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

Mohamed Helal, Erwan Hingant, Laurent Pujo-Menjouet & Glenn F. Webb

Journal of Mathematical Biology

ISSN 0303-6812

J. Math. Biol.
DOI 10.1007/s00285-013-0732-0

Springer

J. Math. Biol.
DOI 10.1007/s00285-013-0732-0

Mathematical Biology

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

Mohamed Helal · Erwan Hingant · Laurent Pujo-Menjouet · Glenn F. Webb

Received: 27 February 2013 / Revised: 1 August 2013

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.

Keywords 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 Postoctoral Grant no. 3130318 (Chile).

M. Helal
Département de Mathématique, Faculté des Sciences, Université Djillali Liabes,
22000 Sidi Bel Abbès, Algeria
e-mail: mhelal_abbes@yahoo.fr

E. Hingant (✉)
CI^2MA, Universidad de Concepción, Concepción, Chile
e-mail: ehingant@ci2ma.udec.cl

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

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

Published online: 22 October 2013

Mathematics Subject Classification (2000) 35F61 · 92B05 · 34L30

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 according to Wimo and Prince (2010). 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, e.g. Wimo and Prince 2010). The human and social impact 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 (Cissé and Mucke 2009; Cissé et al. 2011; Gimbel et al. 2010; Laurén et al. 2009; Nath et al. 2012). 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 (Duyckaerts et al. 2009; Hardy and Selkoe 2002). 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 (Chen et al. 2010; Lomakin et al. 1996; Lomakin et al. 1997; Urbanc et al. 1999; Walsh et al. 1997). It has been revealed by Selkoe (2008) 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. 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^Cprotein (Nygaard and Strittmatter 2009; Zou et al. 2011; Resenberger et al. 2011; Gimbel et al. 2010; Laurén et al. 2009) 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 by Gallion (2012). Moreover, the prion protein has also been identified as an APP regulator, which confirms that both are highly related (Nygaard and Strittmatter 2009; Vincent et al. 2008). This discovery offers a new therapeutic target to recover memory in AD patients, or at least slow memory depletion (Freir et al. 2011; Chung et al. 2010).

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^Cproteins. 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 (Achdou et al. 2012; Craft et al.

2002, 2005). Nevertheless, the prion protein has never been taken into account in the way we formulate here, and our model could help in designing new experiments and treatments.

This paper is organized as follows. We present the model in Sect. 2, and provide a well-posedness result in the particular case that β-amyloids are formed at a constant rate. In Sect. 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 Greer et al. 2006; Prigent et al. 2012; Calvez et al. 2009, 2010; Gabriel 2011; Greer et al. 2006, 2007; Laurençot and Walker 2007; Prüss et al. 2006; Simonett and Walker 2006 for modeling approach and analysis). 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^Ccomplex (bounded oligomers) at time t.

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,

Table 1 Parameter description of the model

Parameter/variable	Definition	Unit
t	Time	Days
x	size of β-amyloidplaques	–
x_0	Critical size of β-amyloidplaques	–
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	$(\text{SAF/sq})^{-1}$ *$\cdot$ days^{-1}
$\mu(x)$	Degradation rate of a plaque	Days^{-1}

* SAF/sq means Scrapie-Associated Fibrils per square unit and is explained in detail by Rubenstein et al. (1991) (we consider plaques as being fibrils here)

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 1.

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

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

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

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

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

The term N accounts for the formation rate of a new β-amyloidplaque 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

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

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

Before going further, we emphasis some modeling points:

- Modeling fibril formation involves many more complex features. Indeed, in vivo but also in vitro, their dynamics include phenomena of depolymerization, fragmentation and possible coagulation. A fully developed model would take into account all these processes. In this work we focus on the dynamics of oligomers and their interactions with fibrils and PrP^C. Therefore, we neglect the internal dynamics of polymers and their depolymerization to give priority to an apparent extension rate of fibrils.
- There exist various sizes of Aβ oligomers, from dimer up to ten or so peptides. Nevertheless, these are unstable until they reach a stable structure, and that is why

