$$

so $A = \frac{B_k^0 2\sqrt{\pi}}{d_1\mathrm{i}\sqrt{\delta/d_1}j_0'(\mathrm{i}\sqrt{\delta/d_1}R_0)} - B\frac{y_0'(\mathrm{i}\sqrt{\delta/d_1}R_0)}{j_0'(\mathrm{i}\sqrt{\delta/d_1}R_0)}$. Therefore

$$\begin{aligned}
&-d_1\mathrm{i}\sqrt{\delta/d_1}\left(\left(\frac{B_k^0 2\sqrt{\pi}}{d_1\mathrm{i}\sqrt{\delta/d_1}j_0'(\mathrm{i}\sqrt{\delta/d_1}R_0)} - B\frac{y_0'(\mathrm{i}\sqrt{\delta/d_1}R_0)}{j_0'(\mathrm{i}\sqrt{\delta/d_1}R_0)}\right)j_0'(\mathrm{i}\sqrt{\delta/d_1}R) + By_0'(\mathrm{i}\sqrt{\delta/d_1}R)\right)\\
&\qquad+\gamma\left(\left(\frac{B_k^0 2\sqrt{\pi}}{d_1\mathrm{i}\sqrt{\delta/d_1}j_0'(\mathrm{i}\sqrt{\delta/d_1}R_0)} - B\frac{y_0'(\mathrm{i}\sqrt{\delta/d_1}R_0)}{j_0'(\mathrm{i}\sqrt{\delta/d_1}R_0)}\right)j_0(\mathrm{i}\sqrt{\delta/d_1}R) + By_0(\mathrm{i}\sqrt{\delta/d_1}R)\right) = 0
\end{aligned}$$

Solving for B, we obtain, with $\mathrm{i}\sqrt{\delta/d_1} = z$,

$$B = \frac{B_k^0 2\sqrt{\pi}[d_1 z j_0'(zR) - \gamma j_0(zR)]}{d_1 z[d_1 z y_0'(zR_0)j_0'(zR) - d_1 z y_0'(zR)j_0'(zR_0) - \gamma y_0'(zR_0)j_0(zR) + \gamma y_0(zR)j_0'(zR_0)]} \tag{4.3}$$

and

$$A = -\frac{B_k^0 2\sqrt{\pi}}{d_1\mathrm{i}\sqrt{\delta/d_1}j_0'(\mathrm{i}\sqrt{\delta/d_1}R_0)} + B\frac{y_0'(\mathrm{i}\sqrt{\delta/d_1}R_0)}{j_0'(\mathrm{i}\sqrt{\delta/d_1}R_0)}$$

which yields

$$A = \frac{B_k^0 2\sqrt{\pi}[-d_1 z y_0'(zR) + \gamma y_0(zR)]}{d_1 z[d_1 z y_0'(zR_0)j_0'(zR) - d_1 z y_0'(zR)j_0'(zR_0) - \gamma y_0'(zR_0)j_0(zR) + \gamma y_0(zR)j_0'(zR_0)]}. \tag{4.4}$$

Since m_* needs to be radial by symmetry of the domain and of the boundary datum, we deduce that

$$m_*(r) = (Aj_0(\mathrm{i}\sqrt{\delta/d_1}r) + By_0(\mathrm{i}\sqrt{\delta/d_1}r))\frac{1}{2\sqrt{\pi}}$$

with A and B as in (4.4) and (4.3).

We consider now the problem of the (linear) stability of the equilibrium $u_* = (m_*, 0, \dots, 0)$. Starting from system (1.1), which is in the form

$$\partial_t u = Au + F(u), \tag{4.5}$$

where $A = \mathrm{diag}(d_i\Delta : i = 1, \dots, n)$ and $F(u)$ is as defined in (3.7), with $w = 0$, we compute the system at $u_h = u_* + hf$, where $h > 0$ is a small parameter and $f \in C^\infty([0,T]; C^\infty(\overline{\Omega})^N)$ is the perturbation. Formally substituting u_h in (4.5) gives

$$\partial_t u_h = Au_h + F(u_h),$$

or equivalently

$$\partial_t f = Af + \frac{F(u_h) - F(u_*)}{h}.$$

Letting $h \to 0^+$ we obtain the linearization

$$\partial_t f = Af + JF(u_*)f, \tag{4.6}$$

where JF is the Jacobian of the function $u \mapsto (F_1(u), \dots, F_n(u))$. We have

$$JF(u_*) = \begin{pmatrix}
-\delta & j_{1,2} & j_{1,3} & \dots & \dots & \dots & \dots & \dots & j_{1,n-1} & 0 \\
0 & -a_{1,2}m_* - \beta & (2\beta + b) & 0 & \dots & \dots & \dots & \dots & 0 & 0 \\
\dots & \dots & j_{3,3} & \dots & \dots & \dots & \dots & \dots & \dots & 0 \\
\dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & 0 \\
\dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & \dots & 0 \\
0 & 0 & \dots & \dots & a_{1,l-1}m_* & j_{l,l} & l\beta + b & \dots & 0 & 0 \\
0 & 0 & \dots & \dots & \dots & \dots & \dots & \dots & \dots & 0 \\
0 & 0 & \dots & \dots & \dots & \dots & \dots & \dots & \dots & 0 \\
0 & 0 & \dots & \dots & \dots & \dots & \dots & a_{1,n-2}m_* & j_{n-1,n-1} & 0 \\
0 & 0 & \dots & \dots & \dots & \dots & \dots & 0 & a_{1,n-1}m_* & 0
\end{pmatrix}$$

where we have set

$$j_{1,2} = -a_{1,2}m_* + 2\beta, \quad j_{1,j} = -a_{1,j}m_* + (\beta(j-1) + b),$$
$$j_{l,l} = -a_{1,l}m_* - b - \beta(l-1).$$

We need to consider also the linearisation of the boundary term

$$d_1 \frac{\partial u_1}{\partial \nu} = B_k(t, u_n(t)).$$

This gives

$$d_1 \frac{\partial f_1}{\partial \nu} = B_k^0 \exp\left(-\tau \int_0^t \int_{\Omega \setminus \overline{\omega_k}} |u_n(x,s)| \chi_k(x) dx ds \right) \left(-\tau \int_0^t \int_{\Omega \setminus \overline{\omega_k}} |f_n(x,s)| \chi_k(x) dx ds \right) \Big|_{u=u_*}$$
$$= -B_k^0 \left(\tau \int_0^t \int_{\Omega \setminus \overline{\omega_k}} |f_n(x,s)| \chi_k(x) dx ds \right).$$

In particular, f_j, $j = 2, \dots, n$, satisfies homogeneous Neumann boundary conditions at the boundary of the neurons $\partial\omega_k$, $k = 1, .., J$, and homogeneous Robin boundary conditions at the exterior boundary $\partial\Omega_0$, whereas f_1 satisfies a time-depending, non-symmetric, non-local Robin type condition at the boundary of the neurons $\partial\omega_k$, $k = 1, .., J$.

We will restrict our linear stability analysis to the case $f_n = 0$. The reason is that if $f_n \neq 0$, the presence of the time-dependent boundary condition for f_1 does not allow the linear stability analysis via the eigenvalues of the associated elliptic operator. Even in the case when the diffusion is removed, so that system (1.1) does not depend on the space variable, the analysis of the equilibria with $f_n \neq 0$ seems very complicated and we refer to [8] for some results in that direction for a related ODE system.

In order to study the stability of the solution m_* when $f_n = 0$, we need to consider the system of Laplacian equations $d_i\Delta f_i + [(JF(u_*)f]_i = \lambda f_i$; a sufficient condition for the exponential stability is that all the eigenvalues have strictly negative real part.

