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ALZHEIMER'S DISEASE AND PRION: AN *IN VITRO* MATHEMATICAL MODEL

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Abstract. Alzheimer's disease (AD) is a fatal incurable disease leading to progressive neuron destruction. AD is caused in part by the accumulation in the brain of Aβ monomers aggregating into oligomers and fibrils. Oligomers are amongst the most toxic structures as they can interact with neurons *via* membrane receptors, including PrP^c proteins. This interaction leads to the misconformation of PrP^c into pathogenic oligomeric prions, PrP^{ol}.

We develop here a model describing *in vitro* Aβ polymerization process. We include interactions between oligomers and PrP^c, causing the misconformation of PrP^c into PrP^{ol}. The model consists of nine equations, including size structured transport equations, ordinary differential equations and delayed differential equations. We analyse the well-posedness of the model and prove the existence and uniqueness of the solution of our model using Schauder fixed point and Cauchy-Lipschitz theorems. Numerical simulations are also provided to some specific profiles.

1. Introduction.

1.1. **Alzheimer's disease and interaction with prions.** According to the World Alzheimer Report, in 2015 more than 46 million people were living with dementia worldwide [35]. With 60% to 80% dementia cases, Alzheimer's disease (AD) is considered as the most common dementia subtype [38]. AD is a fatal incurable

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disease leading to progressive neuron destruction, with memory impairment, issues to perform daily tasks and behaviour changes as main consequences.

Aβ monomers. Alzheimer's disease is mainly caused by the accumulation of Aβ monomers inside the brain [25]. Aβ monomers are obtained from an abnormal cleavage of amyloid precursor proteins, that lead Aβ to be released outside the neuron [33]. These monomers are composed of 39 to 43 amino acids and are present in both normal and diseased brain tissues [23]. Most common forms of monomers are those composed by 40 amino acids (Aβ -40) and by 42 amino acids (Aβ -42) [7].

Polymerization of Aβ monomers: two pathways. It has been shown that Aβ monomers have the ability to polymerize following two pathways:

1. One of them is the fibrillation pathway described by the canonical elongation process [29]. It is important to note for the modelling formulation that these amyloid fibrils are able to depolymerize at any size (denoted x in our equations) [9] which involves the reversibility of this process.
2. The second pathway is called oligomerization. Alike fibrillation, elongation through polymerization and depolymerization are similar up to a certain threshold size (denoted x_0 in our equations). Before size x_0 is reached, fibrils are called proto-oligomers. But once this threshold size has been reached, a highly stable Aβ assembly, called oligomer is formed.

Two structures, two behaviours. Oligomers have been proven to appear structurally distinct from Aβ fibrils [32], [3]. Thus, oligomers neither depolymerize nor split into proto-oligomers or any kind of fibrils of smaller size. This is one of the reasons why our mathematical model need to distinguish these two pathways.

An other structure: the amyloid plaque. Insoluble oligomers and fibrils eventually accumulate to form amyloid plaques [2]. In these plaques, fibrils can depolymerize while oligomers cannot. This process may then lead to a potential source of monomers. This has been added in the model too.

Role of the Aβ-42 from Aβ-40 ratio. Another important point resides in distinguishing Aβ-42 from Aβ-40. The biological reason behind this assumption relies in the fact that the two monomer forms oligomerize in different ways [23]. Indeed, Aβ-42 monomers tend to aggregate faster than Aβ-40 and to form larger polymers [7].

Furthermore, in [7] it is actually reported that the Aβ-42 monomer concentration is about 10% of Aβ-40 concentration. And the Aβ-42/Aβ-40 ratio is known as being one of the causes of the Alzheimer disease onset as well as propagation speed [23].

This is why these two sub-populations will appear also in our equations (with a i as index, $i = 1$ for Aβ-40 population, and $i = 2$ for Aβ-42). Note that from a formulation point of view, they will be very similar. But from a qualitative and quantitative side, their different polymerization and depolymerization rates may bring important changes as shown in the numerical simulations section.

Thus, Aβ oligomers are the most toxic form of Aβ , as they are able to directly interact with neurons, *via* membrane receptors, and cause cytotoxic damages [16, 31].

The deadly prion-Aβ interaction. Finally, it is well documented now that several neurotoxic pathways involving Aβ oligomers have been proposed [16], [24], [26]. One in particular kept our attention. It has been indeed recently reported that the binding of Aβ oligomers to prion protein PrP^c under its non-pathogenic

monomeric conformer, is involved in a death-signal transduction into the neurons through the oligomerization of PrP^c [26], [17] into its pathological form PrP^{ol} .

With a still unclear molecular mechanisms of this transduction signal, PrP^{ol} has been proven to be involved in the dead signal transduction [10], [17], [27].

From the physical-chemistry point of view, and thus our mathematical modelling strategy, this PrP^c- Aβ interaction leads to PrP^{ol} in two steps:

1. first both Aβ and PrP^cform complex [13], [15].
2. second, after a fixed period of time that corresponds to a structural rearrangement [22] this PrP^c-Aβ interaction produces PrP^c oligomerization into PrP^{ol} while Aβ are recycled by being recruited again to interact with PrP^c.

This leads necessarily to a large production of PrP^{ol} and thus to a dramatic increase of neuron deaths. Memory impairment results from this process which eventually ends in a fatal issue.

These interactions and the role of each species are difficult to study through biological experiments. This is the reason why mathematical modelling may help to identify and understand the complex mechanisms of AD, in order to bring an overall view for biologists.

1.2. **Alzheimer's disease and prions formation modeling.** There exists a variety of mathematical models that study mechanisms of AD, especially aggregation of Aβ monomers and plaque formation (see for instance [1, 5, 11, 30, 39]). These models are usually based on Becker-Döring equations [4] or Smoluchowski equations [37] to describe polymer lengthening.

Several mathematical models have also been developed to study PrP^c proliferation only ([8, 12, 14, 19, 36], to cite a few). In these models, PrP^c monomers are supposed to aggregate and form pathological prions PrP^{sc}(where sc stands for scrapie). PrP^c are then able to split in two, increasing their number.

However, to the best of our knowledge, only one mathematical model integrates both Aβ oligomers and PrP^c. This model, proposed by Helal *et al.* [21], describes *in vivo* dynamics of Aβ oligomers and PrP^c. Authors assumed that Aβ oligomers can bind to PrP^c, providing a death signal to the neuron, or polymerize into fibrils, leading to plaque formation. However they did not consider the whole process of polymerization, the different types of oligomers, nor PrP^{ol} catalysis by Aβ .

1.3. **Objectives.** Our aim herein is to introduce and study a new model describing the evolution of Aβ polymers and their interactions with PrP^c. We study these mechanisms at the protein level and in a *in vitro* context. We describe Aβ polymerization process and the role of Aβ in the misconformation of PrP^c. As mentioned previously, we also distinguish Aβ -40 from Aβ -42, as they oligomerize in different ways and they ratio impacts the emergence of AD.

These are the reasons why we are interested in modelling distinctly the two dynamics, with different parameter values.

The challenging question which is one of our main result in this present work resides in proving existence of mild solutions of the monomers and polymers populations. Indeed, as introduced in the section 2.2, the polymerization and depolymerization velocities v_i and $v_{f,i}$ depend both on monomer populations and thus change their sign constantly. From a mathematical point of view, this part, as shown below is not easy, and required from us to redefine what a mild solution is in our context.

We also prove, in a more standard way, solutions and uniqueness of prion populations, through delay differential equations. We finally give some numerical simulations to illustrate some of the population behaviours under specific cases.

Note that since *in vitro* experiments are still under process, we are unable to proceed to any parameter estimate for the moment. Besides, even if a sensitivity analysis has been done in a discrete version of this problem [20], we keep this part to a future work, when a comparison with biological data is possible.

Our main focus here is to introduce this full PrP^c-Aβ interaction model, and mathematically prove well-posedness of the solutions.

This paper is organized as follows. In section 2, we first present the mathematical model proposed to describe *in vitro* dynamics of Aβ and prions. In section 3 we investigate its well-posedness by presenting our main results proven in section 4 and 5. Finally, in section 6 we present some numerical simulations and discuss our results.

2. Mathematical modelling.

We choose to build our model in an *in vitro* context, as, to the best of our knowledge, only *in vitro* data will to be available and provided in a short future. And so, to obtain a consistent qualitative behaviour in a first step, then to quantitatively estimate parameters, we decide to study only *in vitro* mechanisms. We therefore consider no source term of monomers or prions and no degradation of any proteins involved either. We study evolution and impact of Aβ seeded at time $t = 0$ in an environment containing PrP^c.

