UNIVERSIDAD DE CONCEPCIÓN

Centro de Investigación en Ingeniería Matemática (CI^{2}MA)

Alzheimer's disease: Analysis of a mathematical model incorporating the role of prions

Mohamed Helal, Erwan Hingant,
Laurent Pujo-Menjouet, Glenn Webb

PREPRINT 2013-06

SERIE DE PRE-PUBLICACIONES

ALZHEIMER'S DISEASE: ANALYSIS OF A MATHEMATICAL MODEL INCORPORATING THE ROLE OF PRIONS

MOHAMED HELAL, ERWAN HINGANT, LAURENT PUJO-MENJOUET, AND GLENN F. WEBB

ABSTRACT. We introduce a mathematical model of the *in vivo* progression of Alzheimer's disease with focus on the role of prions in memory impairment. Our model consists of differential equations that describe the dynamic formation of β-amyloid plaques based on the concentrations of Aβ oligomers, PrP^C proteins, and the Aβ-×-PrP^C complex, which are hypothesized to be responsible for synaptic toxicity. We prove the well-posedness of the model and provided stability results for its unique equilibrium, when the polymerization rate of β-amyloid is constant and also when it is described by a power law.

CONTENTS

1. INTRODUCTION

1.1. **What is the link between Alzheimer disease and prion proteins?** Alzheimer's disease (AD) is acknowledged as one of the most widespread diseases of age-related dementia with ≈ 35.6 million people infected worldwide (World Alzheimer Report 2010 [40]). By the 2050's, this same report has predicted three or four times more people living with AD. AD affects memory, cognizance, behavior, and eventually leads to death. Apart from the social dysfunction of patients, another notable societal consequence of AD is its economic cost (≈ $422 billion in 2009 [40]). The human and social impact

Date: February 27, 2013.
2000 *Mathematics Subject Classification.* 35F61; 92B05; 34L30.
Key words and phrases. Alzheimer; prion; mathematical model; well-posedness; stability.
This work was supported by ANR grant MADCOW no. 08-JCJC-0135-CSD5. E. H. was partially supported by FONDECYT (Grant no. 3130318) and would thanks A. Rambaud for helpfull discussion to improve this paper.

of AD has driven extensive research to understand its causes and to develop effective therapies. Among recent findings are the results that imply cellular prion protein (PrP^C) is connected to memory impairment [7, 8, 17, 23, 27]. This connection is the focus of our modeling here, which we hope will contribute to understanding the relation of AD to prions.

The pathogenesis of AD is related to a gradual build-up of β-amyloid (Aβ) plaques in the brain [13, 20]. β-amyloid plaques are formed from the Aβ peptides obtained from the amyloid protein precursor (APP) protein cleaved at a displaced position. There exist different forms of β-amyloids , from soluble monomers to insoluble fibrillar aggregates [5, 25, 26, 37, 39]. It has been revealed that the toxicity depends on the size of these structures and recent evidence suggest that oligomers (small aggregates) play a key role in memory impairment rather than β-amyloid plaques (larger aggregates) formed in the brain [35]. More specifically, Aβ oligomers cause memory impairment *via* synaptic toxicity onto neurons. This phenomenon seems to be induced by a membrane receptor, and there is evidence that this rogue agent is the PrP^C protein [17, 23, 28, 32, 33] We note that this protein, when misfolded in a pathological form called PrP^{Sc} , is responsible for Creutzfeldt-Jacob disease. Indeed, it is believed that there is a high affinity between PrP^C and Aβ oligomers, at least theoretically [16]. Moreover, the prion protein has also been identified as an APP regulator, which confirms that both are highly related [28, 38]. This discovery offers a new therapeutic target to recover memory in AD patients, or at least slow memory depletion [6, 14].

1.2. **What is our objective?** Our objective here is to introduce and study a new *in vivo* model of AD evolution mediated by PrP^C proteins. To the best of our knowledge, no model such as the one proposed here, has yet been advanced. There exist a variety of models specifically designed for Alzheimer's disease and their treatment, such as in [1, 3, 4, 10, 11, 15, 18, 19, 24, 31, 36]. Nevertheless, the prion protein has never been taken into account in the way we formulate here, and our model could helpful in designing new experiments and treatments..

This paper is organized as follows. We present the model in section 2, and provide a well-posedness result in the particular case that β-amyloids are formed at a constant rate. In section 3 we provide a theoretical study of our model in a more general context with a power law rate of polymerization, *i.e.* the polymerization or build-up rate depends on β-amyloid plaque size.

2. THE MODEL

2.1. **A model for beta-amyloid formation with prions.** The model deals with four different species. First, the concentration of Aβ oligomers consisting of aggregates of a few Aβ peptides; second, the concentration of the PrP^C protein; third, the concentration of the complex formed from one Aβ oligomer binding onto one PrP^C protein. These quantities are soluble and their concentration will be described in terms of ordinary differential equations. Fourth, we have the insoluble β-amyloid plaques described by a density according to their size x. This approach is standard in modeling prion proliferation phenomena (see for instance [4, 18, 30]). Note that the size x is an abstract variable that could be the volume of the aggregate. Here, however, we view aggregates as fibrils that lengthen in one dimension. The size variable x thus belongs to the interval $(x_0, +\infty)$, where $x_0 > 0$ stands for a critical size below which the plaques cannot form. To summarize we denote, for $x \in (x_0, +\infty)$ and $t \geq 0$,

- $f(t,x) \geq 0$: the density of β-amyloid plaques of size x at time t,
- $u(t) \geq 0$: the concentration of soluble Aβ oligomers (unbounded oligomers) at time t,
- $p(t) \geq 0$: the concentration of soluble cellular prion proteins PrP^C at time t,
- $b(t) \geq 0$: the concentration of Aβ-×-PrP^C complex (bounded oligomers) at time t.

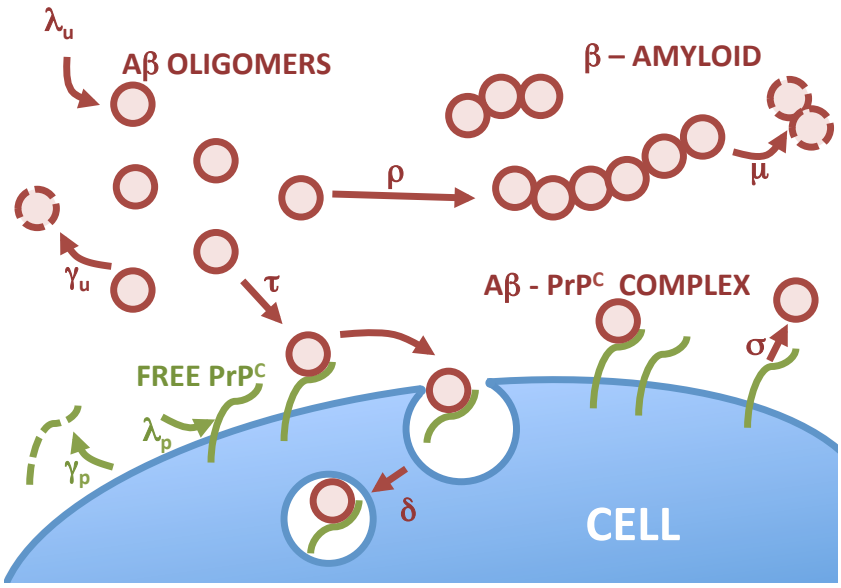

FIGURE 1. Schematic diagram of the evolution processes of β-amyloid plaques, Aβ oligomers (bounded and unbounded), and PrP^C in the model.

Note that β-amyloid plaques are formed from the clustering of Aβ oligomers. The rate of agglomeration depends on the concentration of soluble oligomers and the structure of the amyloid which is linked to its size. It occurs in a mass action between plaques and oligomers at a nonnegative rate given by $\rho(x)$, where x is the size of the plaque. This is the reason why the intentionally misused word "size" considered here (and described above) accounts for the mass of Aβ oligomers that form the polymer. We assume indeed, that the mass of one oligomer is given by a "sufficiently small" parameter $\varepsilon > 0$. Thus, the number of oligomers in a plaque of mass $x > 0$ is x/ε which justifies our assumption that the size of plaques is a continuum. Moreover, amyloids have a critical size $x_0 = \varepsilon n > 0$, where $n \in \mathbb{N}^*$ is the number of oligomers in the critical plaque size. The amyloids are prone to be damaged at a nonnegative rate μ, possibly dependent on the size x of the plaques. All the parameters for Aβ oligomers, PrP^C , and β-amyloid plaques, such as production, binding and degradation rates, are nonnegative and described in table 2.1.

Then, writing evolution equations for these four quantities, we obtain

$$\frac{\partial}{\partial t}f(x,t) + u(t)\frac{\partial}{\partial x}\left[\rho(x)f(x,t)\right] = -\mu(x)f(x,t) \quad \text{on } (x_0,+\infty)\times(0,+\infty), \tag{1}$$

$$\dot{u} = \lambda_u - \gamma_u u - \tau u p + \sigma b - nN(u) - \frac{1}{\varepsilon}u\int_{x_0}^{+\infty}\rho(x)f(x,t)dx \quad \text{on } (0,+\infty), \tag{2}$$

$$\dot{p} = \lambda_p - \gamma_p p - \tau u p + \sigma b \quad \text{on } (0,+\infty), \tag{3}$$

$$\dot{b} = \tau u p - (\sigma+\delta)b \quad \text{on } (0,+\infty). \tag{4}$$

Parameter/Variable	Definition	Unit
t	Time	days
x	size of β-amyloid plaques	–
x_0	Critical size of β-amyloid plaques	–
n	Number of oligomers in a plaque of size x_0	–
ε	Mass of one oligomer	–
λ_u	Source of Aβ oligomers	days^{-1}
γ_u	Degradation rate of Aβ oligomers	days^{-1}
λ_p	Source of PrP^C	days^{-1}
γ_p	Degradation rate of PrP^C	days^{-1}
τ	Binding rate of Aβ oligomers onto PrP^C	days^{-1}
σ	Unbinding rate of Aβ-×-PrP^C	days^{-1}
δ	Degradation rate of Aβ-×-PrP^C	days^{-1}
$\rho(x)$	Conversion rate of oligomers into a plaque	(SAF/sq)$^{-1}$ *·days^{-1}
$\mu(x)$	Degradation rate of a plaque	days^{-1}

TABLE 1. Parameter description of the model. * SAF/sq means Scrapie-Associated Fibrils per square unit and is explained in detail by Rubenstein et al. [34] (we consider plaques as being fibrils here).