Let $T = A + JF(u_*)$, with $\mathrm{dom}(T) = \{v = (v_1, \dots, v_n) \in H^1(\Omega)^n : Tv \in L^2(\Omega)^n\}$ and $A = \mathrm{diag}(d_i\Delta : i = 1, \dots, n)$. We recall that $\sigma(T) \subset \overline{W(T)}$, where

$$W(T) = \{z \in \mathbb{C} : \exists u \in \mathrm{dom}(T), \|u\| = 1, z = (Tu, u)_{L^2(\Omega)^n}\}.$$

Since T has compact resolvent, $\sigma(T) = \sigma_d(T)$, so the spectrum of T is a collection of isolated eigenvalues of finite multiplicity. We note explicitly that the expression (Tu, u) takes the explicit form

$$((Tu)_i, u_j) = -d_1(\nabla u_i, \nabla u_j \delta_{ji}) - \gamma \int_{\Omega_0} u_i u_j \delta_{ji} + ((JF(u_*)u)_i, u_j)$$

for all $i, j = 1, \dots, n$.

We first note the following fact:

Proposition 4.1. *$\sigma(T)$ is contained in the set*

$$S := \{z \in \mathbb{C} : \mathrm{dist}(z, (-\infty, -\lambda_0]) \leq \|JF(u^*)\|_\infty\},$$

where $\lambda_0 = \min_j d_j\lambda_1(-\Delta_{\mathrm{NR}})$ and $\lambda_1(-\Delta_{\mathrm{NR}}) > 0$ is the first eigenvalue of the mixed Neumann-Robin problem

$$\begin{cases} -\Delta u = \lambda u, & \text{in } \Omega, \\ \partial_\nu u + \gamma u = 0, & \text{on } \partial\Omega_0, \\ \partial_\nu u = 0, & \text{on } \partial\omega_k,\ k = 1, \dots, J. \end{cases}$$

Proof. Note that $T = A + JF(u^*)$, where $-A$ is a positive self-adjoint operator. Since $\sigma(A) \subset (-\infty, -\lambda_0]$, $JF(u^*)$ defines a bounded multiplication operator, we conclude that any point $z \in \sigma(T)$ is at distance at most $\|JF(u^*)\|_\infty$ from $\sigma(A)$. □

One can in fact refine the previous proposition by means of the block operator matrix version of the Gershgorin's circle theorem. Recall that given a densely defined closed operator T in a Hilbert space H, the resolvent set of T is $\varrho(T) = \mathbb{C} \setminus \sigma(T) = \{\lambda \in \mathbb{C} : T - \lambda \text{ is invertible}\}$.

Theorem 4.2. *Define $A_{jj} = d_j\Delta + JF(u^*)_{jj}$ and*

$$\mathcal{G}_j = \sigma(A_{jj}) \cup \left\{\lambda \in \varrho(A_{jj}) : \mathrm{dist}(\lambda, \sigma(A_{jj})) \leq \sum_{\substack{i=1 \\ i\neq j}} \left(\|JF(u^*)_{ij}\| \right\}$$

for $j = 1, \dots, n$. Then

$$\sigma(T) \subset \bigcup_{i=1}^{n} \mathcal{G}_j.$$

Proof. Apply Theorem 1.13.1 in [32], by noting that A_{jj} as defined in the theorem is a selfadjoint operator and that the block operator matrix associated with T is diagonally dominant (since the off-diagonal part is bounded). □

Corollary 4.3. *Let $T = A + JF(u_*)$ and m_* be the unique solution to (4.1). If m_* satisfies the following bounds:*

$$\frac{\beta - d_2\lambda_1(-\Delta_{\mathrm{NR}})}{a_{12}} \le m_* \le \frac{3\beta + d_2\lambda_1(-\Delta_{\mathrm{NR}})}{a_{12}} =: M_2 \tag{4.7}$$

$$\frac{2\beta + b - d_3\lambda_1(-\Delta_{\mathrm{NR}})}{a_{13}} \le m_* \le \frac{2\beta + b + d_3\lambda_1(-\Delta_{\mathrm{NR}})}{a_{13}} =: M_3 \tag{4.8}$$

$$\frac{(j-2)\beta + b - d_j\lambda_1(-\Delta_{\mathrm{NR}})}{a_{1j}} \le m_* \le \frac{j\beta + b + d_j\lambda_1(-\Delta_{\mathrm{NR}})}{a_{1j}} =: M_j \tag{4.9}$$

for $4 \le j \le n-1$, then all the eigenvalues of T have negative real part.

We therefore deduce the following condition

Corollary 4.4. *Assume that $d_1 \ge d_2 \ge \cdots \ge d_n$, $n \ge 5$. A sufficient condition for the asymptotic exponential stability of u^* is that*

$$\frac{(n-3)\beta + b}{d_{n-1}} \le \lambda_1(-\Delta_{\mathrm{NR}}), \quad \text{and} \quad \sum_k B_k^0 |\omega_k|^{1/2} \le \min_j M_j$$

where M_j are as defined in Corollary 4.3.

Therefore, if β and b are sufficiently small and B_k^0 are chosen in order to satisfy $\sum_k B_k^0|\omega_k|^{1/2} \le \min_j M_j$ (once β and b have been fixed), then the equilibrium is exponentially stable. This is not surprising: if $B_k^0 \to 0^+$, $m_* \to 0$, which corresponds to the case where the neurons are not producing monomers. If β and b are small, small perturbations of this state will start a production of monomers, which however will be immediately either degraded at rate δ or absorbed by the outer boundary.

5. Global existence

The objective of this section is to assess the existence of global nonnegative solutions for (1.1). We observe that, even in the case of a single semilinear heat equation, superlinear positive nonlinearities might cause blow-up in finite time for large initial data. In system (1.1), several positive nonlinear term are present. However, we note that these terms appear only in the m^{th} equation, $m = 3, \dots, n$, and therefore their growth is balanced by the decay of the first two components of the solution. This fact will allow us to conclude that the mild solutions exists for all times, with uniformly bounded X-norm.

We consider here, to shorten the notation, the semilinear parabolic system (1.1) in the case $n = 5$. Exactly the same argument can be extended to an arbitrary number $n \ge 5$.

Theorem 5.1. *Let $T > 0$, $\Omega_i = \bigcup \omega_k$, and $B(t) := \sum_{k=1}^{J} B_k(t, u_n(t))\chi_{\partial\omega_k}$. Consider the system in $\Omega_T = (0,T) \times \Omega$,*

$$\begin{cases} \partial_t u_1 = d_1\Delta u_1 - \delta u_1 - \sum_{j=2}^4 a_{1j}u_1u_j + 2\beta u_2 + \beta\sum_{j=3}^4 (j-1)u_j + b\sum_{j=3}^4 u_j, \\ \partial_t u_2 = d_2\Delta u_2 - a_{12}u_1u_2 + bu_3 - \beta u_2 + 2\beta u_3 - \sum_{j=2}^4 a_{2j}u_2u_j, \\ \partial_t u_3 = d_3\Delta u_3 - a_{13}u_1u_3 + a_{12}u_1u_2 + bu_4 - (2\beta+b)u_3 + 3\beta u_4 - \sum_{j=2}^4 a_{3j}u_3u_j, \\ \partial_t u_4 = d_4\Delta u_4 - a_{14}u_1u_4 + a_{13}u_1u_3 + a_{22}u_2^2 - bu_4 - 3\beta u_4 - \sum_{j=2}^4 a_{j4}u_ju_4, \\ \partial_t u_5 = d_5\Delta u_5 + a_{14}u_1u_4 + \sum_{j=3}^4 a_{2j}u_2u_j + \sum_{j=2}^4 a_{3j}u_3u_j, \end{cases} \tag{5.1}$$

endowed with the boundary and initial conditions

$$\begin{cases} d_l\frac{\partial u_l}{\partial\nu} = -\gamma u_l, & \text{on } \partial\Omega_0,\ 1\le l\le 5, \\ d_1\frac{\partial u_1}{\partial\nu} = B(t), & \text{on } (0,T)\times\partial\Omega_i, \\ d_l\frac{\partial u_l}{\partial\nu} = 0, & \text{on } (0,T)\times\partial\Omega_i,\ 2\le l\le 5, \\ u_i(0) = \varphi_i, & \text{in } \Omega, \end{cases}$$

for $\varphi_i \in X$, $\varphi_i \ge 0$, $i = 1,\dots,5$. Then there exists a unique componentwise non-negative mild solution u, i.e., $u_j \ge 0$, $j = 1,\dots,5$, which lies in $C^0(\mathbb{R}_{\ge 0}; X)$.