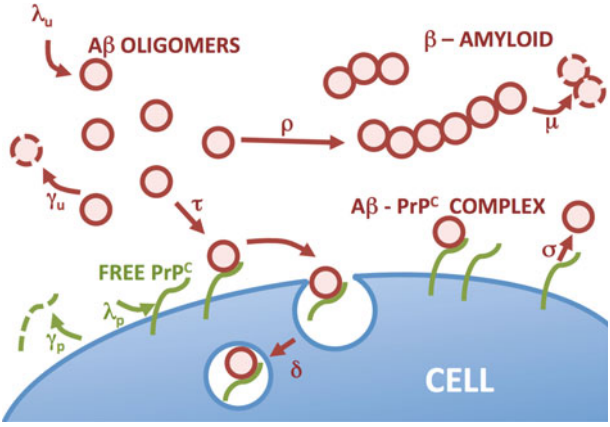

Fig. 1 Schematic diagram of the evolution processes of β-amyloidplaques, Aβ oligomers (bounded and unbounded), and PrP^C in the model

we assume here only one stable oligomer size, which is the one that interacts with PrP^C and that is able to form protofibrils (also called critical plaques here). We refer to the papers by Serpell (2000) and Fawzi et al. (2007) for their discussions about intermediate oligomers, fibril structure, and fibril nucleation.

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 Sect. 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-amyloidplaques, as formulated by Portet and Arino (2009) for filaments, by setting $N(u) = \alpha u^n$, with $\alpha > 0$ the formation rate. It is obtained assuming $n - 1$ reactions lead to a fibril of size n from oligomers:

$$\begin{aligned} u + u &\leftrightharpoons F_2, \\ F_2 + u &\leftrightharpoons F_3 \\ &\cdots \\ F_{n-1} + u &\leftrightharpoons F_n \end{aligned}$$

where F_i are pre-fibrils or aggregates of i-oligomers for $i = 2, \ldots, n$ and the coefficient rate of each equation is given by K_i. So, taking all the equations at the equilibrium, we get $F_2 = K_2 u^2$, $F_3 = K_3 F_2 u = K_3 K_2 u^3$, *etc.* until $F_n = \alpha u^n$, where the formation rate α of a critical plaque, composed of $n \geq 1$ oligomers, is given by $\alpha = K_n \times \cdots \times K_2 > 0$. Once the length n is achieved, we assume the fibrils reach a stable structure. Therefore, we only take into account their polymerization and not their reverse reactions (see, for instance, a discussion about prion fibrils in Serpell (2000), Fawzi et al. (2007).

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 $t \geq 0$

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

which is given by

$$\frac{d}{dt}A(t) - u(t)\rho f(x_0, t) = -\mu A(t).$$

We close the system using expression of the boundary (5), recalling that ρ is constant, and the fact that $N(u) = \alpha u^n$. This method has already been used on the prion model by Greer et al. (2006). Now the problem reads, for $t \geq 0$,

$$\dot{A} = \alpha u^n - \mu A, \tag{8}$$
$$\dot{u} = \lambda_u - \gamma_u u - \tau u p + \sigma b - \alpha n u^n - \rho u A, \tag{9}$$
$$\dot{p} = \lambda_p - \gamma_p p - \tau u p + \sigma b, \tag{10}$$
$$\dot{b} = \tau u p - (\sigma + \delta) b. \tag{11}$$

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

$$\frac{d}{dt} M(t) - x_0 u(t) \rho f(x_0, t) - \int_{x_0}^{+\infty} \rho u(t) f(x,t) dx = -\mu M(t).$$

Indeed, we use once again the boundary condition (5), the expression of the formation rate N and that $x_0 = n$ since $\varepsilon = 1$, in order to get

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

Notice that initial conditions for A and M are given by $A^{in} = \int_{x_0}^{+\infty} f^{in}(x) dx$ and $M^{in} = \int_{x_0}^{+\infty} x f^{in}(x) dx$, 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 nonnegativity, existence, and uniqueness of a global solution to the system (8–11) with classical techniques from the theory of ordinary differential equations.

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 $\mathcal{C}_b^1(\mathbb{R}_+)$ 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 exists 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

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

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

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

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 $A_\infty, u_\infty, p_\infty, b_\infty$ 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 1 (Linear Stability) *Under hypothesis of the 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*

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

Moreover, this equilibrium is locally linearly asymptotically stable.