The term N accounts for the formation rate of a new β-amyloid plaque with size x_0 from the Aβ oligomers. In order to balance this term, we add the boundary condition

$$u(t)\rho(x_0)f(x_0,t) = N(u(t)), \quad t \geq 0. \tag{5}$$

The integral in the right-hand side of equation (2) is the total polymerization with parameters$1/\varepsilon$, since $\mathrm{d}x/\varepsilon$ counts the number of oligomers into a unit of length $\mathrm{d}x$. Finally, the problem is completed with nonnegative initial data, a function $f^{in} \geq 0$ and $u^{in},\ p^{in},\ b^{in} \geq 0$, such that at time $t = 0$

$$f(\cdot, t = 0) = f^{in} \quad \text{on } (x_0, +\infty), \tag{6}$$

and

$$u(t = 0) = u^{in}, \quad p(t = 0) = p^{in} \quad \text{and} \quad b(t = 0) = b^{in}. \tag{7}$$

The above system (1-5) involves two formal balance laws: the first one for prion proteins

$$\frac{d}{dt}(b + p) = \lambda_p - \gamma_p p - \delta b,$$

and the second for Aβ oligomers

$$\frac{d}{dt}\left(b + u + \frac{1}{\varepsilon}\int_{x_0}^{+\infty} xf\,dx\right) = \lambda_u - \gamma_u u - \delta b - \frac{1}{\varepsilon}\int_{x_0}^{+\infty} x\mu f\,dx.$$

The total concentrations of both evolve in time according to the production and degradation rates. In figure 1 we give a schematic representation of these processes.

2.2. **An associated ODE system.** In this section we investigate constant polymerization and degradation rates, *i.e*, rates independent of the size of the plaque involved in the process. This first approach is biologically less realistic, but technically more tractable, yet still quite challenging for an analytical study of the problem. In section 3, the polymerization rate ρ will be taken more realistically as a power of x. Here we assume that $\rho(x) := \rho$ and $\mu(x) := \mu$ are positive constants. Moreover, without loss of generality, we let $\varepsilon = 1$, which only requires a rescaling of the units in the equations. Then, we assume a pre-equilibrium hypothesis for the formation of β-amyloid plaques, as formulated in [29] for filaments,

by setting $N(u) = \alpha u^n$. The formation rate is given by $\alpha > 0$ and the number of oligomers necessary to form a new plaque is an integer, $n \geq 1$. With these assumptions we are able to close the system (1-4) with respect to (5) into a system of four differential equations. Indeed, integrating (1) over $(x_0, +\infty)$ we get formally an equation over the quantity of amyloids at time $t \geq 0$

$$A(t) = \int_{x_0}^{+\infty} f(x,t)dx.$$

This method has already been used on the prion model in [18]. Now the problem reads, for $t \geq 0$,

$$\dot{A} = \alpha u^n - \mu A, \tag{8}$$

$$\dot{u} = \lambda_u - \gamma_u u - \tau up + \sigma b - \alpha n u^n - \rho uA, \tag{9}$$

$$\dot{p} = \lambda_p - \gamma_p p - \tau up + \sigma b, \tag{10}$$

$$\dot{b} = \tau up - (\sigma + \delta)b. \tag{11}$$

The mass of β-amyloid plaques is given by $M(t) = \int_{x_0}^{+\infty} xf(x,t)dx$ which satisfies an equation (formal integration of (1)) that can be solved independently, since

$$\dot{M} = n\alpha u^n + \rho uA - \mu M. \tag{12}$$

Notice that initial conditions for A and M are given by $A^{in} = \int_{x_0}^{+\infty} f^{in}(x)dx$ and $M^{in} = \int_{x_0}^{+\infty} xf^{in}(x)dx$, while the initial conditions for u, p and b are unchanged.

The next subsection is devoted to the analysis of the system (8-11).

2.3. **Well-posedness and stability of the ODE system.** We prove in the following proposition the positivity, existence, and uniqueness of a global solution to the system (8-11) with classical techniques from the theory of ordinary differential equations([21]).

Proposition 1 (Well-posedness)**.** *Assume λ_u, λ_p, γ_u, γ_p, τ, σ, δ, ρ and μ are positive, and let $n \geq 1$ be an integer. For any $(A^{in}, u^{in}, p^{in}, b^{in}) \in \mathbb{R}^4_+$ there exists a unique nonnegative bounded solution (A,u,p,b) to the system (8-11) defined for all time $t > 0$,* i.e*, the solution A, u, p and b belong to $\mathcal{C}^1_b(\mathbb{R}_+)$ and remains in the stable subset*

$$S = \left\{ (A,u,p,b) \in \mathbb{R}^4_+ :\ nA + u + p + 2b \leq nA^{in} + u^{in} + p^{in} + 2b^{in} + \frac{\lambda}{m} \right\} \tag{13}$$

with $\lambda = \lambda_u + \lambda_p$ and $m = \min\{\mu, \gamma_u, \gamma_p, \delta\}$. Furthermore, let $M(t=0) = M^{in} \geq 0$, and then there exist a unique nonnegative solution M to (12)*, defined for all time $t > 0$.*

Proof. Let $F : \mathbb{R}^4 \mapsto \mathbb{R}^4$ be given by

$$F(A,u,p,b) = \begin{pmatrix} F_1 := \alpha u^n - \mu A \\ F_2 := \lambda_u - \gamma_u u - \tau up + \sigma b - \alpha n u^n - \rho uA \\ F_3 := \lambda_p - \gamma_p p - \tau up + \sigma b \\ F_4 := \tau up - (\sigma + \delta)b \end{pmatrix}.$$

F is obviously $\mathcal{C}^1$ and locally Lipschitz continuous on $\mathbb{R}^4$. Moreover, if $(A,u,p,b) \in \mathbb{R}^4_+$, $F_1 \geq 0$ when $A = 0$, $F_2 \geq 0$ when $u = 0$, $F_3 \geq 0$ when $p = 0$, and $F_4 \geq 0$ when $b = 0$. Thus, the system is quasi-positive and the solution remains in $\mathbb{R}^4_+$. Finally, we remark that

$$\frac{d}{dt}\left(nA + u + p + 2b\right) \leq \lambda - m\left(nA + u + p + 2b\right),$$

with $\lambda = \lambda_u + \lambda_p$ and $m = \min\{\mu, \gamma_u, \gamma_p, \delta\} > 0$, and Gronwall's lemma ensures that

$$nA(t) + u(t) + p(t) + 2b(t) \leq nA^{in} + u^{in} + p^{in} + 2b^{in} + \frac{\lambda}{m}.$$

This proves the global existence of a unique nonnegative bounded solution (A, u, p, b). The claim for the mass M is straightforward. □

We next consider the existence of a steady state A_∞, u_∞, p_∞, b_∞ and the asymptotic behavior of solutions to (8-11). It is easy to compute the steady state by solving the problem

$$\mu A_\infty - \alpha u_\infty^n = 0 \tag{14}$$

$$\lambda_u - \gamma_u u_\infty - \tau u_\infty p_\infty + \sigma b_\infty - \alpha n u_\infty^n - \rho u_\infty A_\infty = 0 \tag{15}$$

$$\lambda_p - \gamma_p p_\infty - \tau u_\infty p_\infty + \sigma b_\infty = 0 \tag{16}$$

$$\tau u_\infty p_\infty - (\delta + \sigma) b_\infty = 0 \tag{17}$$

From the structure of the second equation, we cannot give an explicit formula for this problem. To obtain u_∞ we have to solve an algebraic equation, which involves a polynomial of degree n. However, we can prove that the solution exists, and then u_∞ is given implicitly. The next proposition establishes the local stability of the steady state..

Theorem 2 (Linear stability)**.** *Under hypothesis of proposition 1, there exists a unique positive steady state A_∞, u_∞, p_∞ and b_∞ to (8-11) with*

$$A_\infty = \frac{\alpha}{\mu} u_\infty^n, \quad p_\infty = \frac{\lambda_p}{\tau^* u_\infty + \gamma_p}, \quad b_\infty = \frac{1}{\sigma} \frac{\lambda_p(\tau - \tau^*)}{\tau^* u_\infty + \gamma_p} u_\infty,$$

where $\tau^* = \tau(1 - \sigma/(\delta + \sigma)$ and u_∞ is the unique positive root of Q, defined by

$$Q(x) = \gamma_p \lambda_u + ax - P(x), \text{ for every } x \geq 0$$

with $a = \tau^*(\lambda_u - \lambda_p) - \gamma_u \gamma_p$ and

$$P(x) = \tau^* \gamma_u x^2 + \alpha \gamma_p n x^n + (\alpha \tau^* n + \rho \gamma_p \frac{\alpha}{\mu}) x^{n+1} + \rho \tau^* \frac{\alpha}{\mu} x^{n+2}$$

Moreover, this equilibrium is locally linearly asymptotically stable.

Proof. First, equation (14) gives A_∞ with respect to u_∞. Then, combining (16) and (17) we get p_∞ and b_∞ as functions of u_∞. Now replacing p_∞ and b_∞ in (15) we get u_∞ as the root of Q. It is straightforward that Q has a unique positive root. Indeed, it is the intersection between a line and a monotonic polynomial on the half plane. Now, we linearize the system in A_∞, u_∞, p_∞ and b_∞. Let $X = (A, u, p, b)^T$ and the linearized system reads

$$\frac{d}{dt} X = DX,$$

where

$$D = \begin{pmatrix} -\mu & \alpha n u_\infty^{n-1} & 0 & 0 \\ -\rho u_\infty & \gamma_u - \tau p_\infty - \alpha n^2 u_\infty^{n-1} - \rho A_\infty & -\tau u_\infty & \sigma \\ 0 & -\tau p_\infty & -(\gamma_p + \tau u_\infty) & \sigma \\ 0 & \tau p_\infty & \tau u_\infty & -(\sigma + \delta) \end{pmatrix}.$$

The characteristic polynomial is of the form

$$P(\lambda) = \lambda^4 + a_1 \lambda^3 + a_2 \lambda^2 + a_3 \lambda + a_4,$$

with the $a_i > 0$, $i = 1 \dots 4$ given in the appendix. Moreover it satisfies

$$a_1 a_2 a_3 > a_3^2 + a_1^2 a_4.$$

Then, according to the Routh-Hurwitz criterion (see [2, Th. 4.4, page 150]), all the roots of the characterisic polynomial P are negative or have negative real part, thus the equilibrium is locally asymptotically stable. □

To go further, we give a conditional global stability result when no nucleation is considered, *i.e.*, $\alpha = 0$.