Proof. The existence of a mild solution $u \in X_+$ for $t \in [0, T(\varphi))$ was proved in Theorem 3.6. We need to show that $T(\varphi) = +\infty$. In view of Corollary 3.7 it is enough to prove that the solution u has X-norm bounded independently of t.

In order to avoid dealing with the boundary term $B_k(t, u_n(t))$, we prefer to transform system (5.1) in the following

$$\begin{cases} \partial_t u_1 = d_1\Delta u_1 - (u_1+w)\big(\delta + \sum_{j=2}^4 a_{1j}u_j\big) + 2\beta u_2 + \beta\sum_{j=3}^4 (j-1)u_j + b\sum_{j=3}^4 u_j, \\ \partial_t u_2 = d_2\Delta u_2 - a_{12}(u_1+w)u_2 + bu_3 - \beta u_2 + 2\beta u_3 - \sum_{j=2}^4 a_{2j}u_2u_j, \\ \partial_t u_3 = d_3\Delta u_3 - a_{13}(u_1+w)u_3 + a_{12}(u_1+w)u_2 + bu_4 - (2\beta+b)u_3 + 3\beta u_4 - \sum_{j=2}^4 a_{3j}u_3u_j, \\ \partial_t u_4 = d_4\Delta u_4 - a_{14}(u_1+w)u_4 + a_{13}(u_1+w)u_3 + a_{22}u_2^2 - bu_4 - 3\beta u_4 - \sum_{j=2}^4 a_{j4}u_ju_4, \\ \partial_t u_5 = d_5\Delta u_5 + a_{14}(u_1+w)u_4 + \sum_{j=3}^4 a_{2j}u_2u_j + \sum_{j=2}^4 a_{3j}u_3u_j, \end{cases} \tag{5.2}$$

in Ω_T, where w was defined in (3.1), endowed with the boundary conditions

$$\begin{cases} d_l\frac{\partial u_l}{\partial\nu} = -\gamma u_l, & \text{on } \partial\Omega_0,\ 1\le l\le 5, \\ d_1\frac{\partial u_1}{\partial\nu} = 0, & \text{on } (0,T)\times\partial\Omega_i, \\ d_l\frac{\partial u_l}{\partial\nu} = 0, & \text{on } (0,T)\times\partial\Omega_i,\ 2\le l\le 5, \\ u_i(0) = \varphi_i, & \text{in } \Omega. \end{cases}$$

Clearly, if a global solution to (5.2) exists, then the same is true for (5.1), given that w is a global solution bounded for all times see (3.2). We divide the proof in several steps.

Step 1. We claim that the solution u_1 of system (5.2) is bounded in $[0, T(\varphi))$, with a bound independent of T or u_j, $j \ge 2$ (and therefore the same holds for the solution $\tilde{u}_1$ of (5.1) in view of the formula $\tilde{u}_1 = u_1 + w$).

Let

$$\tilde{q}_1(t) = \max\left\{\|\varphi_1\|_X, \frac{2\beta}{a_{12}} - w(t), \frac{2\beta+b}{a_{13}} - w(t), \frac{3\beta+b}{a_{14}} - w(t)\right\}$$

where $w(t) = \max_{x\in\Omega} w(t,x)$. Note that, even though $\tilde{q}_1(t)$ depends on t, we always have $\tilde{q}_1(t) \le q_1$, with

$$q_1 = \max\left\{\|\varphi_1\|_X, \frac{2\beta}{a_{12}}, \frac{2\beta+b}{a_{13}}, \frac{3\beta+b}{a_{14}}\right\},$$

because $w(t) \geq 0$. Define

$$f(t) := \int_\Omega ((u_1(t) - q_1)^+)^2 dx, \quad t \in [0, T).$$

Note that $f(0) = 0$ and $f(t) \geq 0$ for all $t \in [0, T)$. Moreover,

$$f'(t) = 2\int_\Omega (u_1(t) - q_1)^+ \partial_t u_1.$$

In view of (5.2), we multiply both hand-sides of the first equation by $(u_1 - q_1)^+$ and we integrate by parts (where possible). We deduce that

$$\begin{aligned} f'(t) = &-2d_1 \int_{\Omega\cap\{u_1>q_1\}} |\nabla u_1(t)|^2 - 2\gamma \int_{\partial\Omega_0} u_1(u_1 - q_1)^+ \\ &- 2\int_\Omega (a_{12}(u_1 + w) - 2\beta)u_2(u_1 - q_1)^+ - 2\delta \int_\Omega (u_1 + w)(u_1 - q_1)^+ \\ &- 2\int_\Omega (a_{13}(u_1 + w) - (2\beta + b))u_3(u_1 - q_1)^+ - 2\int_\Omega (a_{14}(u_1 + w) - (3\beta + b))u_4(u_1 - q_1)^+ \end{aligned} \tag{5.3}$$

Since $u_1 + w > u_1 > \max\left\{\frac{2\beta}{a_{12}}, \frac{2\beta+b}{a_{13}}, \frac{3\beta+b}{a_{14}}\right\}$ in $\{u_1 > q_1\}$, we deduce that the right-hand side of (5.3) is non-positive. Therefore,

$$f'(t) \leq 0, \text{ in } [0, T) \quad \Rightarrow 0 \leq f(t) \leq f(0) = 0, \text{ in } [0, T),$$

and then $f = 0$ in $[0, T)$, implying $0 \leq u_1(t) \leq q_1$ for all $t \in [0, T)$.

We then come back to the solution $\tilde{u}_1$ of system (5.1). By (3.2) we have $\tilde{u}_1 = u_1 + w \leq q_1 + C \max_k B_0^k := \overline{q}_1$ where $\overline{q}_1$ is independent on T and on u_j for $j \geq 2$.

Step 2. We claim that u_j is bounded in $[0, T(\varphi))$, with a bound independent of T or u_k, $j \neq k$, for $j = 1, \ldots, 4$

Repeating the same argument as in Step 1 it is not difficult to prove that $u_j(t) \leq q_j$ for all $j = 2, \ldots, 4$, where

$$\begin{aligned} q_2 &= \max\left\{\|\varphi_2\|_X, \frac{2\beta+b}{a_{23}}\right\}, \\ q_3 &= \max\left\{\|\varphi_3\|_X, \frac{3\beta+b}{a_{34}}, \frac{a_{12}\overline{q}_1}{a_{23}}\right\}, \\ q_4 &= \max\left\{\|\varphi_4\|_X, \frac{a_{22}q_2}{a_{24}}, \frac{a_{13}\overline{q}_1}{a_{34}}\right\}. \end{aligned}$$

Note that all the upper bounds q_j are independent of T.

Step 3. We have proved that u_j, $j = 1, \ldots, 4$ is bounded in $[0, T(\varphi))$, with a bound independent of T or of u_k, $k \neq j$. Set $\bar{u}(t) = (u_1(t), \ldots, u_4(t))$, and $\bar{X} = C^0(\overline{\Omega})^4$. There exists a constant $C > 0$ depending only on the coefficients of system (5.1) such that

$$\|\bar{u}(t)\|_{\bar{X}} \leq C$$

for all $0 \leq t < T(\varphi)$. But since C does not depend on t, $\lim_{t\to T^-} \|\bar{u}(t)\|_{\bar{X}} \leq C$, and therefore $T = +\infty$ by Corollary 3.7 (we note that the Corollary is stated for the whole system, but since the dependence on u_5 in these equations is uniformly bounded for all times $t \geq 0$, it still applies here).