As mentioned in the introduction, Aβ -40 (respectively Aβ -42) monomers are able to aggregate to form small polymers that can polymerize and depolymerize into bigger structures, by attaching or loosing one monomer. These structures as referred to as Aβ -40 (respectively Aβ -42) proto-oligomers. Once these proto-oligomers reach a maximal size x_0, they are supposed to become stable structures called oligomers. We also consider that Aβ -40 (respectively Aβ -42) monomers can form Aβ -40 (respectively Aβ -42) fibrils in addition to proto-oligomers. These fibrils can polymerize and depolymerize, and can be carried out to β-amyloid plaques (*in vivo* by astrocytes). In our *in vitro* model, we assume the existence of one big amyloid plaque in which fibrils can still depolymerize. This makes some sense here since only concentration measurement will be experimentally provided. Which means, no spatial structure taken into account (this is left for a future work dealing with an *in vivo* description of the process). Therefore monomers can be released from there. For both proto-oligomers and fibrils, we assume that they cannot be composed by a mix of Aβ -40 and Aβ -42 monomers.

Once they have reached the maximal size x_0, Aβ oligomers are able to interact with prions PrP^c, and misfold them into PrP^{ol} . It requires a fixed duration τ during which Aβ oligomer and PrP^c form a complex. Once the process ends, the oligomer is released and can bind to an other prion. Aβ oligomers can also be carried out to β-amyloid plaque (*in vivo* by astrocytes). We assume that they are gathered into the same plaque as fibrils, with the difference that oligomers cannot depolymerize.

2.1. Notations.

To study the evolution of different concentrations, defined at time $t \geqslant 0$, let us denote by:

- $m_i(t)$: concentration of Aβ monomers,
- $u_i(t, x)$: size density of Aβ proto-oligomers, with $0 \leqslant x < x_0$,
- $f_i(t, x)$: size density of Aβ fibrils, with $x \geqslant 0$,
- $f_{a,i}(t, x)$: size density of Aβ fibrils inside Aβ plaque, with $x \geqslant 0$,

- $u_i^0(t)$: concentration of Aβ oligomers,
- $u_{a,i}(t)$: concentration of Aβ oligomers inside Aβ plaque,
- $p_c(t)$: concentration of $\mathrm{PrP^c}$,
- $p_{ol}(t)$: concentration of $\mathrm{PrP^{ol}}$,
- $C_i(t)$: concentration of complex Aβ /$\mathrm{PrP^c}$,

where $i = 1$ (respectively $i = 2$) stands for Aβ -40 (respectively Aβ -42). Definitions of model parameters (rates and growth velocities) are reported in Table 1.

Parameter/ Variable	Definition
t	Time
x	Size of fibrils and proto-oligomers
x_0	Maximal size of Aβ proto-oligomers
$\mu(x)$	Spontaneous creation of proto-oligomers or fibrils
$v_i(t,x)$	Polymerization/depolymerization rate of Aβ proto-oligomers
$v_{f,i}(t,x)$	Polymerization/depolymerization rate of Aβ fibrils
$g_i(x)$	Rate at which Aβ monomers are added to proto-oligomers
$g_{f,i}(x)$	Rate at which Aβ monomers are added to fibrils
b_i	Rate at which Aβ monomers are lost from proto-oligomers
$b_{f,i}$	Rate at which Aβ monomers are lost from fibrils
$b_{a,i}(t)$	Rate of Aβ monomers escaping amyloid plaque
γ_i	Displacement rate of Aβ oligomers into the plaque
$\gamma_{f,i}$	Displacement rate of Aβ fibrils into the plaque
δ_i	Reaction rate between Aβ oligomers and $\mathrm{PrP^c}$
τ	Duration of $\mathrm{PrP^{ol}}$ catalysis, with Aβ oligomers

Table 1. Description of model parameters. Parameters are given for $i = 1, 2$, $i = 1$ corresponding to parameters related to Aβ -40.

Figure 1 displays a schematic representation of the whole model, with all interactions that are taken into account between the different structures.

2.2. **Model for Aβ -40 and -42 polymerization.** The first submodel describing the process of Aβ -40 and Aβ -42 polymerization formally consists of six partial differential equations and two ordinary differential equations (system (I)). As the equations are similar for both Aβ -40 and Aβ -42, we give the model for $i = 1, 2$, where $i = 1$ refers to the model for Aβ -40. Our model is based on Lifshitz-Slyozov equations [28], describing the growth process of grains, with a continuous size x.

$$
\begin{cases}
\partial_t u_i(t,x) + \partial_x(v_i(t,x)u_i(t,x)) = \mu(x)m_i(t), & (1)\\
\partial_t f_i(t,x) + \partial_x(v_{f,i}(t,x)f_i(t,x)) = \mu(x)m_i(t) - \gamma_{f,i}f_i(t,x), & (2)\\
\partial_t f_{a,i}(t,x) - b_{a,i}(t)\partial_x f_{a,i}(t,x) = \gamma_{f,i}f_i(t,x), & (3)\\
\dot{m}_i(t) = & \\
-m_i(t)\left(\displaystyle\int_0^{+\infty} x\mu(x)dx + \int_0^{x_0} x\mu(x)dx + \int_0^{+\infty} g_{f,i}(x)f_i(t,x)dx + \int_0^{x_0} g_i(x)u_i(t,x)dx\right) & \\
\qquad + b_{a,i}(t)\displaystyle\int_0^{+\infty} f_{a,i}(t,x)dx + b_{f,i}\int_0^{+\infty} f_i(t,x)dx + b_i\int_0^{x_0} u_i(t,x)dx, & (4)
\end{cases}
$$

with $t \in [0, +\infty)$ and $x \in [0, x_0)$ in equation (1) and $x \in [0, +\infty)$ in equations (2)–(3).

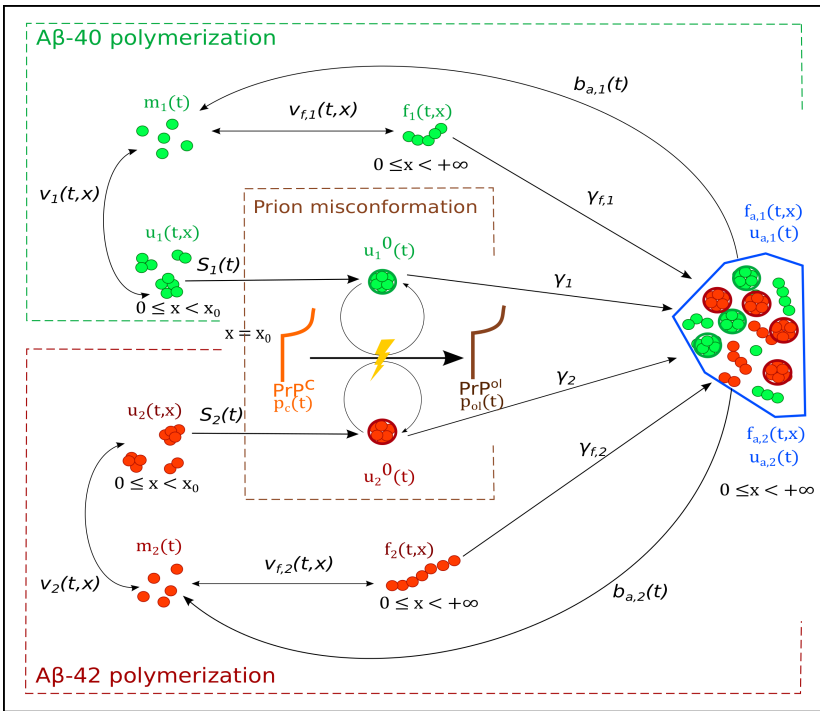

Figure 1. Schematic representation of Aβ polymerization processes and interactions with PrP^c prions. All parameters, quantities and interactions are described in the main text.

Equations (1)–(2) describe Aβ polymerization in proto-oligomers or fibrils, through standard size structured advection-reaction equations. As proposed in [18], the polymerization rates are given by:

$$\begin{cases} v_i(t,x) = g_i(x)m_i(t) - b_i, \quad (t,x) \in [0,+\infty) \times [0,x_0), \\ v_{f,i}(t,x) = g_{f,i}(x)m_i(t) - b_{f,i}, \quad (t,x) \in [0,+\infty) \times [0,+\infty), \end{cases}$$

for $i = 1, 2$. We further assume that g_i and $g_{f,i}$ are increasing functions of x. Thus, these rates express a constant depolymerization of all polymers, while the polymerization process is accelerated by a high concentration of monomers and facilitated for longer polymers. Further assumptions on polymerization rates are given in Hypothesis 1.

Hypothesis 1. *Polymerization rates*

Rates v_i and $v_{f,i}$, for $i = 1, 2$, are required to satisfy the following conditions:

- $b_i > 0, \quad b_{f,i} > 0,$
- $g_i(0) = 0, \quad g_{f,i}(0) = 0, \quad \lim\limits_{x\to+\infty} g_i(x) = +\infty, \quad \lim\limits_{x\to+\infty} g_{f,i}(x) = +\infty,$
- $g_i \in C^0([0,+\infty)) \cap C^1((0,+\infty)), \quad g_{f,i} \in C^0([0,+\infty)) \cap C^1((0,+\infty)),$
- for all $\varepsilon_0 > 0$, there is a constant $G_i > 0$, such as for all $x \geqslant \varepsilon_0$, $0 \leqslant g_i'(x) \leqslant G_i$,
- for all $\varepsilon_0 > 0$, there is a constant $G_{f,i} > 0$, such as for all $x \geqslant \varepsilon_0$, $0 \leqslant g_{f,i}'(x) \leqslant G_{f,i}$.