Proposition 3 (Global stability)**.** *Assume that* $\alpha = 0$*. Under the condition*

$$\left(1 + 2\frac{\delta + \gamma_u}{\sigma}\right) > \frac{\delta}{2\gamma_p} > \frac{\gamma_p}{\sigma},$$

the unique equilibrium is given by

$$A_\infty = 0, \quad p_\infty = \frac{\lambda_p}{\tau^* u_\infty + \gamma_p}, \quad b_\infty = \frac{1}{\sigma}\frac{\lambda_p(\tau - \tau^*)}{\tau^* u_\infty + \gamma_p} u_\infty,$$

where u_∞ *is the unique positive root of* $Q(x) = \gamma_p\lambda_u + ax - \tau^*\lambda_u x^2$*, with* $a = \tau^*(\lambda_u - \lambda_p) - \gamma_u\gamma_p$*. Further, this equilibrium is globally asymptotically stable in the stable subset S defined in* (13)*.*

Proof. The proof is given by a Lyapunov function Φ stated in the appendix. It is positive when the condition above is fulfilled and its derivative along the solution to the system (8-11) is negative definite. Thus, from the LaSalle's invariance principle, we get that under these hypotheses the equilibrium of (8-11) is globally asymptotically stable. □

3. A POWER LAW POLYMERIZATION RATE

The assumption that the polymerization rate ρ and the degradation rate μ are constant is not always biologically realistic, as recognized in [3, 15]. Consequently, we study here the more realistic case $\rho(x) \sim x^\theta$, and in the following we restrict our analysis to $\theta \in (0,1)$. We will see that we are able to obtain a result of existence and uniqueness of solutions for this more general case.

3.1. **Hypotheses and main result.**

We are interested in nonnegative solutions to the system (1-4) with the boundary condition (5), completed by initial data (6) and (7), but with the new assumption $\rho(x) \sim x^\theta$. Moreover, we require that our solution preserves the total mass of β-amyloid in order to be biologically relevant. Hence, the solution f will be sought in the natural space $L^1(x_0, +\infty; xdx)$, since xdx measures the mass at any time. Our hypotheses for the system (1-4) are

(H1) $f^{in} \in L^1(x_0, +\infty; xdx)$, $f^{in} \geq 0$, *a.e.* $x > x_0$.

(H2) $\rho \geq 0$, $\rho \in W^{2,\infty}([x_0, \infty))$, $\quad \mu \geq 0$, $\mu \in W^{1,\infty}([x_0, \infty))$.

(H3) $N \geq 0$, $N \in W^{1,\infty}_{loc}(\mathbb{R}_+)$, $N(0) = 0$.

(H4) $\lambda_u, \gamma_u, \lambda_p, \gamma_p, \tau, \sigma, \delta > 0$.

We note that (H2) implies the existence of a constant $C > 0$ such that $\rho(x) \leq Cx$, with for example, $C = 2\|\rho'\|_{L^\infty} + \rho(x_0)/x_0$. For any $x \geq x_0$, we have

$$\rho(x) \leq \|\rho'\|_{L^\infty}(x+x_0) + \rho(x_0) \leq \left(2\|\rho'\|_{L^\infty} + \frac{\rho(x_0)}{x_0}\right) x.$$

We remark that this kind of regularity of the rate ρ covers the case that $\rho(x) \sim x^\theta$ with $\theta \in (0;1)$. Also, (H3) implies the existence of a constant $K_M > 0$ such that $N(w) \leq K_M w$, for any $w \in [0,M]$. Further, The nonnegativity of the parameters of table 2.1 (hypothesis (H4)) is a natural assumption with regard to their biological meaning.

We introduce the definition of a solution to system (1-4).

Definition 1. *Consider a function f^{in} satisfying (H1) and let u^{in}, p^{in}, b^{in} be three nonnegative real data. Assume that ρ, μ, N and all the parameters of table 2.1 verify assumptions (H2) - (H4), and let $T > 0$. Then a quadruplet (f,u,p,b) of nonnegative functions is said to be a* solution *on the interval $(0,T)$ to the system (1-4) with the boundary condition* (5) *and the initial data* (6) *and* (7)*, if it satisfies, for any $\varphi \in \mathcal{C}_c^\infty([0,T] \times [x_0,+\infty))$ and $t \in (0,T)$*

$$\int_{x_0}^{+\infty} f(x,t)\varphi(x,t)dx = \int_{x_0}^{+\infty} f^{in}(x)\varphi(x,0)dx + \int_0^t N(u(s))\varphi(x_0,s)ds + \int_0^t \int_{x_0}^{+\infty} f(x,s)\left[\frac{\partial}{\partial t}\varphi(x,s) + u(s)\rho(x)\frac{\partial}{\partial x}\varphi(x,s) - \mu(x)\varphi(x,s)\right] dxds,$$

and

$$u(t) = u^{in} + \int_0^t \left[\lambda_u - \gamma_u u - \tau up + \sigma b - x_0 N(u) - u\int_{x_0}^{+\infty} \rho(x)f(x,s)dx\right] ds,$$
$$p(t) = p^{in} + \int_0^t \left[\lambda_p - \gamma_p p - \tau up + \sigma b\right] ds,$$
$$b(t) = b^{in} + \int_0^t \left[\tau up - (\sigma+\delta)b\right] ds,$$

with the regularity $f \in L^\infty\left(0,T;L^1(x_0,+\infty;xdx)\right)$ and $u,p,b \in C^0(0,T)$.

Theorem 4 (Well-posedness)**.** *Let f^{in} be a nonnegative function satisfying (H1), let u^{in}, p^{in} and b^{in} be nonnegative real numbers, and assume hypothesis (H2) to (H4). Let $T > 0$. There exists a unique nonnegative solution (f,u,p,b) to (1-4) with* (5) *and initial conditions given by* (6) *and* (7)*, in the sense of definition 1, such that $f \in C^0\left([0,T],L^1(x_0,+\infty;x^r dx)\right)$ for every $r \in [0,1]$, and $u,p,b \in C_b^1(0,T)$.*

The proof of the theorem 4 is decomposed into two parts. First, we study the initial boundary value problem

$$\frac{\partial}{\partial t}f(x,t) + u(t)\frac{\partial}{\partial x}\left[\rho(x)f(x,t)\right] = -\mu(x)f(x,t) \quad \text{on } (x_0,+\infty)\times(0,+\infty), \tag{18}$$

$$u(t)\rho(x_0)f(x_0,t) = N(u(t)), \quad \text{on } (0,+\infty), \tag{19}$$

$$f(\cdot,t=0) = f^{in}, \quad \text{on } (x_0,+\infty). \tag{20}$$

We prove in the subsection 3.2 the following proposition:

Proposition 5. *Let $u \in \mathcal{C}_b^0(\mathbb{R}_+)$, let f^{in} satisfy (H1), and assume hypothesis (H2) to (H3). For any $T > 0$, there exists a unique nonnegative solution f to (18-20) in the sense of distributions, such that $f \in C^0\left([0,T],L^1(x_0,+\infty;x^r dx)\right)$ for every $r \in [0,1]$.*

The proof is in the spirit of the proof in [9] for the Lifshitz-Slyozov equation. It consists of a proof based on the concept of a mild solution in the sense of distributions, with the additional requirement of continuity from time into $L^1(xdx)$ space.

The second step of the proof of theorem 4 is performed in subsection 3.3. Precisely, once we have the existence of a unique density f, when u is given, we are able to construct the operator

$$\begin{array}{rcccl} S & : & C^0([0,T])^3 & \mapsto & C^0([0,T])^3 \\ & & (u,p,b) & \mapsto & (S_u,S_p,S_b) = S(u,p,b), \end{array} \tag{21}$$

$$\begin{aligned} S_u &= u^{in} + \int_0^t \left[\lambda_u - \gamma_u u - \tau u p + \sigma b - x_0 N(u) - u \int_{x_0}^{+\infty} \rho(x) f(x,s) dx \right] ds, \\ S_p &= p^{in} + \int_0^t \left[\lambda_p - \gamma_p p - \tau u p + \sigma b \right] ds, \\ S_b &= b^{in} + \int_0^t \left[\tau u p - (\sigma + \delta) b \right] ds, \end{aligned}$$

where f is the unique solution associated to u given by proposition 5. Then, theorem 4 is finally proven in subsection 3.3 applying the Banach fixed point theorem to the operator S.

3.2. **Existence of a solution to the autonomous problem.** In the following we let $u \in \mathcal{C}_b^0(\mathbb{R}_+)$ and we use the notations $a(x,t) = u(t)\rho(x)$ and $c(x,t) = -u(t)\rho'(x)$ for every $(x,t) \in [x_0,+\infty) \times \mathbb{R}_+$. From (H2) and noting that $\rho(x) \leq Cx$, we have for any $t > 0$

$$a(t,x) \leq Ax, \text{ for } x > x_0, \tag{22}$$

$$|a(t,x) - a(t,y)| \leq A|x-y|, \text{ for } x,y > x_0, \tag{23}$$

$$|c(t,x)| \leq B, \tag{24}$$

where $A = \max\left(C\|u\|_{L^\infty}, \|u\|_{L^\infty}\|\rho'\|_{L^\infty}\right)$ and $B = \|u\|_{L^\infty}\|\rho'\|_{L^\infty(x_0,+\infty)}$. In order to establish the mild formulation of the problem, we define the characteristic which reaches $x \geq x_0$ at time $t \geq 0$, that is, the solution to

$$\begin{aligned} &\frac{d}{ds} X(s;x,t) = a(t, X(s;x,t)), \\ &X(t;x,t) = x. \end{aligned} \tag{25}$$

From property (23), their exists a unique characteristic that reaches (x,t).We note that it makes sense as long as $X(s;x,t) \geq x_0$. Thus, we define the starting time of the characteristic as

$$s_0(x,t) := \inf\{s \in [0,t] : X(s;x,t) \geq x_0\}.$$

The characteristic will be defined for any time $s \geq s_0$ and takes its origin from the initial or the boundary condition, respectively, if $s_0 = 0$ or $s_0 > 0$. We recall the classical properties of these characteristics

$$\begin{aligned} &X(s;X(\sigma;x,t),\sigma) = X(s;x,t) \\ &J(s;x,t) := \frac{\partial}{\partial x} X(s;x,t) = \exp\left(\int_s^t c(\sigma, X(\sigma;x,t)) d\sigma \right) \\ &\frac{\partial}{\partial t} X(s;x,t) = -a(t,x) J(s;x,t). \end{aligned}$$

Also, remarking that $s_0(X(t;x_0,0),t) = 0$, then by monotonicity and continuity of X for any $t > 0$, we get $x \in (x_0, X(t;x_0,0)) \iff s_0(x,t) \in (0,t)$, and for any $x \in (x_0, X(t;x_0,0))$ we have $X(s_0(x,t);x,t) = x_0$.