Step 4. To show that $\sup_t \|u_5(t)\|_\infty < \infty$, we will use the exponential decay of the $\mathcal{L}(C^0(\overline{\Omega}))$ norm of the heat semigroup as stated in Corollary 3.5.10 in [10].

We recall (see (3.37) in [10]) that

$$\|\mathcal{T}(t)v\|_{L^\infty(\Omega)} \leq Me^{-\lambda t}\|v\|_{L^\infty(\Omega)}$$

for all $t > 0$, $v \in C^0(\overline{\Omega})$, where $\lambda > 0$ is the first eigenvalue of $-\Delta_{NR}$ in Ω, and $M = \frac{e^{\lambda|\Omega|}}{4\pi}$. Recalling the integral formula for the solution u_5 of system (5.2), given by (3.9):

$$u_5(t) = \mathcal{T}(t)\varphi_5 + \int_0^t \mathcal{T}(t-s)Q(s,x)ds$$

with $Q(s,x) = a_{14}(u_1+w)u_4 + \sum_{j=3}^4 a_{2j}u_2u_j + \sum_{j=2}^4 a_{3j}u_3u_j$, we conclude that

$$\|u_5(t)\|_\infty \leq Me^{-\lambda t}\|\varphi_5\|_\infty + \left(\int_0^t Me^{-\lambda(t-s)}ds\right)\sup_{0\leq s\leq t}\|Q(s,x)\|_{L^\infty(\Omega)}.$$

Step 1-3 imply that $\sup_{0\leq s\leq t}\|Q(s,x)\|_{L^\infty(\Omega)} < C$, for a suitable $C > 0$, so

$$\|u_5(t)\|_{L^\infty(\Omega)} \leq Me^{-\lambda t}\|\varphi_5\|_\infty + M\left(1 - \frac{e^{-\lambda t}}{\lambda}\right)\sup_{0\leq s\leq t}\|Q(s,x)\|_{L^\infty(\Omega)}.$$

The right-hand side is uniformly bounded in t by Step 3, so we conclude

$$\sup_{t\in[0,+\infty)} \|u_5(t)\|_{L^\infty(\Omega)} < +\infty.$$

This shows that $T(\varphi) = +\infty$ and concludes the proof. □

Remark 5.2. We note that the proof of Theorem 5.1 fails when $\gamma = 0$, because in that situation the associated linear operator is the Neumann Laplacian, that does not admit a positive first eigenvalue.

Corollary 5.3. *In the assumptions of Theorem 5.1, suppose that $\varphi_1 > 0$, and $\varphi_2 = .. = \varphi_5 = 0$. Then the componentwise nonnegative solutions of system (5.1) are in the form $u = (u_1, 0, \ldots, 0)$, where $u_1 > 0$ in $[0,\tau) \times \Omega$. If instead at least one among $\varphi_2, .., \varphi_5$ is not identically zero and $\varphi_j \geq 0$ for all j, the componentwise nonnegative solutions of system (3.6) are in the form $u = (u_1, \ldots, u_n)$, with $u_j \neq 0$ for all $j = 1, \ldots, n$.*

Proof. Let us assume that $u_2 = 0$ in $K = [0,\tau_0] \times \Omega$. From the second equation of (5.1) we deduce that

$$\frac{\partial u_2}{\partial t} = d_2\Delta u_2 - a_{12}u_1u_2 - \beta u_2 - a_{22}u_2^2 - \xi u_2 + L$$

with

$$\xi = \sum_{j=3}^{n-1} a_{2j} u_j, \qquad L = (2\beta + b)u_3.$$

Since $u_2 = 0$ in K, also $u_3 = 0$ in K. Arguing in a similar way for all the equations, we deduce that $u_j = 0$ in K for $j = 2, \dots, n$. We then go back to the first equation. We obtain

$$\frac{\partial u_1}{\partial t} = d_1 \Delta u_1 - \delta u_1$$

in K, with inhomogeneous boundary condition $\partial_\nu u_1 = B_k^0$ on $[0, \tau_0] \times \partial\omega_k$. Due to Theorem A.9, $u_1 > 0$ in K. This proves the first part of the statement.

For the second part, suppose that $\varphi_2 \not\equiv 0$ and assume for a contradiction that some u_j, $j \geq 3$ is identically zero. Without loss of generality we may assume $u_3 = 0$ in K. But then, looking at the third equation in (5.1) we see that $u_3 = 0$ in K implies $u_1 u_2 = 0$ in K and $u_4 = 0$. But $\varphi_1 > 0$ and $\varphi_2 \not\equiv 0$, so the condition $u_1(0, x)u_2(0, x) = \varphi_1(x)\varphi_2(x)$ for all $x \in \Omega$ gives a contradiction. Therefore, $u_j \not\equiv 0$ for all $j = 1, \dots, n$ in K. □

6. Numerical experiments

In the numerical simulations we considered the concrete situation of a small bidimensional section of the human brain of circular shape, containing 4 neurons displaced in symmetric fashion.

• *Geometric setting*

We consider a two-dimensional circular domain Ω_0 of radius 100 µm with four small circular holes ω_1, ω_2, ω_3 and ω_4 of radius 6 µm. The domain $\Omega = \Omega_0 \setminus \bigcup_{k=1}^4 \overline{\omega}_k$ represents a small section of the human brain, whereas the holes ω_k represents the neurons.

• *Adimensional reformulation*

Following [5], to simplify numerical simulations, we first nondimensionalize the model. First, we specify the unit system employed. In this work, we use SI units, where lengths are measured in meters (m), time in seconds (s), and concentrations in molar units (M), where $1\,\mathrm{M} = 1\,\mathrm{mol\,L^{-1}}$. Based on this unit system, we define the following characteristic scales:

- *Spatial scale:* The characteristic length of the domain is denoted as L, typically on the order of 100 µm.
- *Time scale:* The characteristic time is denoted as T, typically around 100 s.
- *Concentration scale:* The characteristic concentration is represented by C_0, approximately 10^{-9} M.

Using these scales, we nondimensionalize the model variables. Throughout this section, nondimensional variables are indicated with a superscript *. The nondimensional variables are defined as:

$$t^* = \frac{t}{T}, \quad x^* = \frac{x}{L}, \quad y^* = \frac{y}{L}, \quad \xi^*(t^*, x^*) = \frac{\xi(t, x)}{C_0}, \quad \xi = u_1, \dots, u_n. \tag{6.1}$$

The nondimensional operators are given by:

$$\frac{\partial}{\partial t} = \frac{1}{T}\frac{\partial}{\partial t^*}, \quad \nabla = \frac{1}{L}\nabla^*, \quad \Delta = \frac{1}{L^2}\Delta^*. \tag{6.2}$$

Table 1
Values of the (non-rescaled) parameters.