Proof First, Eq. (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 $A_\infty, u_\infty, p_\infty$ 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 $a_i > 0, i = 1 \ldots 4$ 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 Allen 2007*Th. 4.4, page 150), all the roots of the characteristic 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 2 (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. □

In the next section we will study from a mathematical point of view a more realistic model. Nevertheless, our model emphasizes a major dilemma in AD. Indeed, consider the steady state given in Theorem 1. If the rate of polymerization increases, it increases the growth rate of the polynomial P, so the intersection occurs faster (the positive root of Q). This means that u_∞ decreases, and likewise b_∞. The balance law of oligomers suggests that when b_∞ decreases in such a way, the mass of fibrils M will increase. So a question remains, what is the less toxic quantity, and is there any criteria under which we could optimize ρ.

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 by Calvez et al. (2010) and Gabriel (2011). 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-amyloidin 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) $\quad f^{in} \in L^1(x_0, +\infty; xdx),\ f^{in} \geq 0,\ a.e.\ x > x_0.$

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

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

(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 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 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

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

$$p(t) = p^{in} + \int_0^t \left[\lambda_p - \gamma_p p - \tau u p + \sigma b\right] ds,$$

$$b(t) = b^{in} + \int_0^t \left[\tau u p - (\sigma + \delta) b\right] ds,$$

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

Theorem 2 (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 2 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 Sect. 3.2 the following proposition:

Proposition 3 *Let $u \in C_b^0(\mathbb{R}_+)$, 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 proposed by Collet and Goudon (2000) 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 $L^1(x dx)$ space.

The second step of the proof of Theorem 2 is performed in Sect. 3.3. Precisely, once we have the existence of a unique density f, when u is given, we are able to construct the operator

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

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

$$S_p = p^{in} + \int_0^t \left[\lambda_p - \gamma_p p - \tau u p + \sigma b\right] ds,$$

$$S_b = b^{in} + \int_0^t \left[\tau u p - (\sigma + \delta) b\right] ds,$$

where f is the unique solution associated to u given by Proposition 3. Then, Theorem 2 is finally proven in Sect. 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 reaching $x \geq x_0$ at time $t \geq 0$, that is, the solution to

$$\frac{d}{ds}X(s;x,t) = a(t, X(s;x,t)),$$

$$X(t;x,t) = x. \tag{25}$$

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

$$X(s; X(\sigma;x,t), \sigma) = X(s;x,t)$$

$$J(s;x,t) := \frac{\partial}{\partial x}X(s;x,t) = \exp\left(\int_s^t c(\sigma, X(\sigma;x,t))d\sigma\right)$$

$$\frac{\partial}{\partial t}X(s;x,t) = -a(t,x)J(s;x,t).$$

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 belongs to $(x_0,X(t;x_0,0))$

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

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

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

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 Lemma 1 from the paper by Collet and Goudon (2000).

Lemma 1 *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 the proof given by Collet and Goudon (2000), 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

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

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 1, 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 2 *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 $L^\infty\left(0, T; L^1(x_0, +\infty; xdx)\right)$, 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

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

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

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

still using the change of variable mentioned above and

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

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 3 *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

$$I_1 = \int_{x_0}^{X(t;x_0,0)} x^r \, |f(x, t+\delta t) - f(x,t)| \, dx,$$

$$I_2 = \int_{X(t;x_0,0)}^{X(t+\delta t;x_0,0)} x^r \, |f(x, t+\delta t) - f(x,t)| \, dx,$$

$$I_3 = \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r \, |f(x, t+\delta t) - f(x,t)| \, dx.$$

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 $x \geq X(t+\delta t; x_0, 0) \geq X(t; x_0, 0)$, it follows that

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

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

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

where

$$I_3^1 = \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r \big| f^{in}(X(0;x,t+\delta t)) - f_\varepsilon^{in}(X(0;x,t+\delta t)) \big| \times J(0;x,t+\delta t) e^{-\int_0^{t+\delta t} \mu(X(\sigma;x,t+\delta t))d\sigma} dx,$$

$$I_3^2 = \int_{X(t+\delta t;x_0,0)}^{+\infty} x^r \big| f_\varepsilon^{in}(X(0;x,t+\delta t)) J(0;x,t+\delta t) \times e^{-\int_0^{t+\delta t} \mu(X(\sigma;x,t+\delta t))d\sigma} - f_\varepsilon^{in}(X(0;x,t)) J(0;x,t) e^{-\int_0^t \mu(X(\sigma;x,t))d\sigma} \big| dx,$$

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

Dropping the exponential term, which is bounded by one, and changing 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 1. Next we bound I_3^2 by