It follows that for every $x \in (x_0, X(t;x_0,0))$

$$I(x,t) := -\frac{\partial}{\partial x} s_0(x,t) = J(s_0(x,t);x,t)/a(s_0(x,t),x_0).$$

Considering the derivative of $f(s,X(s;x,t))$ in s, and integrating over (s_0,t) we obtain the mild formulation of the problem. The mild solution is defined for *a.e.* $(x,t) \in (x_0,+\infty)\times\mathbb{R}_+$ by

$$f(x,t) = \begin{cases} f^{in}(X(0;x,t))J(0;x,t)\exp\left(-\displaystyle\int_0^t \mu(X(\sigma;x,t))d\sigma\right) & x \geq X(t;x_0,0), \\ N(u(s_0(x,t)))I(x,t)\exp\left(-\displaystyle\int_{s_0(x,t)}^t \mu(X(\sigma;x,t))d\sigma\right) & x \in (x_0, X(t;x_0,0)). \end{cases} \tag{26}$$

We infer from the formulation (26) that for *a.e* $(x,t) \in [x_0,+\infty)\times\mathbb{R}_+$, f is nonnegative, since J and I are nonnegative, and f^{in} satisfies (H1). We recall some useful properties that are derived in [9, Lemma 1].

Lemma 6. *Let $u \in \mathcal{C}_b^0(\mathbb{R}_+)$ be a given data and assume that (H2) holds. Then for any $x \geq x_0$ and $t > 0$, as long as the characteristic curve $s \mapsto X(s;x,t)$ defined in* (25) *exists,* i.e.*, $s \geq s_0(x,t)$, we have*

$$\begin{aligned} &\text{for } s_1 \leq s_2,\ X(s_1;x,t) \leq X(s_2;x,t) \leq X(s_1;x,t)e^{A(s_2-s_1)} \\ &\text{if } x_n \to +\infty, \text{ then for all } t \geq s \geq 0,\ X(s;x,t) \to +\infty \\ &\text{for } s \geq t,\ X(s;x,t) \leq xe^{A(s-t)}. \end{aligned}$$

Proof. We refer to [9, Lemma 1], where the result follows from the fact that for any $x \geq x_0$, $t > 0$ and $s_0(x,t) \leq s_1 \leq s_2$, we have

$$x_0 \leq X(s_2;x,t) = X(s_1;x,t) + \int_{s_1}^{s_2} a(s,X(s;x,t))ds \leq X(s_1;x,t) + A\int_{s_1}^{s_2} X(s;x,t)ds,$$

where A is given by (22). □

In the sequel we will repeatedly refer to the changes of variables

$$\begin{aligned} y = X(0;x,t) \text{ over } x \in (X(t,x_0,0),+\infty), \text{ with Jacobian } J(0;x,t), \\ s = s_0(x,t) \text{ over } x \in (x_0, X(t;x_0,0)), \text{ with Jacobian } -I(x,t). \end{aligned}$$

The first is a $\mathcal{C}^1$ - diffeomorphism from $(X(t,x_0,0),+\infty)$ into $(x_0,+\infty)$, and the second from $(x_0,X(t;x_0,0))$ into $(0,t)$. Integrating f defined by (26) over $(0,R)$ with $R > X(t;x_0,0)$, using the change of variables above, using lemma 6, and taking the limit $R \to +\infty$, we get

$$\begin{aligned} \int_{x_0}^{+\infty} x|f(t,x)|dx &\leq \int_{x_0}^{+\infty} X(t;y,0)|f^{in}(y)|dy + \int_0^t X(t;s,x_0)|N(u(s))|ds \\ &\leq e^{At}\left(\int_{x_0}^{+\infty} y|f^{in}(y)|dy + \int_0^t x_0|N(u(s))|ds\right), \end{aligned} \tag{27}$$

where we have split the integral into two parts and uses both the previous changes of variables. Thus,for any $T > 0$, $f \in L^\infty\left(0,T;L^1(x_0,+\infty;xdx)\right)$, and therefore in $L^\infty\left(0,T;L^1(x_0,+\infty;x^r dx)\right)$, for any $r \in [0,1]$. In the next lemma we claim that f defined by (26) is a weak solution.

Lemma 7. *Let f be the mild solution defined by* (26)*. Then for any $t > 0$*

$$\begin{aligned} \int_{x_0}^{+\infty} f(x,t)\varphi(x,t)dx = &\int_{x_0}^{+\infty} f^{in}(x)\varphi(x,0)dx + \int_0^t N(u(s))\varphi(x_0,s)ds \\ &+ \int_0^t \int_{x_0}^{+\infty} f(x,s)\left[\frac{\partial}{\partial t}\varphi(x,s)u(s)\rho(x)\frac{\partial}{\partial x}\varphi(x,s) - \mu(x)\varphi(x,s)\right]dxds, \end{aligned}$$

for all $\varphi \in \mathcal{C}_c^\infty([0,T]\times[x_0,+\infty))$.

Proof. Since f belongs to $f \in L^\infty\left(0,T;L^1(x_0,+\infty;xdx)\right)$, it is possible to multiply the mild solution f against a test function $\varphi \in \mathcal{C}_c^\infty([0,T]\times[x_0,+\infty))$ and integrate over $(x_0,+\infty)$ to obtain

$$\int_{x_0}^{+\infty} f(x,t)\varphi(x,t)dx = \int_{x_0}^{+\infty} f^{in}(y)\varphi(X(t;y,0))e^{-\int_0^t \mu(X(\sigma;y,0))d\sigma}dy - \int_0^t N(u(s))\varphi(X(t;x_0,s),t)e^{-\int_s^t \mu(X(\sigma;x_0,s))d\sigma}ds, \quad (28)$$

by the same change of variable made above for (27). Furthermore, we have

$$\begin{aligned}\int_0^t \int_{x_0}^{X(s;x_0,0)} & f(x,s)\left[\partial_t\varphi(x,s)+a(s,x)\partial_x\varphi(x,s)-\mu(x)\varphi(x,s)\right]dxds \\ &= \int_0^t \int_{x^0}^{+\infty} f^{in}(x)\frac{d}{ds}\left(\varphi(X(s;x,0),s)e^{-\int_0^s \mu(X(\sigma;x,0))d\sigma}\right)dyds \\ &= \int_{x_0}^{+\infty} f^{in}(x)\varphi(X(t;x,0),t)e^{-\int_0^t \mu(X(\sigma;y,0))d\sigma}dx - \int_{x_0}^{+\infty} f^{in}(x)\varphi(x,0)dx, \end{aligned} \quad (29)$$

still using the change of variable mentioned above and

$$\begin{aligned}\int_0^t \int_{X(s;x_0,0)}^{\infty} & f(x,s)\left[\partial_t\varphi(x,s)+a(s,x)\partial_x\varphi(x,s)-\mu(x)\varphi(x,s)\right]dxds \\ &= -\int_0^t \int_0^s N(u(z))\frac{d}{ds}\left(\varphi(X(s;x_0,z),s)e^{-\int_z^s \mu(X(\sigma;x_0,z))d\sigma}\right)dzds \\ &= -\int_0^t N(u(s))\varphi(X(t;x_0,s),t)e^{-\int_s^t \mu(X(\sigma;x_0,s))d\sigma}dzds - \int_0^t N(u(s))\varphi(x_0,s)ds. \end{aligned} \quad (30)$$

Finally, combining (28), (29) and (30) we obtain that f is a weak solution. □

The aim of the following lemma is to prove that the moments of f less than 1 are continuous in time.

Lemma 8. *Let hypothesis (H1) to (H3) hold. Let f be the mild solution given by* (26)*. Then for any $T>0$,*

$$f \in C^0\left([0,T],L^1(x_0,+\infty;x^r dx)\right), \quad \text{for every } r\in[0,1].$$

Proof. Let $T>0$ and $r\in[0,1]$, since $f \in L^\infty_{loc}\left(\mathbb{R}_+,L^1(x_0,+\infty;x^r dx)\right)$, we have for any $t>0$ and $\delta t>0$ such that $t+\delta t \le T$

$$\int_{x_0}^{+\infty} x^r\left|f(x,t+\delta t)-f(x,t)\right|dx = I_1+I_2+I_3,$$

where

$$\begin{aligned} I_1 &= \int_{x_0}^{X(t;x_0,0)} x^r\left|f(x,t+\delta t)-f(x,t)\right|dx, \\ I_2 &= \int_{X(t;x_0,0)}^{X(t+\delta t;x_0,0)} x^r\left|f(x,t+\delta t)-f(x,t)\right|dx, \\ I_3 &= \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r\left|f(x,t+\delta t)-f(x,t)\right|dx. \end{aligned}$$

Our goal is to prove that each term goes to zero when δt goes to zero. We first bound I_3, which results from the initial condition, since for $x \ge X(t+\delta t;x_0,0) \ge X(t;x_0,0)$, it follows that

$$I_3 = \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r\left|f^{in}(X(0;x,t+\delta t))J(0;x,t+\delta t)e^{-\int_0^{t+\delta t}\mu(X(\sigma;x,t+\delta t))d\sigma} - f^{in}(X(0;x,t))|J(0;x,t)e^{-\int_0^t \mu(X(\sigma;x,t))d\sigma}\right|dx.$$

Let $f_\varepsilon^{in} \in \mathcal{C}_0^\infty$ with compact support $supp(f_\varepsilon^{in}) \subset (0,R_\varepsilon)$ and converge in $L^1([x_0,+\infty),xdx)$ to f^{in}. We write I_3 as follows

$$I_3 = I_3^1 + I_3^2 + I_3^3, \tag{31}$$

where

$$\begin{aligned}
I_3^1 &= \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r \left| f^{in}(X(0;x,t+\delta t)) - f_\varepsilon^{in}(X(0;x,t+\delta t)) \right| \\
&\qquad \times J(0;x,t+\delta t) e^{-\int_0^{t+\delta t} \mu(X(\sigma;x,t+\delta t))d\sigma} dx, \\
I_3^2 &= \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r \left| f_\varepsilon^{in}(X(0;x,t+\delta t)) J(0;x,t+\delta t) \right. \\
&\qquad \times e^{-\int_0^{t+\delta t} \mu(X(\sigma;x,t+\delta t))d\sigma} \\
&\qquad \left. - f_\varepsilon^{in}(X(0;x,t)) J(0;x,t) e^{-\int_0^t \mu(X(\sigma;x,t))d\sigma} \right| dx, \\
I_3^3 &= \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r |f_\varepsilon^{in}(X(0;x,t)) - f^{in}(X(0;x,t))| \\
&\qquad \times J(0;x,t) e^{-\int_0^t \mu(X(\sigma;x,t))d\sigma} dx.
\end{aligned}$$