Parameters	Value	Unit	Description
T	50000	s	Time scale
L	100	µm	Length scale
C_0	10^{-9}	M	Concentration scale
n	20		Length of oligomers
d_i	$d_1/i^{1/3}$	$\mathrm{m}^2\,\mathrm{s}^{-1}$	Diffusion coefficient of the i-th protooligomer [5]
d_1	2.210^{-14}	$\mathrm{m}^2\,\mathrm{s}^{-1}$	Diffusion coefficient of the monomers [5]
δ	$5 \cdot 10^{-4}$	s^{-1}	Degradation coefficient of the monomers [5]
γ	1	$\mathrm{m} \cdot \mathrm{s}^{-1}$	Absorption coefficient [5]
a_{1j}	10^7	$\mathrm{M}^{-1}\,\mathrm{s}^{-1}$	Polymerization rate [5]
a_{lk}	variable	$\mathrm{M}^{-1}\,\mathrm{s}^{-1}$	Concatenation rate
b	10^{-3}	s^{-1}	Polymerization rate [5]
β	10^{-4}	s^{-1}	Fragmentation rate [5]
τ	10^{10}	$\mathrm{M}^{-1} \cdot \mathrm{s}^{-1}$	Infectivity rate [5]
B_k^0	$3.183 \cdot 10^{-13}$	$\mathrm{M} \cdot \mathrm{s}^{-1} \cdot \mu\mathrm{m}$	Initial monomer production rate of the k-th neuron [5]

Substituting these into the equations of the model yields the nondimensionalized equations. The equations retain the same form as in the original model, but the operators are replaced with their nondimensional counterparts, and the coefficients are adjusted as follows:

$$\begin{aligned} &d^* = \frac{dT}{L^2}, \quad a^*_{1,j} = a_{1,j} C_0 T, \quad b^* = bT, \quad \beta^* = \beta T, \quad \delta^* = \delta T, \\ &\gamma^* = \frac{\gamma T}{L}, \quad (B_k^0)^* = \frac{B_k^0 T}{L C_0}, \quad \tau^* = \tau C_0 T. \end{aligned} \tag{6.3}$$

We choose the parameters in accordance with the previous literature. For the simulations we will use the values given in Table 1.

• *Description of the numerical simulations*

The simulations are performed in FreeFEM++ and visualized in Paraview. We use the parameters described in Table 1.

We use a forward Euler scheme with implicit diffusion (solved via the function *problem* in FreeFEM++) and explicit reaction. Namely, we discretise in the time variable; at each step we solve each equation with the diffusion variable computed at time t_{k+1}, while the nonlinear part is explicit and obtained by evaluating the function F at the values of the variable at time t_k.

More explicitly, we first rewrite system (1.1) in variational form. Given a time step $h > 0$, we consider the time discretisation:

$$\frac{u_i(t_{k+1}, x) - u_i(t_k, x)}{h} = d_i \Delta u_i(t_{k+1}, x) + F_i(u_1, \dots, u_n)(t_k, x)$$

for $k = 1, \dots, [T/h]$, $i = 1, \dots, n$, where $t_{k+1} = t_k + h = \cdots = kh$. Given a test function ψ, the weak formulation of the i-th equation is

$$\begin{aligned} &\int_\Omega (u_i(t_{k+1}, x) - u_i(t_k, x))\, \psi(x) dx - h \int_\Omega \nabla u_i(t_{k+1}, x) \cdot \nabla \psi(x) dx \\ &+ h \int_{\partial\Omega_0} \gamma u_i(t_{k+1}, x) \psi(x) d\sigma(x) - h \sum_l \int_{\partial\omega_l} d_i \partial_\nu u_i(t_{k+1}, x) \psi(x) d\sigma(x) \\ &- \int_\Omega h F_i(u_1, \dots, u_n)(t_k, x) \psi(x) dx = 0 \end{aligned}$$

Since we are imposing an homogeneous Neumann boundary condition at the neurons for u_i, $i = 2, \dots, n$, we see that the term

$$-h \sum_l \int_{\partial\omega_l} d_i \partial_\nu u_i(t_{k+1}, x)\psi(x)d\sigma(x)$$

is always vanishing, unless $i = 1$, in which case we obtain the integral

$$-h \sum_l \int_{\partial\omega_l} d_1 B_l(t_{k+1})\psi(x)d\sigma(x)$$

Since we need to evaluate $B_l(t_{k+1})$ (which depends on u_n) before we compute $u_1(t_{k+1}, \cdot)$, we solve the system backward starting from the n-th equation, and ending with the monomer equation.

The initial data for the monomers are concentrated around the central neurons and are symmetric, whereas the initial datum for the oligomers is concentrated around the external neurons in a asymmetric way (see Fig. 1, top two figures). After rescaling, the maximum value of the initial datum for the monomers is $4 \cdot 10^{-2}$ whereas the maximum value of the initial datum for the oligomers is of order $1.8 \cdot 10^{-2}$.

We repeated the simulations varying in particular the values of the concatenation parameters a_{ij}, $i, j > 1$, whose value is of the same order of magnitude of the concatenation parameters in [6]. With respect to the simulations in [5], we note that allowing for concatenation of proto-oligomers results in a faster transformation of monomers into oligomers, that are therefore increasing in many regimes. We note that higher values of the concatenation parameters results in a more reaction-centred dynamics (see Fig. 2), whereas lower concatenation results in a more diffusion-centred one.

Indeed, while the evolution of the monomers is qualitatively left unchanged by the different concatenation values, the oligomers distribution is quite different already after 7500s (compare the third row left in Fig. 1 and Fig. 2). In the high concatenation regime, we see that the maximum of the oligomer distribution tend to move faster towards the central healthy neurons, where the majority of the monomers are; the dynamics of the oligomers seems highly affected by the nonlinear aggregation terms in this regime, see Fig. 2, bottom row.

We then compare our results to those of [5] by modifying the fragmentation parameter. In the high concatenation regime (Fig. 4) we note that low fragmentation implies a faster movement of the oligomer peak towards the healthy neurons, resulting in a faster death of the neurons, see Fig. 4. This is partially in contrast with the results in [5], where low fragmentation implies that there is no relevant passage of neurotoxic oligomers from one neuron to the other. However, they are considering there a model with no concatenation, where therefore the main mechanism of transformation of monomers in oligomers is the polymerization.

In the high concatenation regime combined with high fragmentation (Fig. 3) we observe a dynamics that is similar to the one in Fig. 1. This should be understood as a competing effect between the high concatenation, that tends to increase the oligomer concentration at the price of reducing the other proto-oligomer populations, and the high fragmentation that tends to increase the proto-oligomers populations at the price of decreasing the oligomer concentration.