It is important to note that for each time t, there exists a critical size $\overline{x}(t) > 0$, for which polymerization rate is null, this critical size depending of the monomer concentration at time t. Therefore, polymers of size smaller than $\overline{x}(t)$ depolymerize whereas polymers of size greater than $\overline{x}(t)$ tend to attach more monomers. This phenomenon is referred to as Ostwald ripening [34]. Let us remark that $\overline{x}(t)$ can be greater than x_0, and all proto-oligomers depolymerize in this case.

Finally, the term $\mu(x)$ in equations (1)–(2) represents the ability of monomers to spontaneously aggregate in polymers smaller than x_0, to start the polymerization process. In our model, this function allows the creation of small proto-oligomers that could otherwise not exist due to the depolymerization of small polymers.

Hypothesis 2. *Function μ*

We assume that μ is a positive function with compact support, defined for all x in $[0, +\infty)$. Moreover, the function μ is in $L^1([0, +\infty), (1 + x)dx) \cap L^\infty([0, +\infty))$.

Finally, equation (4), describing the evolution of Aβ monomers, is given by the gain and loss in monomer from every fibrils and proto-oligomers.

To complete the system, initial conditions are given by:

$$\begin{cases} u_i(t = 0, x) = u_i^{in}(x) \geqslant 0, & x \in [0, x_0), \\ f_i(t = 0, x) = f_i^{in}(x) \geqslant 0, & x \in [0, +\infty), \\ f_{a,i}(t = 0, x) = f_{a,i}^{in}(x) \geqslant 0, & x \in [0, +\infty), \\ m_i(0) = m_i^0 > 0. \end{cases} \tag{5}$$

We further assume that:

Hypothesis 3. *Initial conditions* Initial condition u_i^{in} is in $L^1([0, x_0), (1 + x)dx) \cap L^\infty([0, x_0))$. Initial conditions f_i^{in} and $f_{a,i}^{in}$ are in $L^1(\mathbb{R}+, (1 + x)dx) \cap L^\infty(\mathbb{R}+)$.

We also need boundary conditions in $x = x_0$, for proto-oligomers:

$$\lim_{x \to x_0} u_i(t, x) = 0, \quad \text{if} \quad v_i(t, x_0) \leqslant 0, i = 1, 2. \tag{6}$$

This condition represents the fact that no oligomers of size x_0 depolymerize, even if the rate of polymerization is negative. From Hypothesis 1 let mention that no boundary condition is required at $x = 0$, for the simple reason that the polymerization/depolymerization rates for proto-oligomers and fibrils are negative when x tends to 0.

2.3. **Model for Aβ -Prion interaction.** We now introduce the second submodel, describing the interactions between Aβ oligomers and PrP^c. Misconformation process of PrP^c into PrP^{ol} takes an incompressible duration, denoted τ, during which Aβ oligomer and PrP^c form a complex. The oligomer is then released and can bind to another PrP^c. This reaction leads to a system of delayed differential equations (system (II)):

$$\begin{cases} \dot{u}_i^0(t) = S_i(t) - \gamma_i u_i^0(t) - \delta_i p_c(t) u_i^0(t) + \delta_i p_c(t - \tau) u_i^0(t - \tau), & (7) \\ \dot{u}_{a,i}(t) = \gamma_i u_i^0(t), & (8) \\ \dot{p}_c(t) = -\delta_1 p_c(t) u_1^0(t) - \delta_2 p_c(t) u_2^0(t), & (9) \\ \dot{p}_{ol}(t) = \delta_1 p_c(t - \tau) u_1^0(t - \tau) + \delta_2 p_c(t - \tau) u_2^0(t - \tau), & (10) \\ \dot{C}_i(t) = \delta_i p_c(t) u_i^0(t) - \delta_i p_c(t - \tau) u_i^0(t - \tau), & (11) \end{cases}$$

for $t \in [\tau, +\infty)$, and $i = 1, 2$, $i = 1$ corresponding to equations for Aβ -40 .

Equation (7) describes the evolution of Aβ -40 and Aβ -42 oligomers, with time. The first term $S_i(t)$ stands for the source term of oligomers. It represents the creation rate of Aβ oligomers from proto-oligomers that reached the maximal size x_0, and is the coupling with the previous system. The last terms describe the interaction between Aβ oligomers and PrP^c, leading to the formation of PrP^{ol} after a duration of τ units of time. Equation (8) describes the displacement of Aβ oligomers into amyloid plaques. Finally, equations (9)–(11) describe the evolution of prions and complexes.

We assume that PrP^c are the only prion proteins initially in the experiment, *ie* all initial conditions at $t = 0$ are null, except for $p_c(0)$, which is equal to p_c^0 and is positive. Then, on $[0, \tau)$, the model is described using equations (7)–(11), without any delayed part, as no PrP^{ol} and oligomer are released from a complex during the first τ units of time.

We now want to determine the expressions of $S_1(t)$ and $S_2(t)$, representing the source terms of Aβ -40 and Aβ -42 oligomers, that is the coupling between the first submodel and this second one. To do so, we use the property of mass conservation of the system. Indeed, as we are in an *in vitro* context, the total mass $Q(t)$ remains the same during the study (no source term and no loss). We first compute the value of Q, denoting m_p the size of a prion PrP^c or PrP^{ol} :

$$Q(t) = \sum_{i=1}^{2}\Bigg(m_i(t) + \int_0^{+\infty} x f_i(t,x)dx + \int_0^{+\infty} x f_{a,i}(t,x)dx + \int_0^{x_0} x u_i(t,x)dx + x_0(u_i^0(t) + u_{a,i}(t))\Bigg) + m_p(p_c(t) + p_{ol}(t)) + (x_0 + m_p)(C_1(t) + C_2(t)). \tag{12}$$

We then compute $\dot{Q}(t)$, using equations (1)–(4) and (7)–(11). We finally obtain:

$$\dot{Q}(t) = x_0\left(S_1(t) - v_1(t,x_0)\lim_{x\to x_0} u_1(t,x) + S_2(t) - v_2(t,x_0)\lim_{x\to x_0} u_2(t,x)\right),$$

which must be equal to zero. This equation gives sufficient conditions on S_i:

$$S_i(t) = v_i(t,x_0)\lim_{x\to x_0} u_i(t,x), \quad i = 1,2. \tag{13}$$

This condition gives an expression for the source term of oligomers, which is exactly the flow of proto-oligomers reaching the size x_0. We can note that these source terms are non-negative, thanks to condition (6), and continuous.

3. Main results.

3.1. Existence of solutions for the system (I).

To show the existence of solutions for the system (I), we based our analysis on the notion of "mild" solutions by introducing the characteristic curves associated to the kinetic rates at which monomers are added to or removal from fibrils or proto-oligomers. In the following definition we specify how "mild" solutions to equations (1)-(3) should be understood:

Definition 1. *Mild solutions*

Let $L \in (0,\infty)$, $T > 0$; $a, b : [0,T] \times [0,L) \to \mathbb{R}$ and $u_0 : [0,L) \to \mathbb{R}$. We assume that a is a continuous function and satifies

- a is a $\mathcal{C}^1$ function in variable x on $(0,L)$,
- a is a globally Lipschitz function in x uniformally in time t on $[\varepsilon_0, L)$ for all $\varepsilon_0 \in (0,L)$,
- $a(t,0) < 0$ for all $t \in [0,T]$.

We also assume that b is a continuous function with respect to t and x.

Let consider the linear transport problem that consists to find a solution $U : [0,T] \times [0,L) \to \mathbb{R}$ such that

$$\begin{cases} \partial_t U + \partial_x(aU) = b, & (t,x) \in [0,T] \times [0,L), \\ U(t=0,x) = U_0(x), & x \in [0,L) \end{cases} \tag{14}$$

where in the case $L < \infty$ we add the following boundary condition:

$$U(t,L) = 0 \ \text{ if } a(t,L) \leq 0. \tag{15}$$

Let $s \to X(s,t,x)$ the characteristic curve defined for $t \in [0,T]$ and $x \in (0,L)$ by

$$\begin{cases} \dfrac{d}{ds}X(s,t,x) & = a(s,X(s,t,x)), \\ X(t,t,x) & = x. \end{cases} \tag{16}$$

Considering $a_1(t,x) = \frac{\partial a}{\partial x}(t,x)$ the function defined in $[0,T] \times (0,L)$, we denote by $V_{t,x}$ the largest interval of all $s \in [0,T]$ such that $X(s,t,x) \in (0,L)$ for all $t \in [0,T]$. We denote also $\bar{s} = \bar{s}(t,x) = \inf V_{t,x}$.