Dropping the exponential term, which is bounded by one, and changing of variables $y = X(0;x,t+\delta t)$ in I_3^1 and $y = X(0;x,t)$ in I_3^3, we get

$$I_3^1 + I_3^3 \leq 2e^{AT} \int_{x_0}^{+\infty} y^r |f^{in}(y) - f_\varepsilon^{in}(y)| dy = C_3^1(T,\varepsilon), \tag{32}$$

with the help of lemma 6. Next we bound I_3^2 by

$$\begin{aligned}
I_3^2 &\leq \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r |f_\varepsilon^{in}(X(0;x,t+\delta t)) - f_\varepsilon^{in}(X(0;x,t))| J(0;x,t+\delta t) dx \\
&\quad + \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r f_\varepsilon^{in}(X(0;x,t)) |J(0;x,t+\delta t) - J(0;x,t)| dx \\
&\quad + \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r f_\varepsilon^{in}(X(0;x,t)) J(0;x,t) \\
&\qquad \times |e^{-\int_0^{t+\delta t} \mu(X(\sigma;x,t+\delta t))d\sigma} - e^{-\int_0^t \mu(X(\sigma;x,t))d\sigma}| dx,
\end{aligned}$$

and we denote the integrals by J_3^1 to J_3^3, respectively. We remark that $J(0,x,t) \leq e^{BT}$ by (24) and so

$$\begin{aligned}
J_3^1 &\leq e^{BT} \|f_\varepsilon^{in}\|_{L^\infty} \int_{X(t+\delta t;x_0,0)}^{C_\varepsilon} x^r |X(0;x,t+\delta t) - X(0;x,t)| dx \\
&\leq \delta t e^{BT} \|f_\varepsilon^{in}\|_{L^\infty} \int_{X(t+\delta t;x_0,0)}^{C_\varepsilon} x^r \sup_{s\in[t,t+\delta t]} \left| \frac{\partial}{\partial t} X(0;x,s) \right| dx \\
&\leq \delta t A e^{2BT} \|f_\varepsilon^{in}\|_{L^\infty} \int_{x_0}^{C_\varepsilon} x^{r+1} dx,
\end{aligned} \tag{33}$$

where C_ε depends on T, A and R_ε *i.e.*, the compact support of f_ε^{in}. Then

$$J_3^2 \leq e^{BT} \|f_\varepsilon^{in}\|_{L^\infty} \int_{X(t+\delta t;x_0,0)}^{R_\varepsilon} x^r |e^{G(t,\delta t,x)} - 1| dx$$

with

$$\begin{aligned}|G(t,\delta t,x)| &= \Big|\int_0^{t+\delta t} c(\sigma,X(\sigma;x,t+\delta t))d\sigma - \int_0^t c(\sigma,X(\sigma;x,t))d\sigma\Big| \\ &\le \int_0^{t+\delta t}\Big|\rho'(X(\sigma;x,t+\delta t)) - \rho'(X(\sigma;x,t))\Big|u(\sigma)d\sigma \\ &\quad + \int_t^{t+\delta t}\Big|c(\sigma,X(\sigma;x,t))\Big|d\sigma.\end{aligned}$$

Thus, with (22) and (24),

$$\begin{aligned}|G(t,\delta t,x)| &\le K\|u\|_{L^\infty}\int_0^T \Big|X(\sigma;x,t+\delta t) - X(\sigma;x,t)\Big|d\sigma + \delta t B \\ &\le \delta t K\|u\|_{L^\infty}\int_0^T \sup_{s\in[t,t+\delta t]}\left|\frac{\partial}{\partial t}X(\sigma;x,s)\right|d\sigma + \delta t B \\ &\le \delta t\left(K\|u\|_{L^\infty}ATe^{BT}x + B\right),\end{aligned}$$

where K is the Lipschitz constant of ρ'. Since $x \le R_\varepsilon$, let $C_G(T,\varepsilon) = K\|u\|_{L^\infty}ATe^{BT}R_\varepsilon + B$, and if $|x| \le y$, then

$$|e^x - 1| \le |e^y - 1| + \left|e^{-y} - 1\right|.$$

Thus, we get

$$J_3^2 \le e^{BT}\|f_\varepsilon^{in}\|_{L^\infty}\left(\left|e^{\delta t C_G(T,\varepsilon)} - 1\right| + \left|e^{-\delta t C_G(T,\varepsilon)} - 1\right|\right)\int_{x_0}^{R_\varepsilon} x^r dx. \tag{34}$$

Since μ is nonnegative, $J_3^3 \le$

$$e^{BT}\|f_\varepsilon^{in}\|_{L^\infty}\int_{X(t+\delta t;x_0,0)}^{R_\varepsilon} x^r\left|e^{-\left(\int_0^{t+\delta t}\mu(X(\sigma;x,t+\delta t))d\sigma - \int_0^t \mu(X(\sigma;x,t))d\sigma\right)} - 1\right|dx.$$

Exactly as above,

$$\Big|\int_0^{t+\delta t}\mu(X(\sigma;x,t+\delta t))d\sigma - \int_0^t \mu(X(\sigma;x,t))d\sigma\Big| \le \delta t MATe^{BT}x + \delta t\|\mu\|_{L^\infty},$$

with $M =$ Lipschitz constant of μ. Denoting by $C_M(T,\varepsilon) = MATe^{BT}R_\varepsilon + \|\mu\|_{L^\infty}$, we get

$$J_3^3 \le e^{BT}\|f_\varepsilon^{in}\|_{L^\infty}\left(\left|e^{\delta t C_M(T,\varepsilon)} - 1\right| + \left|e^{-\delta t C_M(T,\varepsilon)} - 1\right|\right)\int_{x_0}^{R_\varepsilon} x^r dx. \tag{35}$$

From (32), (33), (34) and (35) we can conclude that for any $\varepsilon > 0$,

$$I_3(\delta t) \le C_3^1(T,\varepsilon) + C_3^2(T,\delta t,\varepsilon), \tag{36}$$

with $\lim_{\varepsilon\to 0} C_3^1(T,\varepsilon) = 0$ and $\lim_{\delta t\to 0} C_3^2(T,\delta t,\varepsilon) = 0$.

Next, concerning I_1, f can be written from the boundary condition. Let $u^\varepsilon \in \mathcal{C}_0^\infty$ such that $u^\varepsilon \longrightarrow u$ uniformly on $[0,T]$. Then we write I_1 as follows:

$$\begin{aligned} I_1 \leq & \int_{x_0}^{X(t+\delta t;x_0,0)} x^r |N(u(s_0(x,t+\delta t)) - N(u^\varepsilon(s_0(x,t+\delta t))| I(x,t+\delta t) dx \\ & + \int_{x_0}^{X(t;x_0,0)} x^r \Big| N(u^\varepsilon(s_0(x,t+\delta t)) I(x,t+\delta t) e^{-\int_{s_0(x,t+\delta t)}^t \mu(X(\sigma;x,t+\delta t))d\sigma} \\ & \qquad - N(u^\varepsilon(s_0(x,t)) I(x,t) e^{-\int_{s_0(x,t)}^t \mu(X(\sigma;x,t))d\sigma} \Big| dx \\ & + \int_{x_0}^{X(t;x_0,0)} x^r |N(u(s_0(x,t)) - N(u^\varepsilon(s_0(x,t))| I(x,t) dx. \end{aligned}$$

From (H3) we obtain, similarly to I_3, that there exist two constants $C_1^1(T,\varepsilon)$ and $C_1^2(T,\delta t,\varepsilon)$ such that

$$I_1(\delta t) \leq C_1^1(T,\varepsilon) + C_1^2(T,\delta t,\varepsilon), \tag{37}$$

with $\lim_{\varepsilon\to 0} C_1^1(T,\varepsilon) = 0$ and $\lim_{\delta t\to 0} C_1^2(T,\delta t,\varepsilon) = 0$.

Finally, for I_2, we use the two formulas of f,

$$\begin{aligned} I_2 = \int_{X(t;x_0,0)}^{X(t+\delta t;x_0,0)} x^r \Big| & N(u(s_0(x,t+\delta t))) I(x,t+\delta t) e^{-\int_{s_0(x,t+\delta t)}^{t+\delta t} \mu(X(\sigma;x,t+\delta t))d\sigma} \\ & - f^{in}(X(0;x,t)) J(0;x,t) e^{-\int_{s_0(x,t)}^t \mu(X(\sigma;x,t))d\sigma} \Big| dx \end{aligned}$$

Using the Lipschitz constant of N denoted by K_N, from the definition of I and with the help of lemma 6, we get

$$\begin{aligned} I_2 \leq & \, x_0^r e^{(rA+B)T} K_N |X(t+\delta t;x_0,0) - X(t;x_0,0)| \\ & + x_0^r e^{rAT} \int_{X(t;x_0,0)}^{X(t+\delta t;x_0,0)} \left| f^{in}(X(0;x,t)) J(0;x,t) \right| dx. \end{aligned}$$

Using the regularization f_ε^{in} of f^{in}, there exist two constants $C_2^1(T,\varepsilon)$ and $C_2^2(T,\delta t,\varepsilon)$ such that for any $\varepsilon > 0$,

$$I_2(\delta t) \leq C_2^1(T,\varepsilon) + C_2^2(T,\delta t,\varepsilon), \tag{38}$$

with $\lim_{\varepsilon\to 0} C_2^1(T,\varepsilon) = 0$ and $\lim_{\delta t\to 0} C_2^2(T,\delta t,\varepsilon) = 0$.

In conclusion, combining (36), (37) and (38), we get for any $\varepsilon > 0$ and $\delta t > 0$,

$$\int_{x_0}^{+\infty} x^r |f(x,t+\delta t) - f(x,t)| dx \leq C^1(T,\varepsilon) + C^2(T,\delta t,\varepsilon),$$

where $C^1(T,\varepsilon)$ and $C^2(T,\delta t,\varepsilon)$ are two constants such that $\lim_{\varepsilon\to 0} C^1(T,\varepsilon) = 0$ and $\lim_{\delta t\to 0} C^2(T,\delta t,\varepsilon) = 0$. Noticing that the proof remains the same when δt is negative, taking the lim sup in δt we get

$$0 \leq \limsup_{\delta t\to 0} \int_{x_0}^{+\infty} x^r |f(x,t+\delta t) - f(x,t)| dx \leq C^1(T,\varepsilon), \text{ for any } \varepsilon > 0.$$

The proof is completed by taking the limit as ε goes to zero, which yields to the require regularity, $f \in \mathcal{C}^0([0,T], L^1([x_0,+\infty), x^r dr)$ for all $r \in [0,1]$. □

We finish this section with a useful estimate for the uniqueness investigation.