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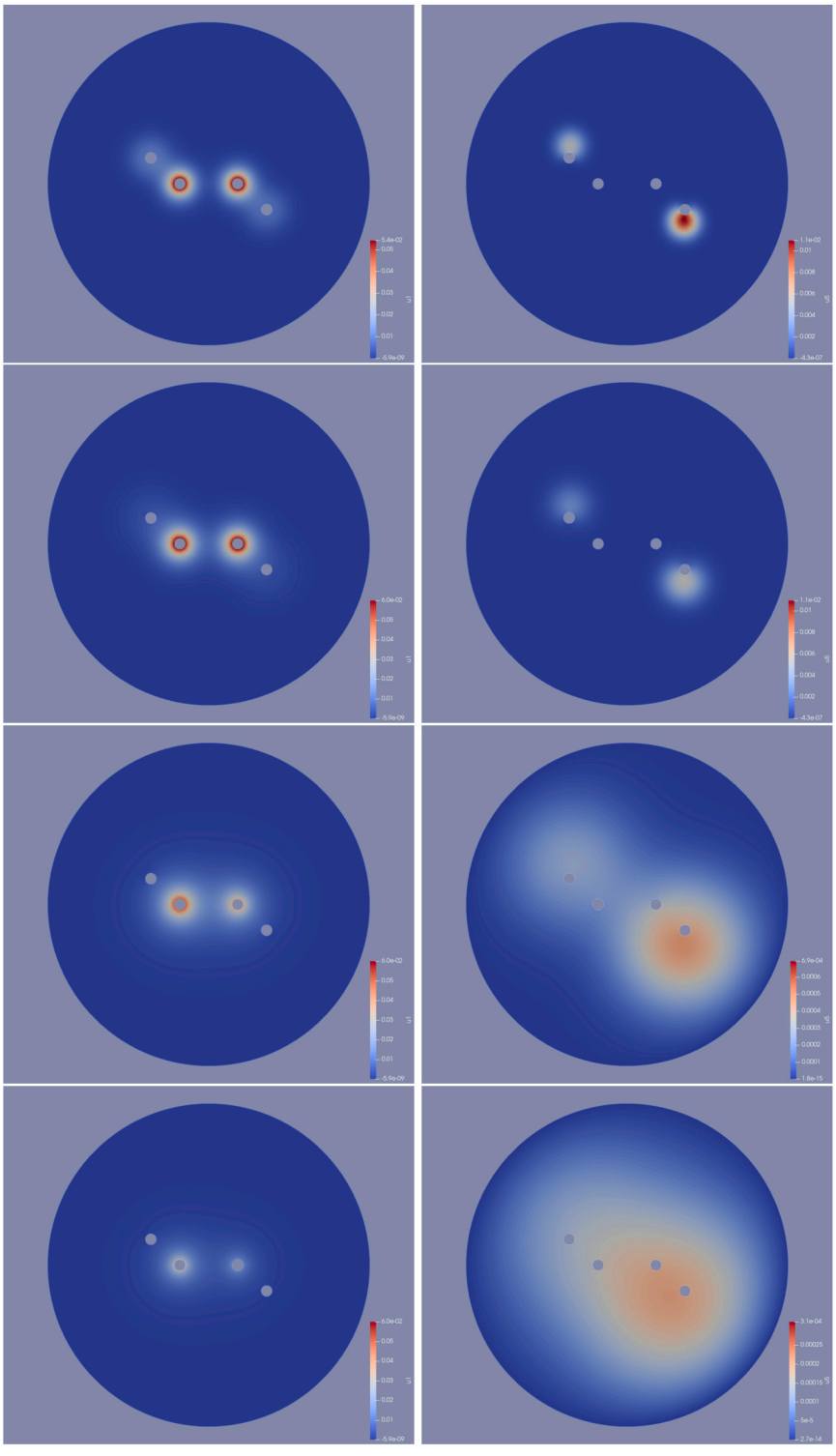


Fig. 1. Evolution of the monomers (left) and oligomers (right) at time $t = 350, 750, 7500, 18000$ seconds (from top to bottom). The concatenation parameters a_{ij} are taken of order $(10^2)/(ij)$. Please note the different scale in each picture. (For interpretation of the colours in the figure(s), the reader is referred to the web version of this article.)

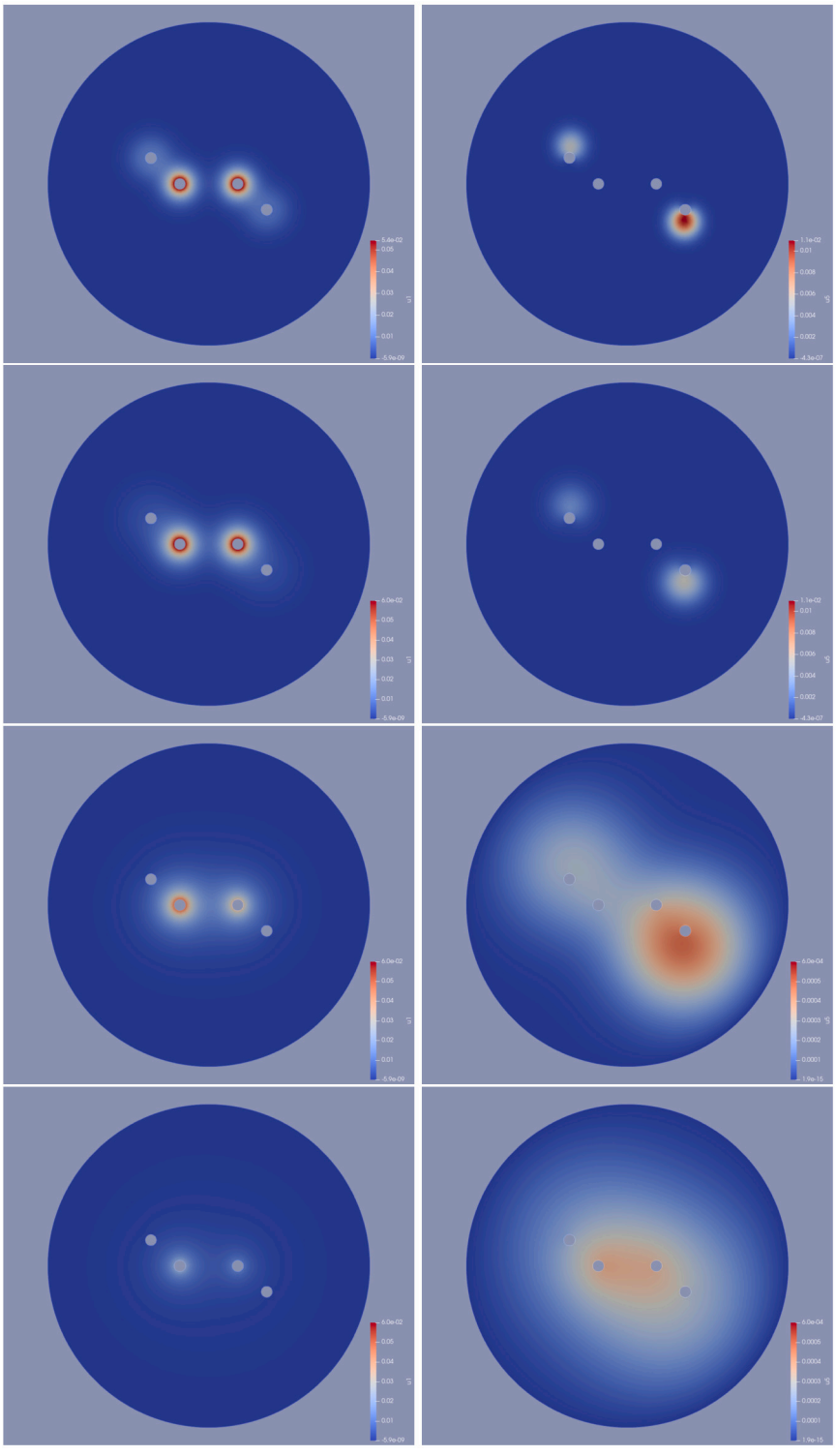


Fig. 2. Evolution of the monomers (left) and oligomers (right) at time $t = 350, 750, 7500, 18000$ seconds (from top to bottom). The concatenation parameters a_{ij} are taken of order $(3 \cdot 10^3)/(ij)$. Please note the different scale in each picture.