So, we call U to be a "mild" solution of (14)-(15) if for all $(t,x) \in [0,T] \times (0,L)$ we have that the function $s \in V_{t,x} \to U(s,X(s,t,x))$ satisfies the following system

$$\begin{cases} \dfrac{d}{ds}U = -a_1(s,X(s,t,x))U + b(s,X(s,t,x)), & forall\ s \in V_{t,x}, \\ U(0,X(0,t,x)) = U_0(X(0,t,x)), & \text{if } \bar{s} = 0, \\ U(\bar{s},X(\bar{s},t,x)) = 0, & \text{if } \bar{s} > 0. \end{cases} \tag{17}$$

With the previous definition, one can remark that $X(\bar{s},t,x)$ is defined as the continuous extension of $X(s,t,x)$ at $\bar{s} \in \overline{V}_{t,x}$. Such extension always exists.

Theorem 1. ***Existence of solutions for system (I)***

Let ***Hypotheses 1, 2 and 3*** *hold. Then, for non-negative initial conditions, there exists T in $(0,+\infty)$ such that the system (I) has a unique non-negative "mild" solution $(u_i, f_i, f_{a,i}, m_i)$ defined for any t in $[0,T]$. Moreover : u_i is in $L^\infty([0,T] \times [0,x_0)) \cap L^\infty([0,T]; L^1([0,x_0),(1+x)dx) \cap C^0([0,T]; L^1([0,x_0)))$, f_i and $f_{a,i}$ are in $L^\infty([0,T] \times \mathbb{R}_+) \cap L^\infty([0,T]; L^1(\mathbb{R}_+,(1+x)dx)) \cap C^0([0,T]; L^1(\mathbb{R}_+))$ and m_i is in $L^\infty([0,T]) \cap C^0([0,T])$.*

Proof of existence of solutions follows an iterative process which is based on the fact that for a given function $\tilde{m}_i$, we can compute the mild solutions $\tilde{u}_i$, $\tilde{f}_i$ and $\tilde{f}_{a,i}$, $i = 1,2$. Using these mild solutions, we can now compute m_i as the solution of equation (4). We build an application h that links each function $\tilde{m}_i$ to the function m_i, and show that it admits a fixed point, using Schauder fixed point theorem. This implies the existence of at least one solution of our model, corresponding to this fixed point. The whole proof is presented in section 4.

3.2. **Existence of solutions for the system (II).** We now focus on the system of delayed differential equations. We state our main results for this submodel.

Theorem 2. *System (II) admits a unique solution on $[0,+\infty)$. Besides, these solutions are non-negative for non-negative initial conditions.*

We first prove existence and uniqueness of solutions on $[0,\tau)$ with Cauchy-Lipschitz theorem, and extend this result to well-chosen time intervals, likewise for the non-negativity. The whole proof is given in section 5.

4. System (I)-Proof of the main results.

4.1. Mild solutions.

Lemma 1. *Let m_i, $i = 1, 2$ be a continuous function defined for all t in $[0, T]$, with $T > 0$. We assume that **Hypotheses 1, 2 and 3** are satisfied. Then, there exist unique mild solutions u_i, f_i and $f_{a,i}$, $i = 1, 2$ of equations (1)-(3) and they verify, for all t in $[0, T]$:*

$$\begin{cases} \displaystyle\int_0^{x_0} u_i(t,x)dx \leqslant ||u_i^{in}||_{L^1} + ||\mu||_{L^1} \int_0^t m_i(s)ds, \\ \displaystyle\int_0^{x_0} g_i(x)u_i(t,x)dx \leqslant ||g_i u_i^{in}||_{L^1} + ||g_i\mu||_{L^1} \int_0^t m_i(s)ds, \\ \displaystyle\int_0^{+\infty} f_i(t,x)dx \leqslant ||f_i^{in}||_{L^1} + ||\mu||_{L^1} \int_0^t m_i(s)ds, \\ \displaystyle\int_0^{+\infty} g_{f,i}(x)f_i(t,x)dx \leqslant ||g_{f,i} f_i^{in}||_{L^1} + ||g_{f,i}\mu||_{L^1} \int_0^t m_i(s)ds, \\ \displaystyle\int_0^{+\infty} f_{a,i}(t,x)dx \leqslant ||f_{a,i}^{in}||_{L^1} + \gamma_{f,i}(||f_i^{in}||_{L^1} + ||\mu||_{L^1} \int_0^t m_i(s)ds). \end{cases} \tag{18}$$

Proof. **Equation (1)**:

For $i = 1, 2$, we rewrite as follow the equation (1) which models the dynamics of the two family of proto-oligomers (Aβ -40 and Aβ -42)

$$\begin{cases} \dfrac{\partial u_i}{\partial t} + \dfrac{\partial (v_i u_i)}{\partial x} = \mu(x) m_i(t), & t \in [0,T];\ x \in (0, x_0), \\ u_i(0,x) = u_i^{\text{in}}(x), & x \in (0, x_0), \\ u_i(t, x_0) = 0, & \text{if } v_i(t, x_0) \leq 0,\ t \in [0,T], \\ v_i(t,x) = g_i(x) m_i(t) - b. \end{cases}$$

Using the method of characteristics as depicted in **Definition 1** of "mild" solution, we obtain

$$u_i(t,x) = \tilde{u}_i^{in}(\bar{s}, X_{u,i}(\bar{s}; t, x)) J_{u,i}(\bar{s}; t, x) + \int_{\bar{s}}^t \mu(X_{u,i}(s; t, x)) m_i(s) J_{u,i}(s; t, x) ds \tag{19}$$

where $\tilde{u}_i^{in}(\sigma, y) = \begin{cases} 0 & \text{if } \sigma > 0, \\ u_i^{\text{in}}(y) & \text{if } \sigma = 0 \end{cases}$ is defined in the set $\{t = 0\} \cup \{x = x_0\}$ of the boundary of the domain of (t, x), $J_{u,i}(s; t, x) = \exp(-\int_s^t \partial_x v_i(\sigma, X_{u,i}(\sigma; t, x)) d\sigma)$ is the Jacobian and $X_{u,i}$ is the characteristic curve associated v_i.

For $\bar{s}$, on can easily check, by using the argument that characteristics not cross each other, that:

i) For all fixed $t \in (0, T]$, the function $x \in (0, x_0) \to \bar{s}(t, x)$ is increasing. Therefore, for all $t \in (0, T]$ the following limit exists: $\lim\limits_{x \to x_0, x < x_0} \bar{s}(t, x)$ and we denote it by $\bar{s_0}(t)$.

ii) For all fixed $t \in (0, T]$, for all $x_1, x_2 \in (0, x_0)$ with $x_1 < x_2$ and for all $\sigma \in V_{t,x_1} \cap V_{t,x_2}$ we have $X(\sigma; t, x_1) < X(\sigma; t, x_2)$.

Lemma 2. *With the additional assumption: u_i^{in} continuous on $[0, x_0]$, one obtains for all $t \in (0, T]$ the existence of the following limit $\lim\limits_{x \to x_0, x < x_0} u_i(t, x)$ that we denote by $\bar{u}_i(t)$.*

The proof of the lemma 2 stands on two cases:

case 1: Let assume $\bar{s_0}(t) = 0$. So, we have $\bar{s}(t,x) = 0$ for all $x < x_0$ and the "mild" solution take the form

$$u_i(t,x) = u_i^{in}(X_{u,i}(0;t,x))J_{u,i}(0;t,x) + \int_0^t \mu(X_{u,i}(s;t,x))m_i(s)J_{u,i}(s;t,x)ds.$$

Let denote by $X^0_{u,i}(s,t)$ the limit $\lim\limits_{x\to x_0, x<x_0} X_{u,i}(s;t,x)$ for all $s \in (0,t]$. Using the dominated convergence theorem of Lebesgue, one has the existence of the limit $\lim\limits_{x\to x_0, x<x_0} J_{u,i}(s;t,x)$ because $\dfrac{\partial v_i}{\partial x}$ is bounded on $[0,T]\times[\varepsilon_0, x_0)$ for all $\varepsilon > 0$ and the characteristic $X_{u,i}(\sigma;t,x)$ is far from 0. We denote by $J^0_{u,i}$ this limit that means $\lim\limits_{x\to x_0, x<x_0} J_{u,i}(s;t,x) = J^0_{u,i}(s,t)$.