Proposition 9. *Let $T > 0$ and u_1, $u_2 \in \mathcal{C}_b^0(0,T)$. Let f_1 and f_2 be two mild solutions to* (18)-(20)*, associated, respectively to u_1 and u_2, with initial data f_1^{in}, f_2^{in} given by formula* (26)*. Then, for any $t \in (0,T)$*

$$\int_{x_0}^{+\infty} x|f_1(x,t)-f_2(x,t)|\,dx \le \int_{x_0}^{+\infty} x\left|f_1^{in}(x)-f_2^{in}(x)\right|dx - \int_0^t\int_{x_0}^{+\infty}\mu(x)x\left|f_1^{in}(x,s)-f_2^{in}(x,s)\right|dxds + A_1\int_0^t\int_{x_0}^{+\infty} x|f_1(x,s)-f_2(x,s)|\,dxds + \int_0^t\left(K_{1,2}+C\|f_2(\cdot,s)\|_{L^1(xdx)}\right)|u_1(s)-u_2(s)|\,ds,$$

where A_1 is given by (22) *for u_1 and $K_{1,2}$ is the Lipschitz constant of N on $[0,R]$ with $R=\max(\|u_1\|_{L^\infty(0,T)}, \|u_2\|_{L^\infty(0,T)})$. Finally $C>0$ denotes a constant such that $\rho(x)<Cx$.*

Proof. This estimation is obtained from a classical argument of approximation. Let $h=f_1-f_2$ and

$$\int_{x_0}^{+\infty} h(x,t)\varphi(x,t)dx = \int_{x_0}^{+\infty} h^{in}(x)\varphi(x,0)dx + \int_0^t\left(N(u_1(s))-N(u_2(s))\right)\varphi(x_0,s)ds + \int_0^t\int_{x_0}^{+\infty} h(x,s)\left[\frac{\partial}{\partial t}\varphi(x,s)+a_1(s,x)\frac{\partial}{\partial x}\varphi(x,s)-\mu(x)\varphi(x,s)\right]dxds + \int_0^t\int_{x_0}^{+\infty}\left(a_1(s,x)-a_2(s,x)\right)f_2(x,s)\frac{\partial}{\partial x}\varphi(x,s)dxds.$$

Let h_ε be a regularization of h and S_δ a regularization of the *Sign* function. Take $\varphi(x,s)=S_\delta(h_\varepsilon(s,x))g(x)$ with $g\in\mathcal{C}_c^\infty([x_0,+\infty))$. Then, letting $\delta\to 0$ and then $\varepsilon\to 0$, we get

$$\begin{aligned}\int_{x_0}^{+\infty}|h(x,t)|g(x)dx &= \int_{x_0}^{+\infty}|h^{in}(x)|g(x)dx \\ &+ \int_0^t\left|N(u_1(s))-N(u_2(s))\right|Sign(h_0(x_0))g(x_0)ds \\ &+ \int_0^t\int_{x_0}^{+\infty}|h(x,s)|\left[a_1(s,x)\frac{\partial}{\partial x}g(x)-\mu(x)g(x)\right]dxds \\ &+ \int_0^t\int_{x_0}^{+\infty}\left(a_1(s,x)-a_2(s,x)\right)f_2(x,s)Sign(h(s,x))\frac{\partial}{\partial x}g(x)dxds.\end{aligned}$$

Finally, we approximate the identity function with a regularized function $\eta_R\in\mathcal{C}_c^\infty([x_0,+\infty))$ such that $\eta_R(x)=x$ over $(0,R)$, and then taking the limit $R\to+\infty$ ends the proof.

□

We get straightforward from proposition 7 that f defined by (26) is a weak solution and the only one from proposition 9. Indeed, getting $u_1=u_2$ and $f_1^0=f_2^0$ in proposition 9 leads to the uniqueness. Finally, proposition 8 provides the continuity in time of the moments with order less or equal to one. This concludes the proof of proposition 5

3.3. **Proof of the well-posedness.** In this section we prove theorem 4. We first study the operator S in (21).

Lemma 10. *Consider hypothesis (H2) to (H4). Let u^{in}, p^{in} and b^{in} be nonnegative initial data, and let f^{in} satisfy (H1). Let $M>0$ be large enough such that $u^{in},p^{in},b^{in}<M/2$ and define*

$$X_M=\left\{(u,p,b)\in\mathcal{C}^0([0,T])^3 : 0\le u,p,b\le M\right\}$$

where $\mathcal{C}^0([0,T])^3$ is equipped with the uniform norm. Then, there exists $T>0$ (small enough) such that $S:X_M\mapsto X_M$ is a contraction.

Proof. Let M be sufficiently large such that $\max(u^{in}, p^{in}, b^{in}) < M/2$, and let $T > 0$ be small enough such that

$$\begin{aligned}
&(\gamma_u + \tau M + \sigma + x_0 C_1(M) + C_2(M,T))MT \leq M/2,\\
&(\gamma_p + \tau M)MT \leq M/2,\\
&(\sigma + \delta)MT \leq M/2,\\
&(\lambda_u + \sigma M)T \leq M/2,\\
&(\lambda_p + \sigma M)T \leq M/2,\\
&\tau M^2 T \leq M/2,
\end{aligned}$$

where $C_1(M)$ is the Lipschitz constant of N on $(0,M)$ and

$$C_2(M,T) = Ce^{MCT}\left(\|f^{in}\|_{L^1(xdx)} + C_1(M)MT\right), \tag{39}$$

where C is the constant such that $\rho(x) \leq Cx$, see (27). This assumption ensures that for any $(u,p,b) \in X_M$, then $S(u,p,b) \in X_M$, *i.e*, the solution is bounded by M and is nonnegative. It remains to prove that S is a contraction. Let (u_1,p_1,b_1) and (u_2,p_2,b_2) belong to X_M. Then

$$\begin{aligned}
\|S_{u_1} - S_{u_2}\|_\infty \leq \gamma_u T\|u_1 - u_2\|_\infty + \tau T\|u_1p_1 - u_2p_2\|_\infty + \sigma T\|b_1 - b_2\|_\infty\\
+ x_0 TC_1(M)\|u_1 - u_2\|_\infty\\
+ T\sup_{t\in[0,T]}\left|u1\int_{x_0}^{+\infty}\rho(x)f_1(x,s)dx - u2\int_{x_0}^{+\infty}\rho(x)f_2(x,s)dx\right|.
\end{aligned} \tag{40}$$

Then,

$$\|u_1p_1 - u_2p_2\|_\infty \leq M\|u_1 - u_2\|_\infty + M\|p_1 - p_2\|_\infty, \tag{41}$$

$$\begin{aligned}
&\sup_{t\in[0,T]}\left|u1\int_{x_0}^{+\infty}\rho(x)f_1(x,s)dx - u2\int_{x_0}^{+\infty}\rho(x)f_2(x,s)dx\right|\\
&\qquad\leq C_2(M,T)\|u_1 - u_2\|_\infty + CM\sup_{t\in[0,T]}\left|\int_{x_0}^{+\infty}x|f_1(x,t) - f_2(x,t)|dx\right|,
\end{aligned} \tag{42}$$

and from Proposition 9,

$$\sup_{t\in[0,T]}\left|\int_{x_0}^{+\infty}x|f_1(x,t) - f_2(x,t)|dx\right| \leq T\left(C_1(M) + CC_2(M,T)\right)\|u_1 - u_2\|_\infty. \tag{43}$$

We get similar bounds for $|S_{p_1} - S_{p_2}|_\infty$ and $|S_{b_1} - S_{b_2}|_\infty$. We infer that there exists a constant $C(M,T)$ depending only on M and T such that

$$\|(S_{u_1}, S_{p_1}, S_{b_1}) - (S_{u_2}, S_{p_2}, S_{b_2})\|_\infty \leq C(M,T)T\|(u_1,p_1,b_1) - (u_2,p_2,b_2)\|_\infty, \tag{44}$$

with $C(M,T)T \to 0$, when T goes to 0. Hence, if T is small enough such that $C(M,T)T < 1$, then S is a contraction. □

From Lemma 10, we have a local nonnegative solution on $[0,T]$, which is unique with the solution (u,p,b) bounded by the constant M. The solution satisfies $f \in C^0(0,T;L^1(xdx))$ and $u,p,b \in C^0(0,T)$. Futhermore from (H3), N is continuous and from (H2), $\rho(x) \leq Cx$ where C is a positive constant. Thus $\rho f \in C^0(0,T;L^1(dx))$. We conclude that u, p and b defined in definition 1 have continuous derivatives.

Now we remark that the solutions satisfies on $[0,T]$

$$\frac{\mathrm{d}}{\mathrm{d}t}(u+p+2b) = \lambda_u + \lambda_p - \gamma_u u - \gamma_p p - \delta 2b - nN(u) \\ - \frac{1}{\varepsilon} u \int_{x_0}^{+\infty} \rho(x) f(x,t) dx \leq \lambda - m(u+p+2b),$$

with $m = \min(\gamma_u, \gamma_p, \delta)$ and $\lambda = \lambda_u + \lambda_p$. Using Gronwall's lemma, the solutions remain bounded, at any time by

$$u + p + 2b \leq u^{in} + p^{in} + 2b^{in} + \frac{\lambda}{m}. \tag{45}$$

From this global bound on u, p and b, we can construct the solution on any interval of time by repetition of the local argument. The proof of the theorem is complete.

4. Summary

The connection of prions and AD is not fully understood, but recent research suggests that soluble Aβ oligomers are possible inducers of AD neuropathology. The key element of this hypothesis is that β−amyloid plaques increase their size over disease progression by the clustering of Aβ oligomers, which are bound to PrP^C proteins. Aβ oligomers exist both as bounded and unbounded to PrP^C proteins, and the agglomerartion rate in the formation of β−amyloid plaques depends on the concentrations of the bound and unbound Aβ oligomers, the concentration of soluble PrP^C , and the size of the β−amyloid plaques. We have introduced a mathematical model of the evolution of AD based on these hypotheses, and presented a mathematical analysis of its fundamental properties. Specifically, we have analyzed in detail the existence and uniqueness properties of solutions, as well as the qualitative properties of solution behavior. In specific cases we have quantified the stabilization of the solutions to steady state, a well-known feature of AD progression. In future work we will explore applications of this model to specific AD laboratory and clinical data.