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

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

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

Thus, with (22) and (24),

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

where K is the Lipschitz constant of ρ'. Since $x \le R_\varepsilon$, let

$$
C_G(T,\varepsilon) = K\|u\|_{L^\infty} A T e^{BT} R_\varepsilon + B,
$$

and if $|x| \le y$, then

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

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,

$$\left| \int_0^{t+\delta t} \mu(X(\sigma; x, t+\delta t))d\sigma - \int_0^t \mu(X(\sigma; x, t))d\sigma \right| \leq \delta t M A T e^{BT} x + \delta t \|\mu\|_{L^\infty},$$

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

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

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

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

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,

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

Using the Lipschitz constant of N denoted by K_N, from the definition of I and with the help of Lemma 1, we get

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

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 required 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 4 *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

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

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

$$\int_{x_0}^{+\infty}|h(x,t)|g(x)dx=\int_{x_0}^{+\infty}|h^{in}(x)|g(x)dx$$
$$+\int_0^t\int_{x_0}^{+\infty}|h(x,s)|\left[a_1(s,x)\frac{\partial}{\partial x}g(x)-\mu(x)g(x)\right]dxds$$

$$+\int_0^t |N(u_1(s)) - N(u_2(s)))\, Sign(h_0(x_0))g(x_0)ds$$
$$+\int_0^t \int_{x_0}^{+\infty} (a_1(s,x) - a_2(s,x))\, f_2(x,s) Sign(h(s,x)) \frac{\partial}{\partial x} g(x) dx ds.$$

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

It is straightforward from Proposition 2 that f defined by (26) is a weak solution and the only one from Proposition 4. Indeed, getting $u_1 = u_2$ and $f_1^0 = f_2^0$ in Proposition 4 leads to the uniqueness. Finally, Proposition 3 provides the continuity in time of the moments with order less or equal to one. This concludes the proof of Proposition 3.

3.3 Proof of the well-posedness

In this section we prove Theorem 2. We first study the operator S defined by (21).

Lemma 4 *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

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

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

$$\begin{aligned}\|S_{u_1} - S_{u_2}\|_\infty &\leq \gamma_u T\|u_1 - u_2\|_\infty + \tau T\|u_1 p_1 - u_2 p_2\|_\infty + \sigma T\|b_1 - b_2\|_\infty \\ &+ x_0 T C_1(M)\|u_1 - u_2\|_\infty \\ &+ T \sup_{t\in[0,T]} \left| u1 \int_{x_0}^{+\infty} \rho(x) f_1(x,s)dx - u2 \int_{x_0}^{+\infty} \rho(x) f_2(x,s)dx \right|. \end{aligned} \tag{40}$$

Then,

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

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

and from Proposition 4,

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

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 we are able to get $C(M, T)T < 1$, then S is a contraction. □

From Lemma 4, 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 $u, p, b \in C^0(0, T)$. Furthermore 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 satisfy 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 Perspectives and biological implications

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 the formation of a neurotoxic complex Aβ-×-PrP^C, which is created by the association of Aβ oligomers and PrP^C proteins, and not only the progression of β-amyloid plaques by the clustering of Aβ oligomers.

We believe the model developed and studied here is a step forward in the understanding of the mechanisms underlying AD progression. We have introduced a mathematical model of the evolution of AD based on the hypotheses that Aβ oligomers exist both as bounded and unbounded to PrP^C proteins, and the agglomeration 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. Specifically, we have analyzed in detail the existence and uniqueness properties of solutions of the model, as well as the qualitative properties of solution behavior. In specific cases we have quantified the stabilization of the solutions to steady state. In future work, we will explore applications of this model to specific AD laboratory and clinical data. Nevertheless, from this approach we can deduce some suggestions for further research:

- The model suggests a stabilization to steady state for the quantities incorporated into the model. Such phenomena can be very difficult to ascertain in a progressive disease such as AD. Nevertheless, any experimental data quantifying stabilization of AD progression can be valuable in identifying the parameters of the model.
- From an experimental point of view, the investigation of the size distribution of the fibrils is an important consideration. Indeed, we have neglected some phenomena in our study (such as fragmentation-coagulation and depolymerization), and thus it remains to clarify these assumptions. Moreover, in the case of a size-dependent polymerization rate, we would also investigate the character of the polymerization rate from experimental data.