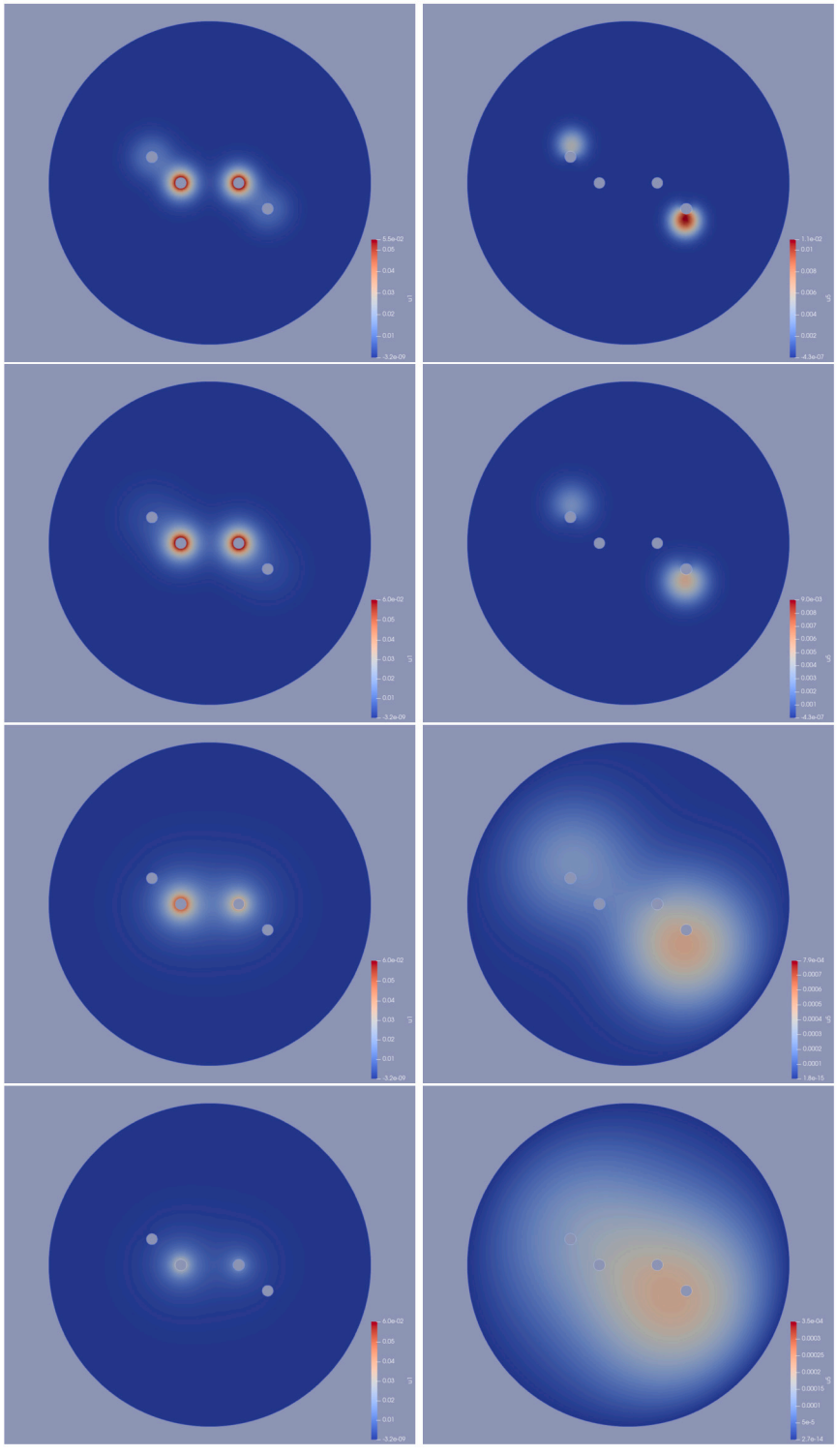


Fig. 3. Evolution of the monomers (left) and oligomers (right) at time $t = 350, 750, 7500, 18000$ seconds (from top to bottom). The concatenation parameters a_{ij} are taken of order $(3 \cdot 10^3)/(ij)$, whereas the fragmentation is of order 10^{-1}. Please note the different scale in each picture.

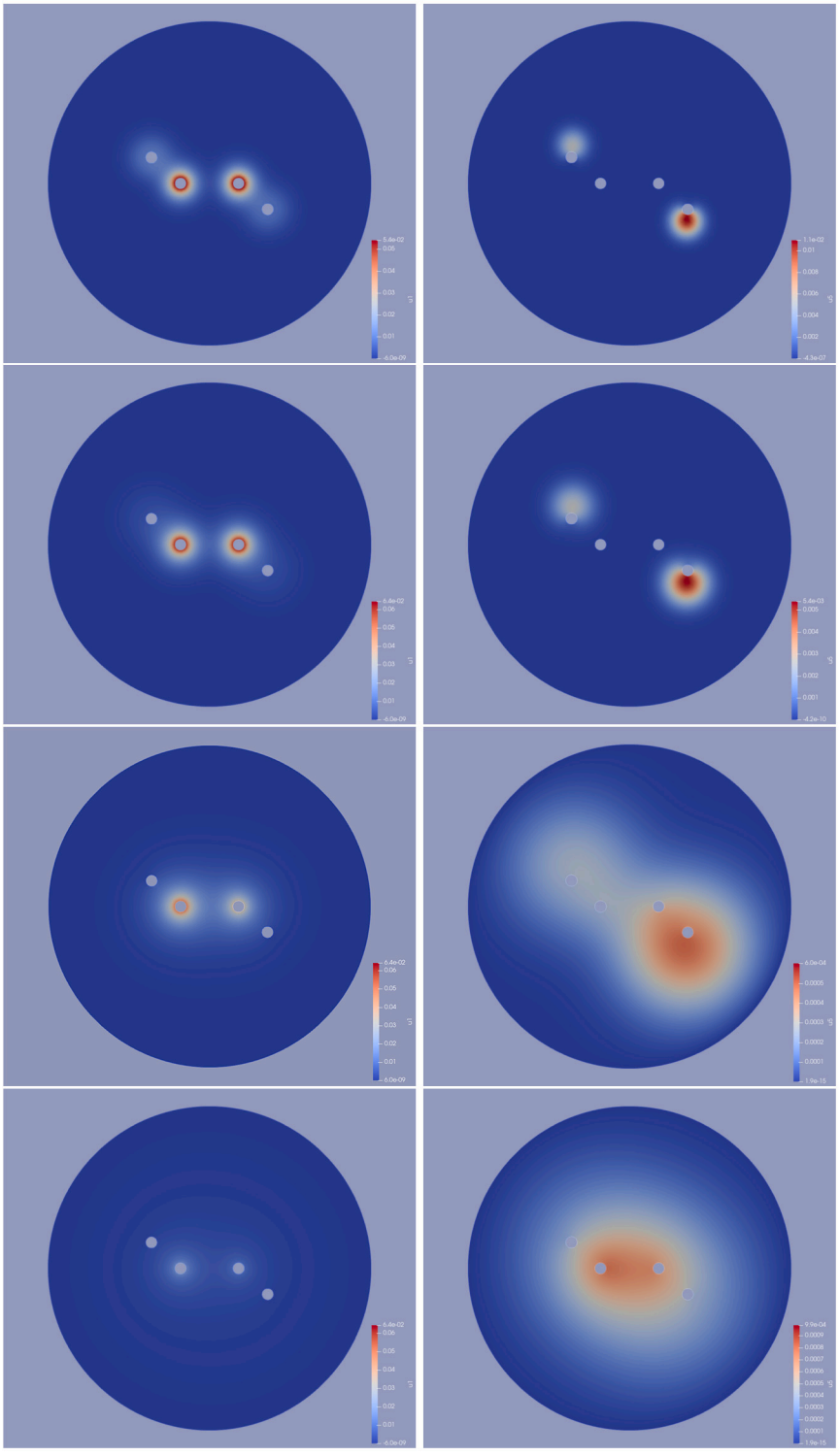


Fig. 4. Evolution of the monomers (left) and oligomers (right) at time $t = 350, 750, 7500, 18000$ seconds (from top to bottom). The concatenation parameters a_{ij} are taken of order $(3 \cdot 10^3)/(ij)$, whereas the fragmentation is of order 10^{-5}. Please note the different scale in each picture.

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Appendix A

• **Semigroup theory**

We prefer to recall here, for the convenience of the reader, some basic notions and results from semigroup theory. We refer to the classical monographs [10,14] for further information.

Notation. We will denote by X a Banach space (usually either $X = L^p(\Omega)^n$ or $X = C^0(\overline{\Omega})^n$) endowed with the norm $\|\cdot\|_X$. Given a linear operator A acting on X, we will denote by $\mathrm{dom}(A) \subset X$ a linear subspace of X called the domain of A. Note that we do not assume at this stage that $\mathrm{dom}(A)$ is dense in X. We further define $\mathcal{L}(X) = \{T : X \to X,\ T \text{ linear and bounded}\}$, endowed with the usual operator norm $\|T\|_{\mathcal{L}(X)} = \sup_{u\in X} \frac{\|Tu\|_X}{\|u\|_X}$.