Appendix A. Characteristic polynomials of the linearized ODE system

Here we give the coefficient a_i, $i = 1, \ldots, 4$ for the characteristic polynomial of the linearized system in proposition 2:

$$\begin{aligned}
a_1 &= \left(\mu + \gamma_u + \tau \frac{\lambda_p}{\tau^* u_\infty + \gamma_p} + \alpha n^2 u_\infty^{n-1} + \rho \frac{\alpha}{\mu} u_\infty^n + \gamma_p + \tau u_\infty + \sigma + \delta\right), \\
a_2 &= \left(\mu + \gamma_u + \alpha n^2 u_\infty^{n-1} + \rho \frac{\alpha}{\mu} u_\infty^n\right)(\gamma_p + \tau u_\infty + \sigma + \delta) + \gamma_p \sigma + (\gamma_p + \tau u_\infty)\delta \\
&\quad + \mu\left(\gamma_u + \tau \frac{\lambda_p}{\tau^* u_\infty + \gamma_p} + \alpha n^2 u_\infty^{n-1} + \rho \frac{\alpha}{\mu} u_\infty^n\right) + \rho \alpha n u_\infty^n + \tau(\gamma_p + \delta) \frac{\lambda_p}{\tau^* u_\infty + \gamma_p}, \\
a_3 &= \left(\mu + \gamma_u + \alpha n^2 u_\infty^{n-1} + \rho \frac{\alpha}{\mu} u_\infty^n\right)(\gamma_p \sigma + (\gamma_p + \tau u_\infty)\delta) + (\gamma_p \delta + (\gamma_p + \delta)\mu)\tau \frac{\lambda_p}{\tau^* u_\infty + \gamma_p} \\
&\quad + \left\{\mu\left(\gamma_u + \alpha n^2 u_\infty^{n-1} + \rho \frac{\alpha}{\mu} u_\infty^n\right) + \rho \alpha n u_\infty^n\right\}(\gamma_p + \tau u_\infty + \sigma + \delta), \\
a_4 &= \mu \gamma_p \delta \tau \frac{\lambda_p}{\tau^* u_\infty + \gamma_p} + \left\{\mu\left(\gamma_u + \alpha n^2 u_\infty^{n-1} + \rho \frac{\alpha}{\mu} u_\infty^n\right) + \rho \alpha n u_\infty^n\right\}(\gamma_p \sigma + (\gamma_p + \tau u_\infty)\delta).
\end{aligned}$$

APPENDIX B. LYAPUNOV FUNCTIONNAL

In order to obtain a Lyapunov function for system (8-11), we approached the problem in a backward manner as described in [21, Chap. 4 - p. 120]. We investigated an expression for the derivative $\dot{\Phi}$ and went back to chose the parameters of Φ so as to make $\dot{\Phi}$ negative definite. This is useful idea to searching for a lyapunov function. Using this method we can derive the global stability in proposition 3. The Lyapunov function for the system (8-11) is:

$$\begin{aligned}\Phi &= \frac{1}{2}\left(\frac{2\gamma_p}{\delta}\right)s_1\theta_1^2+\frac{1}{2}\left(1+2\frac{\delta+\gamma_u+\rho(A_\infty+\theta_1)}{\sigma}\right)\theta_2^2+\frac{1}{2}\left(\frac{2\gamma_p}{\delta}\right)\theta_3^2\\ &+\frac{1}{2}\left(\frac{\sigma}{\gamma_p}\right)\theta_4^2+\left(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}\right)\theta_1\theta_2+\theta_1\theta_3+\theta_2\theta_3\\ &+\left(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}+1+\frac{\rho}{\tau}\right)\theta_1\theta_4+2\theta_2\theta_4+\left(\frac{2\gamma_p}{\delta}\right)\theta_3\theta_4,\end{aligned}$$

where $\theta_1 = A-A_\infty$, $\theta_2 = u-u_\infty$, $\theta_3 = p-p_\infty$, $\theta_4 = b-b_\infty$, with $s_1 = \max(T_1,T_2)$ such that

$$T_1 = \frac{\rho^2\delta u_\infty^2(1+2\frac{1+\delta}{\sigma})}{8\mu\gamma_p}+\frac{(\gamma_p+\mu)^2(\frac{\delta}{2\gamma_p})^2}{4\gamma_p\mu}+\frac{[(\delta+\mu)(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}+1)+(\sigma+\delta+\mu)\frac{\rho}{\tau}+2\rho u_\infty]^2}{8\mu\sigma},$$

$$\begin{aligned}T_2 &= \frac{\left(\frac{\delta}{2\gamma_p}\right)^2\left(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}\right)^2\left(\frac{2\sigma+\delta}{2\gamma_p}\right)}{\left(1+2\frac{\delta+\gamma_u}{\sigma}-\frac{\delta}{2\gamma_p}\right)\left(\frac{\delta}{2\gamma_p}\frac{\sigma}{\gamma_p}-1\right)}+\frac{\left(\frac{\delta}{2\gamma_p}\right)^2\left(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}\right)\left[2+4\frac{\rho}{\tau}\frac{\delta+\gamma_u}{\sigma}\right]}{\left(1+2\frac{\delta+\gamma_u}{\sigma}-\frac{\delta}{2\gamma_p}\right)\left(\frac{\delta}{2\gamma_p}\frac{\sigma}{\gamma_p}-1\right)}\\ &+\frac{\left(\frac{\delta}{2\gamma_p}\right)^3\left[\frac{\rho}{\tau}\left(2+\frac{\rho}{\tau}\right)+\frac{\sigma}{\gamma_p}+2\frac{\delta+\gamma_u}{\gamma_p}\right]}{\left(1+2\frac{\delta+\gamma_u}{\sigma}-\frac{\delta}{2\gamma_p}\right)\left(\frac{\delta}{2\gamma_p}\frac{\sigma}{\gamma_p}-1\right)}+\frac{\left(\frac{\delta}{2\gamma_p}\right)^2\left(1+\frac{\rho}{\tau}\right)\left[1+2\frac{\delta+\gamma_u}{\sigma}\right]\frac{\rho}{\tau}}{\left(1+2\frac{\delta+\gamma_u}{\sigma}-\frac{\delta}{2\gamma_p}\right)\left(\frac{\delta}{2\gamma_p}\frac{\sigma}{\gamma_p}-1\right)}\\ &+\left(\frac{\delta}{2\gamma_p}\right)\left(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}\right)^2\left(\frac{1}{1+2\frac{\delta+\gamma_u}{\sigma}}\right)+\frac{\left(1+2\frac{\delta+\gamma_u}{\sigma}\right)\left(\frac{\delta}{2\gamma_p}\right)^2}{\left(1+2\frac{\delta+\gamma_u}{\sigma}-\frac{\delta}{2\gamma_p}\right)}.\end{aligned}$$

This Lyapunov function Φ is positive when $\left(1+2\frac{\delta+\gamma_u}{\sigma}\right) > \frac{\delta}{2\gamma_p} > \frac{\gamma_p}{\sigma}$. Its derivative along the solutions to the system (8-11) is

$$\begin{aligned}\dot{\Phi} &= -\left(\mu s_1+\rho u\frac{\rho\frac{\delta}{2\gamma_p}p_\infty}{\gamma_u+\rho A_\infty+\mu}\right)\theta_1^2-\rho u_\infty\left(1+2\frac{\gamma_u+\rho(A_\infty+\theta_1)+\delta}{\sigma}\right)\left(\frac{\delta}{2\gamma_p}\right)\theta_1\theta_2\\ &-\left(\frac{2(\gamma_u+\rho(A_\infty+\theta_1)+\tau p)(\gamma_u+\rho(A_\infty+\theta_1)+\delta)}{\sigma}+\gamma_u+\rho(A_\infty+\theta_1)\right)\left(\frac{\delta}{2\gamma_p}\right)\theta_2^2\\ &-\left((\delta+\mu)\left(\frac{\rho p_\infty}{\gamma_u+\rho A_\infty+\mu}+1\right)+(\sigma+\delta+\mu)\frac{\rho}{\tau}+2\rho u_\infty\right)\left(\frac{\delta}{2\gamma_p}\right)\theta_1\theta_4\\ &-\left(\frac{\delta\tau u}{2\gamma_p}+\gamma_p\right)\theta_3^2-\delta\left(\frac{\sigma}{\gamma_p}\frac{\delta}{2\gamma_p}\right)\theta_4^2-(\gamma_p+\mu)\left(\frac{\delta}{2\gamma_p}\right)\theta_1\theta_3.\end{aligned}$$

$\dot{\Phi}$ is non-positive. Furthermore, $\dot{\Phi}=0$ if and only if $\theta_1=\theta_2=\theta_3=\theta_4=0$. LaSalle's invariant principle then implies that the unique equilibrium is globally asymptotically stable in the stable subset defined in (13) [22].

REFERENCES

[1] Y. Achdou, B. Franchi, N. Marcello, and Tesi M. C., *A qualitative model for aggregation and diffusion of* β*-amyloid in Alzheimer's disease*, Journal of Mathematical Biology (2012), 1–24.

[2] L.J.S. Allen, *An introduction to mathematical biology*, Prentice Hall, 2007.

[3] V. Calvez, N. Lenuzza, M. Doumic, J.-P. Deslys, F. Mouthon, and B. Perthame, *Prion dynamics with size dependency-strain phenomena*, Journal of Biological Dynamics **4** (2010), no. 1, 28–42.

[4] V. Calvez, N. Lenuzza, D. Oelz, J.-P. Deslys, P. Laurent, F. Mouthon, and B. Perthame, *Size distribution dependence of prion aggregates infectivity*, Mathematical Biosciences **217** (2009), no. 1, 88–99.

[5] S. Chen, S. P. Yadav, and W. K. Surewicz, *Interaction between human prion protein and amyloid-β (Aβ) oligomers: Role of N-terminal residues*, The Journal of Biological Chemistry **285** (2011), 26377–83.

[6] E. Chung, Y. Ji, Y. Sun, Ri. Kascsak, Re. Kascsak, P. Mehta, S. Strittmatter, and T. Wisniewski, *Anti-prpc monoclonal antibody infusion as a novel treatment for cognitive deficits in an Alzheimer's disease model mouse*, BMC Neuroscience **11** (2010), no. 130.

[7] M. Cisse and L. Mucke, *A prion protein connnection*, Nature **457** (2009), no. 26, 1090–1091.

[8] M. Cisse, B. Halabiski, J. Harris, N. Devidze, D. B. Dubal, B. Sun, A. Orr, G. Lotz, D. H. Kim, P. Hamto, K. Ho, G-Q. Yu, and L. Mucke, *Reversing EphB2 depletion rescues cognitive functions in Alzheimer model*, Nature **469** (2011), no. 7328, 47–52.

[9] J.-F. Collet and T. Goudon, *Classification and basic pathology of Alzheimer disease*, Nonlinearity **13** (2009), no. 4, 1239–62.