– Finally, we emphasize one further point. One of the main issues in AD is to mitigate progressive memory impairment. Both Aβ-$\times$-PrP^{C}and β-amyloidplay a key role in the evolution of disease progression, but disappearance of β-amyloid plaques *via* a vaccine does not mitigate neurodegeneration (Holmes et al. 2008). One simple answer would be to increase the degradation rate of Aβ-$\times$-PrP^C by some treatments, which are at present not available. But, as suggested by the model, the polymerization rate could be a key point in the control of disease progression. Indeed, increasing this rate would exhaust the availability of oligomers, and thus reduce the formation of complexes. An important issue remains, namely, what is the best balance between Aβ-$\times$-PrP^C and β-amyloid plaques such that AD patients live the longest without toxicity effects. Perhaps the solution is not to suppress the β-amyloid plaques, but rather control their progression. The question is open and a deeper analysis of the model, together with biological data, would provide understanding in this direction.

Acknowledgments The authors thanks the Reviewers for their usefull comments and suggestions. E.H. thanks A. Rambaud for helpful discussions, which improved the paper.

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 Theorem 1:

$$a_1 = \left(\mu + \gamma_u + \tau\frac{\lambda_p}{\tau^* u_\infty + \gamma_p} + \alpha n^2 u_\infty^{n-1} + \rho\frac{\alpha}{\mu}u_\infty^n + \gamma_p + \tau u_\infty + \sigma + \delta\right),$$

$$a_2 = \left(\mu + \gamma_u + \alpha n^2 u_\infty^{n-1} + \rho\frac{\alpha}{\mu}u_\infty^n\right)(\gamma_p + \tau u_\infty + \sigma + \delta) + \gamma_p\sigma + (\gamma_p + \tau u_\infty)\delta$$
$$+\mu\left(\gamma_u + \tau\frac{\lambda_p}{\tau^* u_\infty + \gamma_p} + \alpha n^2 u_\infty^{n-1} + \rho\frac{\alpha}{\mu}u_\infty^n\right) + \rho\alpha n u_\infty^n + \tau(\gamma_p + \delta)\frac{\lambda_p}{\tau^* u_\infty + \gamma_p},$$

$$a_3 = \left(\mu + \gamma_u + \alpha n^2 u_\infty^{n-1} + \rho\frac{\alpha}{\mu}u_\infty^n\right)(\gamma_p\sigma + (\gamma_p + \tau u_\infty)\delta) + (\gamma_p\delta + (\gamma_p + \delta)\mu)\tau\frac{\lambda_p}{\tau^* u_\infty + \gamma_p}$$
$$+\left\{\mu\left(\gamma_u + \alpha n^2 u_\infty^{n-1} + \rho\frac{\alpha}{\mu}u_\infty^n\right) + \rho\alpha n u_\infty^n\right\}(\gamma_p + \tau u_\infty + \sigma + \delta),$$

$$a_4 = \mu\gamma_p\delta\tau\frac{\lambda_p}{\tau^* u_\infty + \gamma_p} + \left\{\mu\left(\gamma_u + \alpha n^2 u_\infty^{n-1} + \rho\frac{\alpha}{\mu}u_\infty^n\right) + \rho\alpha n u_\infty^n\right\}(\gamma_p\sigma + (\gamma_p + \tau u_\infty)\delta).$$

Appendix B: Lyapunov functional

Here we detail a Lyapunov function Φ which is the key ingredient to prove global stability of system (8–11) in Proposition 2. This function appears to be a bit tricky,

but determining it rest upon the backward method described for instance Chapter 4, p. 120, in the book by Khalil (1996). It consists in investigate an expression of the derivative Φ' and then going back to chose the parameters Φ such as Φ' is negative definite. After tedious calculus, a Liapunov function Φ for system (8–11) is given by

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

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

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

and $T_2 = \Gamma\left(\frac{\delta}{2\gamma_p}\right)^2 T_2'$ with

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

and

$$\Gamma = \frac{1}{\left(1+2\frac{\delta+\gamma_u}{\sigma}-\frac{\delta}{2\gamma_p}\right)\left(\frac{\delta}{2\gamma_p}\frac{\sigma}{\gamma_p}-1\right)}.$$

We remark that $T_1 > 0$ so that $s_1 > 0$, and then we deduce that the Lyapunov function Φ is positive when condition $\left(1+2\frac{\delta+\gamma_u}{\sigma}\right) > \frac{\delta}{2\gamma_p} > \frac{\gamma_p}{\sigma}$ holds true. In such case, its derivative along the solutions of system (8–11) is given by

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

and remains nonpositive. Furthermore, $\Phi' = 0$ if and only if $\theta_1 = \theta_2 = \theta_3 = \theta_4 = 0$. The conclusion holds by the LaSalle Invariance Principle LaSalle (1976).