We apply again the dominated convergence theorem of Lebesgue and deduce from the previous form of the "mild solution" the existence of the limit

$$\lim_{x\to x_0, x<x_0} u_i(t,x) = u_i^{in}(X^0_{u,i}(0,t))J^0_{u,i}(0,t) + \int_0^t \mu(X^0_{u,i}(s,t))m_i(s)J^0_{u,i}(s,t)ds.$$

case 2: Let assume $\bar{s_0}(t) > 0$. For this case there exists $x_t \in (0,x_0)$ such that $\bar{s}(t,x) > 0$ for all $x \in (x_t, x_0)$. So we get the following expression for the "mild" solution

$$u_i(t,x) = \int_{\bar{s}(t,x)}^t \mu(X_{u,i}(s;t,x))m_i(s)J_{u,i}(s;t,x)ds.$$

Let consider the sequence $(x_k)_{k\in\mathbb{N}} \to x_0$, with $x_k < x_0$ and let prove the following convergence

$$u_i(t,x_k) \underset{k\to+\infty}{\longrightarrow} \int_{\bar{s_0}(t)}^t \mu(X^0_{u,i}(s,t))m_i(s)J^0_{u,i}(s,t)ds. \tag{20}$$

To prove the relation (20) we know that $\bar{s}(t,x_k) < \bar{s_0}(t)$, so one can compute

$$\begin{aligned}
|u_i(t,x_k) - \int_{\bar{s_0}(t)}^t \mu(X^0_{u,i}(s,t))m_i(s)J^0_{u,i}(s,t)ds| \leq \\
|\int_{\bar{s_0}(t)}^t m_i(s)\Big(\mu(X_{u,i}(s,t,x_k))J_{u,i}(s;t,x_k) - \mu(X^0_{u,i}(s,t))J^0_{u,i}(s,t)\Big)ds| \\
+|\int_{\bar{s}(t,x_k)}^{\bar{s_0}(t)} \mu(X_{u,i}(s,t,x_k))m_i(s)J_{u,i}(s;t,x_k)ds.|
\end{aligned}$$

The first term converge to 0 thanks to the dominated convergence theorem of Lebesgue and the second term goes to 0 thanks to the fact that $\bar{s}(t,x_k) \to \bar{s_0}(t)$ and that the term under the integral is bounded. That achieves the proof of the convergence result.

Lemma 3. *Under assumptions of lemma 2, the limit* $\bar{u}_i(t) = \lim\limits_{x\to x_0, x<x_0} u_i(t,x)$ *is a measurable and bounded function which means* $\bar{u}(t)$ *belongs to* $L^\infty(0,T)$.

Proof. In this proof we drop the index i for sake of simplicity.

Let first prove the measurability of $\bar{u}(t)$ thanks to the fact that the function $(t,x) \in [0,T]\times(0,x_0) \to \bar{s}(t,x)$ is measurable (see Annexe 1 for the proof).

Step 1. Let's prove that the "mild" solution given by (19) is a measurable function at (t,x). Let introduce the sets $A_+ = \{(t,x) : \bar{s}(t,x) > 0\}$ and $A_0 = \{(t,x) : \bar{s}(t,x) = 0\}$. We split the solution as follows $u = u^1 + u^2$ where

$$u^1(t,x) = \begin{cases} 0 & \text{if } (t,x) \in A_+, \\ u^{in}(X_u(0,t,x))m(s)J_u(0,t,x) & \text{if } (t,x) \in A_0, \end{cases} \tag{21}$$

$$u^2(t,x) = \int_{\bar{s}(t,x)}^{t} \mu(X_u(s,t,x))m(s)J_u(s,t,x)ds. \tag{22}$$

From the measurability of $\bar{s}$ we deduce that A_+ and A_0 are measurable. Knowing that $(t,x) \to u^{in}(X_u(0,t,x))J_u(0,t,x)$ is a continuous function on A_0, so it is also measurable on A_0. That achieves the proof of the measurability for u^1.

For the measurability of u^2, we put $D = \left\{(t,x,y) \in \mathbb{R}^3 : (t,x) \in [0,T] \times (0,x_0); y \in \overline{V}_{t,x} \cap [0,t[\right\}$ and introduce the function $\phi : D \to \mathbb{R}$ such that $\phi(t,x,y) = \int_y^t \mu(X_u(s,t,x))m(s)J_u(s,t,x)ds$. Let check the continuity of ϕ on D. We consider the sequence $(t_k,x_k,y_k)_{k\in\mathbb{N}} \in D$ such that $(t_k,x_k,y_k) \underset{k\to+\infty}{\longrightarrow} (t,x,y)$. The continuity of ϕ requires to prove the convergence to zero when $k \to +\infty$ of

$$\begin{aligned} &\int_0^T \mu(X_u(s,t_k,x_k))m(s)J_u(s,t_k,x_k)\mathbb{I}_{[y_k,t_k]}(s) \\ &- \mu(X_u(s,t,x))m(s)J_u(s,t,x)\mathbb{I}_{[y,t]}(s)ds. \end{aligned} \tag{23}$$

The relation of equation (23) is based on the dominated convergence theorem of Lebesgue. The fact that the functions under the integral are bounded, it suffices to prove that for all $s \in [0,T] - \{y,t\}$ one obtains $\mu(X_u(s,t_k,x_k))m(s)J_u(s,t_k,x_k)\mathbb{I}_{[y_k,t_k]}(s) \underset{k\to+\infty}{\longrightarrow} \mu(X_u(s,t,x))m(s)J_u(s,t,x)\mathbb{I}_{[y,t]}(s)$.

Case 1. Let assume $s \notin (y,t)$. In this case the result is straightforward because all terms vanish when k is high.

Case 2. Let assume $s \in (y,t)$. So, one need just to show $\mu(X_u(s,t_k,x_k))J_u(s,t_k,x_k) \underset{k\to+\infty}{\longrightarrow} \mu(X_u(s,t,x))J_u(s,t,x)$. Knowing that $y_k \to y$ and $t_k \to t$ then for k large enougth we have $s \in (y_k,t_k)$ that implies s belongs either to $V_{t,x}$ and to V_{t_k,x_k}. So $X_u(s,t_k,x_k) \underset{k\to+\infty}{\longrightarrow} X_u(s,t,x)$ thanks to the continuity of the characteristic equation.

It remains to prove the convergence of the sequence of Jacobian functions and for that we need to prove the following result

$$\int_s^T \left\{ \frac{\partial v}{\partial_x}(\sigma, X_u(\sigma,t_k,x_k))\mathbb{I}_{[s,t_k]}(\sigma) - \frac{\partial v}{\partial_x}(\sigma, X_u(\sigma,t,x))\mathbb{I}_{[s,t]}(\sigma) \right\} d\sigma(\sigma) \underset{k\to+\infty}{\longrightarrow} 0.$$

Here also we base our reasoning on the Lebesgue's dominated convergence theorem and achieve the proof by showing the pointwize convergence of the function under the previous integral for almost every $\sigma \in (s,t)$.

Subcase 2.1. If $\sigma \notin [s,t)$ then the result is straightforward because one obtains $0 \to 0$.

Subcase 2.2. If $\sigma \in [s,t)$ then the fact that $\sigma \in [s,t_k]$ for large k implies that one needs just to prove $\frac{\partial v}{\partial x}(\sigma, X_u(\sigma,t_k,x_k)) \underset{k\to+\infty}{\longrightarrow} \frac{\partial v}{\partial x}(\sigma, X_u(\sigma,t,x))$. The proof stands on the fact that σ is chosen in $V_{t,x} \cap V_{t_k,x_k}$ that implies $X_u(\sigma,t_k,x_k) \underset{k\to+\infty}{\longrightarrow}$

$X_u(\sigma,t,x)$. Then from the continuity of $\dfrac{\partial v}{\partial x}$ with respect to X_u we achieve the proof of the continuity of ϕ on D.

For the measurability of u^2, one can write $u^2=\phi\circ\psi$ with $\psi:[0,T]\times(0,x_0)\to\mathbb{R}^3$ such that $\psi(t,x)=(t,x,\bar{s}(t,x))$. We remark that $g([0,T]\times(0,x_0))\subset D$ and is also measurable because $\bar{s}$ is measurable. Then from Rudin's book [Theorem I. 7, page 10] we obtain that u^2 is a measurable function, which completes **Step 1** of the proof.

Step 2. Knowing that $u(t,x)$ is measurable, we apply the Fubini theorem and deduce the existence of $B\subset(0,x_0)$ with $mes(B)=0$ (the measure of B) such that for all $x\in(0,x_0)$ B the function $t\in[0,T]\to u(t,x)$ is measurable. So, for all $k\in\mathbb{N}^*, \exists\, z_k\in(x_0-\frac{1}{k},x_0)$ such that $t\to u(t,z_k)$ is a measurable function. We have $z_k\to x_0$ then we deduce from Lemma 2 that $u(t,z_k)\underset{k\to+\infty}{\longrightarrow}\bar{u}(t)$ for all $t\in[0,T]$. Then $\bar{u}(t)$ is measurable as limit of measurable sequence.