[10] D. L. Craft, L. M. Wein, and D. J. Selkoe, *A mathematical model of the impact of novel treatments on the Aβ burden in the Alzheimer's brain, csf and plasma*, Bulletin of mathematical biology **64** (2002), no. 5, 1011–31.

[11] ———, *The impact of novel treatments on Aβ burden in Alzheimer's disease: Insights from a mathematical model*, Operations research and health care, 2005, pp. 839–865.

[12] M. Doumic, A. Marciniak-Czochra, B. Perthame, and J. P. Zubelli, *A Structured Population Model of Cell Differentiation*, SIAM Journal of Applied. Mathematics **71** (2011), no. 6, 1918–40.

[13] C. Duyckaerts, B. Delatour, and M.-C. Potier, *Classification and basic pathology of Alzheimer disease*, Acta Neuropathologica **118** (2009), 5–36.

[14] D. B. Freir, A. J. Nicoll, I. Klyubin, J. M. Panico S. Mc Donald, E. Risse, E. A. Asante, M. A. Farrow, R. B. Sessions, H. R. Saibil, A. R. Clarke, M. J. Rowan, D. M. Walsh, and J. Collinge, *Interaction between prion protein and toxic amyloid β assemblies can be therapeutically targeted at multiple sites*, Nature Communications **2** (2011), no. 336.

[15] P. Gabriel, *The shape of the polymerization rate in the prion equation*, Mathematical and Computer Modelling **53** (2011), no. 7-8, 1451–56.

[16] S. L. Gallion, *Modeling amyloid-beta as homogeneous dodecamers and in complex with cellular prion protein*, PLoS ONE 7(11) **7** (2012), no. 11, e49375.

[17] D. A. Gimbel, H. B. Nygaard, E. E. Coffey, E. C. Gunther, J. Laurén, Z. A. Gimbel, and S. M. Strittmatter, *Memory impairment in transgenic Alzheimer mice requires cellular prion protein*, The Journal of Neuroscience **30** (2010), no. 18, 6367–74.

[18] M. L. Greer, L. Pujo-Menjouet, and G. F. Webb, *A mathematical analysis of the dynamics of prion proliferation*, Journal of Theoretical Biology **242** (2006), no. 3, 598–606.

[19] M. L. Greer, P. van den Driessche, L. Wang, and G. F. Webb, *Effects of general incidence and polymer joining on nucleated polymerization in a prion disease model*, SIAM Journal of Applied Mathematics **68** (2007), no. 1, 154–170.

[20] J. Hardy and D.J. Selkoe, *The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics*, Science **297** (2002), no. 5580, 353–6.

[21] H.K. Khalil, *Nonlinear systems*, Prentice Hall, 2002.

[22] J.P. LaSalle, *The stability of dynamical systems*, CBMS-NSF Regional Conference Series in Applied Mathematics, SIAM, 1976.

[23] J. Laurén, D. A. Gimbel, H. B. Nygaard, J. W. Gilbert, and S. M. Strittmatter, *Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers*, Nature **457** (2009), no. 7233, 1128–32.

[24] S. L. Laurençcot and C. Walker, *Well-posedness for a model of prion proliferation dynamics*, Journal of Evolution Equations **7** (2007), 241–264.

[25] A. Lomakin, D. S. Chung, G. B. Benedek, Kirschner D. A., and D. B. Teplow, *On the nucleation and growth of amyloid beta-protein fibrils: Detection of nuclei and quantitation of rate constants*, Proceedings of the National Academy of Sciences **93** (1996), no. 3, 1125–29.

[26] A. Lomakin, D. B. Teplow, D. A. Kirschner, and G. B. Benedek, *Kinetic theory of fibrillogenesis of amyloid beta-protein*, Proceedings of the National Academy of Sciences **94** (1997), no. 15, 7942–47.

[27] S. Nath, Agholme L., F. R. Kurudenkandy, B. Granseth, J. Marcusson, and M. Hallbeck, *Spreading of neurodegenerative pathology via neuron-to-neuron transmission of β-amyloid*, Journal of Neuroscience **32** (2012), no. 26, 8777–67.

[28] H. B. Nygaard and S. M. Strittmatter, *Cellular prion protein mediates the toxicity of beta-amyloid oligomers: Implications for Alzheimer disease*, Archives of Neurology **66** (2009), no. 11, 1325–1328.

[29] S. Portet and J. Arino, *An in vivo intermediate filament assembly model*, Mathematical Biosciences and Engineering **6** (2009), no. 1, 117–134.

[30] S. Prigent, A. Ballesta, F. Charles, N. Lenuzza, P. Gabriel, L. M. Tine, H. Rezaei, and M. Doumic, *An efficient kinetic model for assemblies of amyloid fibrils and its application to polyglutamine aggregation*, PLoS ONE **7** (2012), no. 11, e43273.

[31] J. Prüss, L. Pujo-Menjouet, G. F. Webb, and R. Zacher, *Analysis of a model for the dynamics of prions*, Discrete and Continuous Dynamical Systems-Series B **6** (2006), no. 1, 215-225.
[32] Zou W. Q. and Xiao X. Zhou X. Yuan J., *Insoluble cellular prion protein and its association with prion and alzheimer diseases*, Prion **5** (2011), no. 3, 172–178.
[33] U. K. Resenberger, A. Harmeier, A. C. Woerner, J. L. Goodman, V. Müller, R. Krishnan, R. M. Vabulas, H. A. Kretzschmar, S. Lindquist, F. U. Hartl, G. Multhaup, K. F. Winklhofer, and J. Tatzelt, *The cellular prion protein mediates neurotoxic signalling of* β*-sheet-rich conformers independent of prion replication*, The EMBO Journal **30** (2011), no. 10, 2057–70.
[34] R. Rubenstein, P. A. Merz, R. J. Kascsak, C. L. Scalici, M. C. Papini, R. I. Carp, and R. H. Kimberlin, *Scrapie-infected spleens: Analysis of infectivity, scrapie-associated fibrils, and protease-resistant proteins*, The Journal of Infectious Diseases **164** (1991), no. 1, 29–35.
[35] Dennis J Selkoe, *Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior*, Behavioural brain research **192** (2008), no. 1, 106–13.
[36] G. Simonett and C. Walker, *On the solvability of a mathematical model for prion proliferation*, Journal of Mathematical Analysis and Applications **324** (2006), 580–603.
[37] B. Urbanc, L. Cruz, S. V. Buldyrev, S. Havlin, M. C. Irizarry, H. E. Stanley, and B. T. Hyman, *Dynamics of plaque formation in Alzheimer's disease*, Biophysical journal **76** (1999), no. 3, 1330–34.
[38] B. Vincent, M. A. Cisse, C. Sunyach, M.-V. Guillot-Sestier, and F. Checler, *Regulation of* β*APP and PrPc cleavage by* α*-secretase: Mechanistic and therapeutic perspectives*, Current Alzheimer Research **5** (2010), no. 2, 202–211.
[39] D. M. Walsh, Lomakin A., Benedek G. B., Condron M. M., and Teplow D. B., *Amyloid-beta protein fibrillogenesis. detection of a protofibrillar intermediate*, Journal of Biological Chemistry **272** (1997), no. 35, 22364–72.
[40] A. Wimo and M. Prince, *World Alzheimer report 2010: The global economic impact of dementia*, Alzheimer's Disease International, 2010.

Mohamed Helal
Université Djillali Liabes, Faculté des Sciences, Département de Mathématique
Sidi Bel Abbes 22000, Algérie
E-mail: mhelal_abbes@yahoo.fr

Erwan Hingant
CI^{2}MA, Universidad de Concepción, Chile
E-mail: ehingant@ci2ma.udec.cl

Laurent Pujo-Menjouet
Université de Lyon, CNRS UMR 5208, Université Lyon 1, Institut Camille Jordan
43 blvd. du 11 novembre 1918, F-69622 Villeurbanne cedex, France
E-mail: pujo@math.univ-lyon1.fr

Glenn F. Webb
Department of Mathematics, Vanderbilt University
1326 Stevenson Center, Nashville, TN 37240-0001, USA
E-mail: glenn.f.webb@vanderbilt.edu

Centro de Investigación en Ingeniería Matemática (CI^{2}MA)

PRE-PUBLICACIONES 2012 - 2013

2012-21 Raimund Bürger, Pep Mulet, Luis M. Villada: *Implicit-explicit methods for diffusively corrected multi-species kinematic flow models*

2012-22 Raimund Bürger, Stefan Diehl: *Convexity-preserving flux identification for scalar conservation laws modelling sedimentation*

2012-23 Raimund Bürger, Ilja Kröker, Christian Rohde: *A hybrid stochastic Galerkin method for uncertainty quantification applied to a conservation law modelling a clarifier-thickener unit*

2012-24 Felipe Lepe, David Mora, Rodolfo Rodríguez: *Locking-free finite element method for a bending moment formulation of Timoshenko beams*

2012-25 Raimund Bürger, Pep Mulet, Luis M. Villada: *A diffusively corrected multi-class Lighthill-Whitham-Richards traffic model with anticipation lengths and reaction times*

2012-26 Margareth Alves, Jaime Muñoz-Rivera, Mauricio Sepúlveda, Octavio Vera: *Exponential and the lack of exponential stability in transmission problems with localized Kelvin-Voigt dissipation*

2013-01 Jorge Clarke, Ciprian A. Tudor: *Wiener integrals with respect to the Hermite random field and applications to the wave equation*

2013-02 Julio Aracena, Adrien Richard, Lilian Salinas: *Maximum number of fixed points in AND-OR Boolean network*

2013-03 Raimund Bürger, Ricardo Ruiz-Baier, Canrong Tian: *Stability analysis and finite volume element discretization for delay-driven spatial patterns in a predator-prey model*

2013-04 Tomás Barrios, Rommel Bustinza, Galina C. García, María González: *A posteriori error analyses of a velocity-pseudostress formulation of the generalized Stokes problem*

2013-05 Rodolfo Araya, Abner Poza, Frederic Valentin: *An adaptive residual local projection finite element method for the Navier-Stoker equations*

2013-06 Mohamed Helal, Erwan Hingant, Laurent Pujo-Menjouet, Glenn Webb: *Alzheimer's disease: Analysis of a mathematical model incorporating the role of prions*

Para obtener copias de las Pre-Publicaciones, escribir o llamar a: Director, Centro de Investigación en Ingeniería Matemática, Universidad de Concepción, Casilla 160-C, Concepción, Chile, Tel.: 41-2661324, o bien, visitar la página web del centro: `http://www.ci2ma.udec.cl`







Centro de Investigación en
Ingeniería Matemática (CI²MA)
Universidad de Concepción

Casilla 160-C, Concepción, Chile
Tel.: 56-41-2661324/2661554/2661316
http://www.ci2ma.udec.cl