Definition A.1. A linear operator A in X with domain $\mathrm{dom}(A)$ is dissipative if

$$\|u - \lambda Au\|_X \geq \|u\|_X,$$

for all $u \in \mathrm{dom}(A)$, for all $\lambda > 0$. It is called m-dissipative if it is dissipative and there exists $\lambda_0 > 0$ such that $\mathbb{I} - \lambda_0 A : \mathrm{dom}(A) \to X$ is surjective.

Remark A.2. If A is m-dissipative, then $\mathbb{I} - \lambda A$ is boundedly invertible for every $\lambda > 0$ and $\|(\mathbb{I} - \lambda A)^{-1}\|_{\mathcal{L}(X)} \leq 1$.

Example A.3. Let $\Omega \subset \mathbb{R}^N$, $N \geq 2$ be a smooth bounded domain, $X = C^0(\overline{\Omega})$ and let $A = \Delta$, $\mathrm{dom}(A) = \{u \in X \cap H^1(\Omega) : \Delta u \in X\}$. We claim that $\mathrm{dom}(A)$ is dense in X and A is m-dissipative.

The density of $\mathrm{dom}(A)$ in X is a consequence of the density of $C^\infty(\overline{\Omega}) \subset \mathrm{dom}(A)$ in X.

Dissipativity: consider the equation $u - \lambda Au = f$, with $f \in X$ and $\lambda > 0$. In other words, u is the solution of the following boundary value problem for the Neumann Laplacian

$$\begin{cases} u - \lambda \Delta u = f, & \text{in } \Omega, \\ \partial_\nu u = 0, & \text{on } \partial\Omega. \end{cases} \tag{A.1}$$

Observe that $-\lambda^{-1} < 0$ can never be an eigenvalue of $-\Delta$. Let $M = \|f\|_X$. For sure there exists a weak solution $u \in H^1(\Omega)$ to the problem (A.1). Then u is also a weak solution of

$$u - M - \lambda\Delta(u - M) = f - M. \tag{A.2}$$

Set $v = (u - M)^+ \in H^1(\Omega)$. Multiplying (A.2) by v and integrating by parts in Ω, we obtain

$$\int_\Omega v^2 + \lambda \int_\Omega |\nabla v|^2 = \int_\Omega (f - M)v \leq 0,$$

which implies $v = 0$ a.e. in Ω, hence $u \leq M$ a.e. in Ω. Similarly, one obtains $u \geq -M$ a.e. in Ω. Hence $u \in L^\infty(\Omega)$ and

$$\|u\|_X \leq \|f\|_X.$$

This proves that Δ is dissipative in $L^\infty(\Omega)$, and therefore also in X.

Surjectivity: we need to prove that the weak solution u of (A.1) is in fact in X for any choice of the datum $f \in X$.

Since $f \in C^0(\overline{\Omega})$, $f \in L^p(\Omega)$ for all $p \geq 1$. Since $\partial\Omega$ is smooth, the L^p elliptic regularity theory applies, yielding the implication

$$f \in L^p(\Omega) \;\Rightarrow\; u \in W^{2,p}(\Omega).$$

By the Sobolev Embedding Theorem, whenever $2p > N$, $u \in C^{0,\alpha}(\overline{\Omega})$ (in fact, $u \in C^{1,\alpha}(\overline{\Omega})$, but we won't need this here).

As a side remark, if $\partial\Omega$ is only Lipschitz, A fails to be m-dissipative, see [34].

Remark A.4. The Neumann Laplacian in the previous example is also dissipative in $X = L^\infty(\Omega)$; however, it is not densely defined there. Since we are aiming at applying the Hille-Yosida Generation Theorem, which requires the domain of A to be dense, we prefer to work in $X = C^0(\overline{\Omega})$.

Example A.5. Let $\Omega \subset \mathbb{R}^N$, $N \geq 2$ be a smooth bounded domain such that $\partial\Omega = \Gamma_N \cup \Gamma_R$, Γ_N and Γ_R being connected components of $\partial\Omega$. Let $X = C^0(\overline{\Omega})$ and let $A = \Delta$, $\mathrm{dom}(A) = \{u \in X \cap H^1(\Omega) : \Delta u \in X, \partial_\nu u = -\gamma u \text{ on } \Gamma_R\}$. In view of Example A.3, the operator A is m-dissipative in X. Indeed, it is easy to check that the same argument as in Example A.3 works with Robin boundary conditions on Γ_R: the inequality

$$\int_\Omega v^2 + \lambda \int_\Omega |\nabla v|^2 + \gamma \int_{\partial\Gamma_R \cap \{u \geq M\}} [|v|^2 + Mv] = \int_\Omega (f - M)v \leq 0,$$

still implies that $v = 0$ a.e. in Ω. The surjectivity part follows as in Example A.3, as Laplacians with mixed Neumann-Robin still enjoy the maximal L^p regularity.

Definition A.6. A family $(T(t))_{t \geq 0}$ of bounded linear operators in a Banach space X is called a C_0-semigroup (or a strongly continuous semigroup), if it verifies the functional equation

$$\begin{cases} T(t+s) = T(t)T(s), & \text{for all } s, t \geq 0, \\ T(0) = \mathbb{I}_X \end{cases}$$

and all the orbit maps $t \mapsto T(t)x$ are continuous from $\mathbb{R}_{\geq 0}$ into X, for all $x \in X$.

It is called a contraction semigroup if $\|T(t)\|_{\mathcal{L}(X)} \leq 1$ for all $t \geq 0$.

Definition A.7. The generator A of a strongly continuous semigroup $(T(t))_{t \geq 0}$ in X is defined by

$$Ax := \lim_{h \downarrow 0} \frac{T(h)x - x}{h}$$

on its domain $\mathrm{dom}(A) = \{x \in X : \text{the map } t \mapsto T(t)x \text{ is right-differentiable at } t = 0\}$.

Theorem A.8 *(Hille-Yosida). A linear operator A acting in X with domain $\mathrm{dom}(A) \subset X$ is the generator of a contraction semigroup in X if and only if $\mathrm{dom}(A)$ is dense in X and A is m-dissipative.*

• **Comparison principles**

We recall the following comparison principle for solutions of semilinear parabolic equations [27, Thm 10.1], that we state in the following simplified version.

Theorem A.9. *Define*

$$Pu := Au - \partial_t u = d\Delta - \partial_t u$$

and consider the equation

$$Pu(t,x) = f(t,x,u), \qquad \text{in } (0,T)\times\Omega,$$

where f is C^1 in u and Hölder continuous in t and x. Let $u, v \in C^1_t C^2_x([0,T]\times\Omega)$ satisfy the following inequalities

$$\begin{cases} Pu(t,x) - f(t,x,u) \le Pv(t,x) - f(t,x,v), & \text{in } (0,T)\times\Omega, \\ u(0,x) \ge v(0,x), & x \in \Omega, \\ \frac{\partial u}{\partial \nu}(t,x) + \beta u(t,x) \ge \frac{\partial v}{\partial \nu}(t,x) + \beta v(t,x), & \text{on } (0,T)\times\partial\Omega, \end{cases}$$

for $\beta(t,x) \ge 0$. Then $u(t,x) \ge v(t,x)$ for all $(t,x) \in [0,T]\times\overline{\Omega}$. If moreover $u(x,0) > v(x,0)$ for all $x \in \Omega_1 \subset \Omega$, then the strict inequality $u(t,x) > v(t,x)$ holds for all $(t,x) \in [0,T]\times\overline{\Omega_1}$.

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