Now we easily see that u is bounded since we integrate bounded function on bounded intervals. Then we have $\bar{u}\in L^\infty(0,T)$. □

Using the change of variables $y=X_{u,i}(0,t,x)$ in the expression (19), we deduce:

$$\begin{aligned}\int_0^{x_0}u_i(t,x)dx&=\int_0^{x_0}\tilde{u}_i^{in}(X_{u,i}(0;t,x))J_{u,i}(0;t,x)dx\\&\qquad+\int_0^t\left(m_i(s)\int_0^{x_0}\mu(X_{u,i}(s;t,x))J_{u,i}(s;t,x)dx\right)ds,\\&=\int_{X_i(0;t,0)}^{X_i(0;t,x_0)}\tilde{u}_i^{in}(y)dy+\int_0^t m_i(s)\int_{X_i(s;t,0)}^{X_i(s;t,x_0)}\mu(y)dyds,\\&\leqslant||\tilde{u}_i^{in}||_{L^1}+||\mu||_{L^1}\int_0^t m_i(s)ds.\end{aligned}$$

Equation (2). For $i=1,2$, characteristic curves associated to the growth velocity of fibrils $v_{f,i}$ are defined by:

$$\begin{cases}\dfrac{d}{ds}X_{f,i}(s;t,x)=v_{f,i}(s,X_{f,i}(s;t,x)),\\X_{f,i}(t;t,x)=x.\end{cases}\tag{24}$$

As done previously (here, there is no maximal size for the fibrils, $L=\infty$), we obtain the unique mild solution:

$$\begin{aligned}f_i(t,x)=f_i^{in}(X_{f,i}(0;t,x))\mathrm{e}^{-\gamma_{f,i}t}J_{f,i}(0;t,x)\\+\int_0^t\mu(X_{f,i}(s;t,x))m_i(s)\quad\mathrm{e}^{-\gamma_{f,i}(t-s)}J_{f,i}(s;t,x)ds,\end{aligned}$$

where $J_{f,i}(s;t,x)=\partial_x X_{f,i}(s;t,x)=\exp(-\int_s^t\partial_x v_{f,i}(\sigma,X_{f,i}(\sigma;t,x))d\sigma)$ is the Jacobian.

We then have:

$$\int_0^{+\infty}f_i(t,x)dx\leqslant\int_{X_{f,i}(0;t,0)}^{+\infty}f_i^{in}(y)dy+\int_0^t\left(m_i(s)\int_{X_{f,i}(s;t,0)}^{+\infty}\mu(y)dy\right)ds.$$

The estimations are directly derived from this relation.

Equation (3). For the last equations, characteristic curves are defined as follow, for $i = 1, 2$ (no maximal size: $L = +\infty$)

$$\begin{cases} \dfrac{d}{ds} X_{f_a,i}(s;t,x) = -b_{a,i}(s), \\ X_{f_a,i}(t;t,x) = x. \end{cases} \tag{25}$$

So the unique mild solution reads

$$f_{a,i}(t,x) = f_{a,i}^{in}(X_{f_a,i}(0;t,x)) + \gamma_{f,i} \int_0^t f_i(s, X_{f_a,i}(s;t,x))ds,$$

which gives us the last estimation. □

4.2. **Proof of theorem 1.** Let denote by Σ_T the subset of $C([0,T])$ such as:

$$\Sigma_T = \{m_i \in C^0([0,T]) \ / \ 0 \leqslant m_i(t) \leqslant M_T \text{ and } \ m_i(0) = m_i^0\}, \tag{26}$$

where T is in $(0, +\infty)$ and M_T is given by the subset above. We build the following mapping h:

$$h : \begin{cases} \Sigma_T \longrightarrow C^0([0,T]) \\ \tilde{m}_i \longmapsto m_i = h(\tilde{m}_i), \end{cases} \tag{27}$$

with $m_i(t)$ the solution of the following equation:

$$\dot{m}_i(t) = -m_i(t)\tilde{A}_i(t) + \tilde{B}_i(t), \quad i = 1, 2, \tag{28}$$

where

$$\tilde{A}_i(t) = \int_0^{+\infty} x\mu(x)dx + \int_0^{x_0} x\mu(x)dx + \int_0^{+\infty} g_{f,i}(x)\tilde{f}_i(t,x)dx + \int_0^{x_0} g_i(x)\tilde{u}_i(t,x)dx, \tag{29}$$

$$\tilde{B}_i(t) = b_{a,i}(t) \int_0^{+\infty} \tilde{f}_{a,i}(t,x)dx + b_{f,i} \int_0^{+\infty} \tilde{f}_i(t,x)dx + b_i \int_0^{x_0} \tilde{u}_i(t,x)dx, \tag{30}$$

and functions $(\tilde{u}_i, \tilde{f}_i, \tilde{f}_{a,i})$ are solutions of the following system of PDE:

$$\begin{cases} \partial_t \tilde{u}_i(t,x) + \partial_x \left((g_i(x)\tilde{m}_i(t) - b_i)\tilde{u}_i(t,x) \right) = \mu(x)\tilde{m}_i(t), \\ \partial_t \tilde{f}_i(t,x) + \partial_x \left((g_{f,i}(x)\tilde{m}_i(t) - b_{f,i})\tilde{f}_i(t,x) \right) = \mu(x)\tilde{m}_i(t) - \gamma_{f,i}\tilde{f}_i(t,x), \\ \partial_t \tilde{f}_{a,i}(t,x) - b_{a,i}(t)\partial_x \tilde{f}_{a,i}(t,x) = \gamma_{f,i}\tilde{f}_i(t,x). \end{cases} \tag{31}$$

To prove the existence of solutions, we follow a Schauder fixed point theorem.

Lemma 4. *If*

$$0 < T < \frac{1}{\sqrt{||\mu||_{L^1} \max\limits_i (\bar{b}_{a,i}\gamma_{f,i} + b_{f,i} + b_i)}}, \tag{32}$$

with $\bar{b}_{a,i} = \sup\limits_{[0,T]} b_{a,i}(t)$, *then* $h(\Sigma_T)$ *is a subset of* Σ_T.

Proof. Let $(\tilde{u}_i, \tilde{f}_i, \tilde{f}_{a,i})$ be mild solutions of system (31). Then, for all t in $[0,T]$, $\tilde{A}_i$ and $\tilde{B}_i$ are well-defined thanks to lemma 1. Their non-negativity is obvious as soon as initial data verify condition (5).

Equation (28) is an ordinary differential equation and admits a continuous solution on $[0,T]$. This implies that $m_i(t), i = 1, 2$ is bounded by a constant M_T, that can be computed.

$$m_i(t) = m_i(0) \exp\left(-\int_0^t \tilde{A}_i(s)ds \right) + \int_0^t \tilde{B}_i(s) \exp\left(-\int_s^t \tilde{A}_i(\sigma)d\sigma \right) ds.$$

As function $\tilde{A}_i$ is non-negative, we obtain

$$m_i(t) \leqslant m_i(0) + \int_0^t \tilde{B}_i(s)ds \leqslant m_i(0) + T \sup_{[0,T]} \tilde{B}_i(t). \tag{33}$$

We have to determine an upper bound for $\tilde{B}_i(t)$, using equation (30):

$$\tilde{B}_i(t) \leqslant \sup_{[0,T]} \left(b_{a,i}(t) ||\tilde{f}_{a,i}(t,.)||_{L^1} \right) + b_{f,i} \sup_{[0,T]} ||\tilde{f}_i(t,.)||_{L^1} + b_i \sup_{[0,T]} \left(\int_0^{x_0} \tilde{u}_i(t,x)dx \right).$$

Estimations (18) provide the needed upper bounds. Moreover, $\tilde{m}_i$ is upper-bounded by M_T for all t lower than T, as it is in Σ_T. We obtain:

$$\begin{aligned} m_i(t) \leqslant & m_i(0) + T \left(\bar{b}_{a,i} ||f_{a,i}^{in}||_{L^1} + (b_{f,i} + \bar{b}_{a,i}\gamma_{f,i}) ||f_i^{in}||_{L^1} + b_i ||u_i^{in}||_{L^1} \right) \\ & + ||\mu||_{L^1} M_T T^2 (\bar{b}_{a,i}\gamma_{f,i} + b_{f,i} + b_i), \end{aligned}$$

with $\bar{b}_{a,i} = \sup_{[0,T]} b_{a,i}(t)$. This relation gives us the upper bound M_T:

$$\begin{aligned} M_T = & \max_i \left[m_i(0) + T \left(\bar{b}_{a,i} ||f_{a,i}^{in}||_{L^1} + (b_{f,i} + \bar{b}_{a,i}\gamma_{f_i}) ||f_i^{in}||_{L^1} + \left(b_i ||u_i^{in}||_{L^1} \right) \right) \right] \\ & + M_T T^2 ||\mu||_{L^1} \max_i \left(\bar{b}_{a,i}\gamma_{f,i} + b_{f,i} + b_i \right), \end{aligned}$$

$$\begin{aligned} M_T [1 - T^2 ||\mu||_{L^1} \max_i (\bar{b}_{a,i}\gamma_{f,i} + b_{f,i} + b_i)] = & \max_i \left[m_i(0) + T\bar{b}_{a,i} ||f_{a,i}^{in}||_{L^1} \right] \\ & + T \left[\max_i \left(b_{f,i} + \bar{b}_{a,i}\gamma_{f,i} \right) ||f_i^{in}||_{L^1} + b_i ||u_i^{in}||_{L^1} \right]. \end{aligned} \tag{34}$$

Because T verifies relation (32), we have:

$$1 - T^2 ||\mu||_{L^1} \max_i (\bar{b}_{a,i}\gamma_{f,i} + b_{f,i} + b_i) > 0,$$

and the upper bound M_T is well defined. □

Lemma 5. *$h(\Sigma_T)$ is a relatively compact subspace of $C_b^0([0,T])$.*

Proof. We know that $h(\Sigma_T)$ is a bounded subspace of $C_b^0([0,T])$. To use Ascoli theorem, we have to show the uniform equicontinuity of h. Let $\tilde{m}_i$ and $\tilde{n}_i$ be two elements of Σ_T, such as $m_i = h(\tilde{m}_i)$ and $n_i = h(\tilde{n}_i)$. We want to show that there exists a constant $K > 0$ such as

$$\|m_i - n_i\|_{L^\infty([0,T])} \leqslant K \|\tilde{m}_i - \tilde{n}_i\|_{L^\infty([0,T])}, \quad i = 1, 2.$$