References

Achdou Y, Franchi B, Marcello N, Tesi M (2012) A qualitative model for aggregation and diffusion of β-amyloid in alzheimers disease. J Math Biol 1–24

Allen LJS (2007) An introduction to mathematical biology. Pearson/Prentice Hall, Upper Saddle River

Calvez V, Lenuzza N, Oelz D, Deslys JP, Laurent P, Mouthon F, Perthame B (2009) Size distribution dependence of prion aggregates infectivity. Math Biosci 217(1):88–99

Calvez V, Lenuzza N, Doumic M, Deslys JP, Mouthon F, Perthame B (2010) Prion dynamics with size dependency-strain phenomena. J Biol Dyn 4(1):28–42

Chen S, Yadav SP, Surewicz WK (2010) Interaction between human prion protein and amyloid-β (aβ) oligomers role of N-terminal residues. J Biol Chem 285(34):26,377–26,383

Chung E, Ji Y, Sun Y, Kascsak R, Kascsak R, Mehta P, Strittmatter S, Wisniewski T (2010) Anti-prpc monoclonal antibody infusion as a novel treatment for cognitive deficits in an alzheimer's disease model mouse. BMC Neurosci 11(1):130

Cissé M, Mucke L (2009) Alzheimer's disease: a prion protein connection. Nature 457(7233):1090–1091

Cissé M, Halabisky B, Harris J, Devidze N, Dubal DB, Sun B, Orr A, Lotz G, Kim DH, Hamto P et al (2011) Reversing ephb2 depletion rescues cognitive functions in alzheimer model. Nature 469(7328):47–52

Collet JF, Goudon T (2000) On solutions of the lifshitz-slyozov model. Nonlinearity 13(4):1239

Craft DL, Wein LM, Selkoe DJ (2002) A mathematical model of the impact of novel treatments on the aβ burden in the alzheimers brain, csf and plasma. Bull Math Biol 64(5):1011–1031

Craft DL, Wein LM, Selkoe DJ (2005) The impact of novel treatments on aβ burden in alzheimers disease: insights from a mathematical model. In: Brandeau ML, Sainfort F, Pierskalla WP (eds) Operations research and health care, international series in operations research and management science, vol 70. Springer, USA, pp 839–865

Duyckaerts C, Delatour B, Potier MC (2009) Classification and basic pathology of alzheimer disease. Acta Neuropathol 118(1):5–36

Fawzi NL, Okabe Y, Yap EH, Head-Gordon T (2007) Determining the critical nucleus and mechanism of fibril elongation of the alzheimers aβ_{1-40} peptide. J Mol Biol 365(2):535–550

Freir DB, Nicoll AJ, Klyubin I, Panico S, Risse E, Asante EA, Farrow MA, Sessions RB, Saibil HR, Clarke AR, Rowan MJ, Walsh DM, Collinge J (2011) Interaction between prion protein and toxic amyloid β assemblies can be therapeutically targeted at multiple sites. Nat Commun 2:336

Gabriel P (2011) The shape of the polymerization rate in the prion equation. Math Comput Model 53(7):1451–1456

Gallion SL (2012) Modeling amyloid-beta as homogeneous dodecamers and in complex with cellular prion protein. PLoS One 7(11):e49,375

Gimbel DA, Nygaard HB, Coffey EE, Gunther EC, Laurén J, Gimbel ZA, Strittmatter SM (2010) Memory impairment in transgenic Alzheimer mice requires cellular prion protein. J Neurosci 30(18): 6367–6374

Greer ML, Pujo-Menjouet L, Webb GF (2006) A mathematical analysis of the dynamics of prion proliferation. J Theor Biol 242(3):598–606

Greer ML, Van den Driessche P, Wang L, Webb GF (2007) Effects of general incidence and polymer joining on nucleated polymerization in a model of prion proliferation. SIAM J Appl Math 68(1):154–170

Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297(5580):353–356

Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, Zotova E, Nicoll JA (2008) Long-term effects of aβ42 immunisation in alzheimer's disease: follow-up of a randomised, placebo-controlled phase i trial. The Lancet 372(9):216–223. doi:10.1016/S0140-6736(08)61075-2. http://www.sciencedirect.com/science/article/pii/S0140673608610752

Khalil HK (1996) Nonlinear systems. Prentice Hall, Upper Saddle River

LaSalle JP (1976) The stability of dynamical systems. In: CBMS-NSF regional conference series in applied mathematics SIAM

Laurén J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM (2009) Cellular prion protein mediates impairment of synaptic plasticity by amyloid-β oligomers. Nature 457(7233):1128–1132

Laurençot P, Walker C (2007) Well-posedness for a model of prion proliferation dynamics. J Evol Equ 7(2):241–264

Lomakin A, Chung DS, Benedek GB, Kirschner DA, Teplow DB (1996) On the nucleation and growth of amyloid beta-protein fibrils: detection of nuclei and quantitation of rate constants. Proc Natl Acad Sci USA 93(3):1125–1129

Lomakin A, Teplow DB, Kirschner DA, B BG, (1997) Kinetic theory of fibrillogenesis of amyloidβ-protein. Proc Natl Acad Sci USA 94(15):7942–7947

Nath S, Agholme L, Kurudenkandy FR, Granseth B, Marcusson J, Hallbeck M (2012) Spreading of neurodegenerative pathology via neuron-to-neuron transmission of β-amyloid. J Neurosci 32(26):8767–8777

Nygaard HB, Strittmatter SM (2009) Cellular prion protein mediates the toxicity of beta-amyloid oligomers: implications for Alzheimer disease. Arch Neurol 66(11):1325

Portet S, Arino J (2009) An in vivo intermediate filament assembly model. Math Biosci Eng 6(1):117–134

Prigent S, Ballesta A, Charles F, Lenuzza N, Gabriel P, Tine LM, Rezaei H, Doumic M (2012) An efficient kinetic model for assemblies of amyloid fibrils and its application to polyglutamine aggregation. PLoS One 7(11):e43,273

Prüss J, Pujo-Menjouet L, Webb G, Zacher R (2006) Analysis of a model for the dynamics of prions. Discret Contin Dyn Syst Ser B 6(1):225–235

Resenberger UK, Harmeier A, Woerner AC, Goodman JL, Müller V, Krishnan R, Vabulas RM, Kretzschmar HA, Lindquist S, Hartl FU, Gerd M, Winklhofer KF, Tatzelt J (2011) The cellular prion protein mediates neurotoxic signalling of β-sheet-rich conformers independent of prion replication. EMBO J 30(10):2057–2070

Rubenstein R, Merz PA, Kascsak RJ, Scalici CL, Papini MC, Carp RI, Kimberlin RH (1991) Scrapie-infected spleens: analysis of infectivity, scrapie-associated fibrils, and protease-resistant proteins. J Infect Dis 164(1):29–35

Selkoe DJ (2008) Soluble oligomers of the amyloid β-protein impair synaptic plasticity and behavior. Behav Brain Res 192(1):106–113

Serpell LC (2000) Alzheimers amyloid fibrils: structure and assembly. Biochim Biophys Acta Mol Basis Dis 1502(1):16–30

Simonett G, Walker C (2006) On the solvability of a mathematical model for prion proliferation. J Math Anal Appl 324(1):580–603

Urbanc B, Cruz L, Buldyrev S, Havlin S, Irizarry M, Stanley H, Hyman B (1999) Dynamics of plaque formation in Alzheimer's disease. Biophys J 76(3):1330–1334

Vincent B, Cisse MA, Sunyach C, Guillot-Sestier MV, Checler F (2008) Regulation of β app and prpc cleavage by α-secretase: mechanistic and therapeutic perspectives. Curr Alzheimer Res 5(2):202–211

Walsh DM, Lomakin A, Benedek GB, Condron MM, Teplow DB (1997) Amyloid β-protein fibrillogenesis detection of a protofibrillar intermediate. J Biol Chem 272(35):22,364–22,372

Wimo A, Prince M (2010) World Alzheimer report 2010: the global economic impact of dementia. Technical report, Alzheimer's Disease International

Zou WQ, Zhou X, Yuan J, Xiao X (2011) Insoluble cellular prion protein and its association with prion and Alzheimer diseases. Prion 5(3):172–178