To lighten notations, we drop out subscript i for now. We have

$$\begin{aligned} \dot{m}(t) &= -\tilde{A}_m(t)m(t) + \tilde{B}_m(t), \\ \dot{n}(t) &= -\tilde{A}_n(t)n(t) + \tilde{B}_n(t), \end{aligned}$$

where $\tilde{A}_m, \tilde{B}_m, \tilde{A}_n$ and $\tilde{B}_n$ are obtained from system (31). We are interested in the following quantity:

$$\dot{m} - \dot{n} = -\tilde{A}_m m + \tilde{B}_m + \tilde{A}_n n - \tilde{B}_n.$$

We can transform this equality:

$$\begin{aligned} (\dot{m} - \dot{n})(m - n) &= (m - n)(-\tilde{A}_m m + \tilde{B}_m + \tilde{A}_n n - \tilde{B}_n), \\ &= -(m - n)^2 \tilde{A}_n - m(m - n)(\tilde{A}_m - \tilde{A}_n) + (m - n)(\tilde{B}_m - \tilde{B}_n). \end{aligned}$$

We thus have:

$$\frac{1}{2}\frac{d}{dt}(m-n)^2 + (m-n)^2\tilde{A}_n = -m(m-n)(\tilde{A}_m - \tilde{A}_n) + (m-n)(\tilde{B}_m - \tilde{B}_n),$$
$$\frac{1}{2}\frac{d}{dt}(m-n)^2 \leqslant -m(m-n)(\tilde{A}_m - \tilde{A}_n) + (m-n)(\tilde{B}_m - \tilde{B}_n),$$
$$\leqslant (m-n)^2 + \frac{1}{2}M_T^2(\tilde{A}_m - \tilde{A}_n)^2 + \frac{1}{2}(\tilde{B}_m - \tilde{B}_n)^2.$$

According to Grönwall's inequality, we obtain:

$$(m(t)-n(t))^2 \leqslant \int_0^t \left(M_T^2(\tilde{A}_m(s) - \tilde{A}_n(s))^2 + (\tilde{B}_m(s) - \tilde{B}_n(s))^2\right) \mathrm{e}^{2(t-s)} ds. \tag{35}$$

$$\text{Then, } (m(t)-n(t))^2 \leqslant C_T \left(M_T^2 \sup_{[0,T]}(\tilde{A}_m(t) - \tilde{A}_n(t))^2 + \sup_{[0,T]}(\tilde{B}_m(t) - \tilde{B}_n(t))^2\right), \tag{36}$$

where $C_T > 0$.

Lemma 6. *There exists α and β real positive constants, such that*

$$\sup_{[0,T]}(|\tilde{A}_m(t) - \tilde{A}_n(t)|) \leqslant \alpha \sup_{[0,T]}(|\tilde{m}(t) - \tilde{n}(t)|), \tag{37}$$

$$\sup_{[0,T]}(|\tilde{B}_m(t) - \tilde{B}_n(t)|) \leqslant \beta \sup_{[0,T]}(|\tilde{m}(t) - \tilde{n}(t)|). \tag{38}$$

Lemma 6 and relation (36) are sufficient to prove the uniform equicontinuity of h. Then Ascoli theorem gives that $h(\Sigma_T)$ is a relatively compact subspace of $C_b^0([0,T])$. Proof of lemma 6 is given in Appendix B. □

Lemma 7. *The application h defined in system (27) is a continuous application.*

Proof. Let $(\tilde{m}_{i,n})_{n\in\mathbb{N}}$ a sequence of elements from Σ_T which tends to $\tilde{m}_i$ in Σ_T. Is the limit of $h(\tilde{m}_{i,n})$ equal to $h(\tilde{m}_i)$ when n tends to infinity?

We define sequences $(\tilde{u}_{i,n})_{n\in\mathbb{N}}$, $(\tilde{f}_{i,n})_{n\in\mathbb{N}}$ and $(\tilde{f}_{a,i,n})_{n\in\mathbb{N}}$, solutions of the following system of equations:

$$\begin{cases} \partial_t \tilde{u}_{i,n}(t,x) + \partial_x\left((g_i(x)\tilde{m}_{i,n}(t) - b_i)\tilde{u}_{i,n}(t,x)\right) = \mu(x)\tilde{m}_{i,n}(t), \\ \partial_t \tilde{f}_{i,n}(t,x) + \partial_x\left((g_{f,i}(x)\tilde{m}_{i,n}(t) - b_{f,i})\tilde{f}_{i,n}(t,x)\right) = \mu(x)\tilde{m}_{i,n}(t) - \gamma_{f,i}\tilde{f}_{i,n}(t,x), \\ \partial_t \tilde{f}_{a,i,n}(t,x) - b_{a,i}(t)\partial_x \tilde{f}_{a,i,n}(t,x) = \gamma_{f,i}\tilde{f}_{i,n}(t,x). \end{cases}$$

These sequences are used to compute $\tilde{A}_{i,n}$ and $\tilde{B}_{i,n}$ such as:

$$\dot{m}_{i,n}(t) = -\tilde{A}_{i,n}(t)m_{i,n}(t) + \tilde{B}_{i,n}(t),$$

where $m_{i,n} = h(\tilde{m}_{i,n})$.

Likewise, we define $m_i = h(\tilde{m}_i)$;

$$\dot{m}_i(t) = -\tilde{A}_i(t)m_i(t) + \tilde{B}_i(t).$$

We proceed in the same way as in the proof of lemma 5 to obtain the following relation:

$$|m_{i,n}(t) - m_i(t)|^2 \leqslant C_T(M_T^2 \sup_{[0,T]}|\tilde{A}_{i,n} - \tilde{A}_i|^2 + \sup_{[0,T]}|\tilde{B}_{i,n} - \tilde{B}_i|^2).$$

We then apply lemma 6 and show that if $\tilde{m}_{i,n}$ tends to $\tilde{m}_i$ when n tends to infinity, then it implies that $h(\tilde{m}_{i,n})$ tends to $h(\tilde{m}_i)$, which obviously is in Σ_T. □

Then, according to Schauder fixed point theorem, the application h admits a fixed point $m_i^* = h(m_i^*)$. This implies that system (I) admits at least one solution.

Uniqueness: to prove uniqueness of the solution let us assume that $(u_1, f_1, f_{a,1}, m_1)$ and $(u_2, f_2, f_{a,2}, m_2)$ are two solutions of the system (I) with the same initial data $(u^{in}, f^{in}, f_a^{in}, m^0)$ as in equation (5).

Using the same arguments as in the proof of lemma 5 (see equation (35)) one deduces

$$|m_1(t) - m_2(t)|^2 \leqslant \int_0^t \left(M_T^2 |A_1(s) - A_2(s)|^2 + |B_1(s) - |B_2(s)|^2\right) \mathrm{e}^{2(t-s)} ds,$$

so,

$$|m_1(t) - m_2(t)|^2 \leqslant \mathrm{e}^{2T} \int_0^t \left(M_T^2 |A_1(s) - A_2(s)|^2 + |B_1(s) - |B_2(s)|^2\right) ds.$$

Now, using the result of lemma 6 to estimate the right hand side of the previous inequality, we have

$$\begin{aligned} |m_1(t) - m_2(t)|^2 &\leqslant \mathrm{e}^{2T} \int_0^t \left(M_T^2 \alpha^2 + \beta^2\right) |m_1(s) - m_2(s)|^2 ds, \\ &\leqslant \mathrm{e}^{2T} \left(M_T^2 \alpha^2 + \beta^2\right) \int_0^t |m_1(s) - m_2(s)|^2 ds. \end{aligned}$$

So the Grönwall lemma gives

$$|m_1(t) - m_2(t)|^2 \leqslant |m_1(0) - m_2(0)|^2 \mathrm{e}^{\int_0^t \mathrm{e}^{2T}\left(M_T^2\alpha^2 + \beta^2\right) ds},$$

then using the fact that we have the same initial data, means $m_1(0) = m_2(0) = m^0$, we deduce $m_1(t) = m_2(t)$ so $f_1 \equiv f_2$, $u_1 \equiv u_2$ and $f_{a1} \equiv f_{a2}$. That concludes the uniqueness of the solution of (1)–(4).

The non-negativity of the unique solution of (1)–(4) is obvious as soon as initial data fulfill relation (5). The reader can easily check this point from explicit relations of mild solutions.

5. System (II)-Proof of the main results.

5.1. Existence and uniqueness of solutions.

We first prove the existence of initial conditions on $[0, \tau)$, defined by the following system, with $i = 1, 2$:

$$\begin{cases} \dot{\varphi}_i(t) = S_i(t) - \gamma_i \varphi_i(t) - \delta_i \varphi_i(t) \varphi_{p_c}(t), \\ \dot{\varphi}_{a,i}(t) = \gamma_i \varphi_i(t), \\ \dot{\varphi}_{p_c}(t) = -\delta_1 \varphi_1(t) \varphi_{p_c} t) - \delta_2 \varphi_2(t) \varphi_{p_c}(t), \\ \dot{\varphi}_{C_i}(t) = \delta_i \varphi_i(t) \varphi_{p_c}(t), \\ \varphi_{p_c}(0) = p_c^0 \geqslant 0, \varphi_i(0) = \varphi_{a,i}(0) = \varphi_{C_i}(0) = 0 \end{cases} \tag{39}$$

with S_i given by (13).

Due to the non continuity of S_i we cannot directly apply the Cauchy-Lipschitz theorem. So, in order to prove the existence result we use the following change of

unknown $\psi_i(t) = \varphi_i(t) - \int_0^t S_i(\sigma)d\sigma$ which is relevant because $S_i \in L^\infty(0,T)$ thanks to Lemma 3. We rewrite the system (39) as follow

$$\begin{cases} \dot{\psi}_i(t) = -\gamma_i\psi_i(t) - \delta_i\psi_i(t)\varphi_{p_c}(t) - \delta_i\left(\int_0^t S_i(\sigma)d\sigma\right)\varphi_{p_c}(t) - \gamma_i\int_0^t S_i(\sigma)d\sigma, \\ \dot{\varphi}_{a,i}(t) = \gamma_i\psi_i(t) + \gamma_i\int_0^t S_i(\sigma)d\sigma, \\ \dot{\varphi}_{p_c}(t) = -\delta_1\psi_1(t)\varphi_{p_c}(t) - \delta_2\psi_2(t)\varphi_{p_c}(t) - \left(\int_0^t \big(\delta_1 S_1(\sigma) + \delta_2 S_2(\sigma)\big)d\sigma\right)\varphi_{p_c}(t), \\ \dot{\varphi}_{C_i}(t) = \delta_i\psi_i(t)\varphi_{p_c}(t) + \delta_i\left(\int_0^t S_i(\sigma)d\sigma\right)\varphi_{p_c}(t), \\ \varphi_{p_c}(0) = p_c^0 \geqslant 0, \psi_i(0) = \varphi_{a,i}(0) = \varphi_{C_i}(0) = 0. \end{cases} \tag{40}$$

For the existence let us note the vector
$X(t) = {}^{\mathbf{t}}(\psi_1(t), \psi_2(t), \varphi_{a,1}(t), \varphi_{a,2}(t), \varphi_{p_c}(t), \varphi_{C_1}(t), \varphi_{C_2}(t))$.
We have to solve the following Cauchy problem:

$$\begin{cases} \dot{X}(t) = F(t, X(t)), \quad 0 \leqslant t < \tau, \\ X(0) = {}^{t}(0,0,0,0,p_c^0,0,0), \end{cases} \tag{41}$$

where $F(t,X)$ is defined by

$$F(t,X) = \begin{pmatrix} -\gamma_1 X_1 - \delta_1 X_1 X_5 - \delta_1(\int_0^t S_1(\sigma)d\sigma)X_5 - \gamma_1\int_0^t S_1(\sigma)d\sigma \\ -\gamma_2 X_2 - \delta_2 X_2 X_5 - \delta_2(\int_0^t S_2(\sigma)d\sigma)X_5 - \gamma_2\int_0^t S_2(\sigma)d\sigma \\ \gamma_1 X_1 + \gamma_1\int_0^t S_1(\sigma)d\sigma \\ \gamma_2 X_2 + \gamma_2\int_0^t S_2(\sigma)d\sigma \\ -\delta_1 X_1 X_5 - \delta_2 X_2 X_5 - (\int_0^t(\delta_1 S_1 + \delta_2 S_2)(\sigma)d\sigma)X_5 \\ \delta_1 X_1 X_5 + \delta_1(\int_0^t S_1(\sigma)d\sigma)X_5 \\ \delta_2 X_2 X_5 + \delta_2(\int_0^t S_2(\sigma)d\sigma)X_5 \end{pmatrix},$$

$$= \begin{pmatrix} F_1(t,X) \\ F_2(t,X) \\ F_3(t,X) \\ F_4(t,X) \\ F_5(t,X) \\ F_6(t,X) \\ F_7(t,X) \end{pmatrix}.$$

Function F is continuous for t and Lipschitz with respect to the second variable X. Indeed components F_i, $i = 1$ to 7, are continuously differentiable with respect to the second variable. Cauchy-Lipschitz theorem gives the local existence and uniqueness of solution for problem (41). Thereby we have the local existence of solution for the system (39). The global existence of the solution of (39) on $[0,\tau)$ requires the solution $X(t) = {}^{\mathbf{t}}(\varphi_1(t), \varphi_2(t), \varphi_{a,1}(t), \varphi_{a,2}(t), \varphi_{p_c}(t), \varphi_{C_1}(t), \varphi_{C_2}(t))$ to be bounded and non-negative on $[0,\tau)$. To prove that, let us start with the initial conditions defined in system (39). We know that:

$$\dot{\varphi}_{p_c}(t) = -(\delta_1\varphi_1(t) + \delta_2\varphi_2(t))\varphi_{p_c}(t). \tag{42}$$

This equation can easily be written as: $\varphi_{p_c}(t) = p_c^0 \mathrm{e}^{\left(-\int_0^t(\delta_1\varphi_1(s)+\delta_2\varphi_2(s))ds\right)}$, which is positive for all t in $[0,\tau]$, as p_c^0 is greater than 0. In addition it is straightforward that $\varphi_{p_c}(t) \leq p_c^0$.

Then, for $i = 1, 2$, we have

$$\dot{\varphi}_i(t) = S_i(t) - \gamma_i\varphi_i(t) - \delta_i\varphi_i(t)\varphi_{p_c}(t) \geqslant -(\gamma_i + \delta_i\varphi_{p_c}(t))\varphi_i(t),$$
$$\varphi_i(t) \geqslant \varphi_i(0)\exp\left(-\int_0^t \gamma_i + \delta_i\varphi_{p_c}(s)ds\right).$$

As $\varphi_i(0) = 0$, we have the non-negativity of $\varphi_i(t)$ for t in $[0,\tau]$, and $i = 1, 2$. In addition, one can deduce that $\varphi(t) \leq \int_0^\tau S_i(\sigma)d\sigma$.

As $\varphi_1(t)$, $\varphi_2(t)$ and $\varphi_{p_c}(t)$ are greater or equal to 0, for all t in $[0,\tau]$, functions $\varphi_{a,i}$ and $\varphi_{C_i}, i = 1, 2$ are increasing. This implies the non-negativity of these functions for all t in $[0,\tau]$, as $\varphi_{a,i}(0)$ and $\varphi_{C_i}, i = 1, 2$ are null. One can easily verifies that $\varphi_{a,i}$ and $\varphi_{C_i}, i = 1, 2$ are bounded. We further define $X(\tau)$ as $X(\tau) = \lim_{t\to\tau^-} X(t)$.

We prove existence and uniqueness of solutions of system (II) on $[\tau, +\infty)$ with a method of steps. We first study the system (II) on $[\tau, 2\tau)$. We have to solve the following Cauchy problem:

$$\begin{cases} \dot{Y}(t) = G(t, Y(t), Y(t-\tau)), \quad \tau \leqslant t < 2\tau, \\ Y(t) = \tilde{X}(t), \quad 0 \leqslant t \leqslant \tau, \end{cases} \tag{43}$$

where $Y(t) = {}^{\mathbf{t}}\big(u_1^0(t), u_2^0(t), u_{a,1}(t), u_{a,2}(t), p_c(t), p_{ol}(t), C_1(t), C_2(t)\big)$,

$\tilde{X}(t) = {}^{\mathbf{t}}(\varphi_1(t), \varphi_2(t), \varphi_{a,1}(t), \varphi_{a,2}(t), \varphi_{p_c}(t), 0, \varphi_{C_1}(t), \varphi_{C_2}(t))$, and G is defined by:

$$G(t, Y, Z) = \begin{pmatrix} S_1(t) - \gamma_1 Y_1 - \delta_1 Y_1 Y_5 + \delta_1 Z_1 Z_5 \\ S_2(t) - \gamma_2 Y_2 - \delta_2 Y_2 Y_5 + \delta_2 Z_2 Z_5 \\ \gamma_1 Y_1 \\ \gamma_2 Y_2 \\ -\delta_1 Y_1 Y_5 - \delta_2 Y_2 Y_5 \\ \delta_1 Z_1 Z_5 + \delta_2 Z_2 Z_5 \\ \delta_1 Y_1 Y_5 - \delta_1 Z_1 Z_5 \\ \delta_2 Y_2 Y_5 - \delta_2 Y_2 Y_5 \end{pmatrix}.$$

Here, we perform again a change of variable as done previously in order to overcome the non continuity of S_i, $i = 1, 2$. With the same strategy, we can actually re-write system (43) as follow:

$$\begin{cases} \dot{\tilde{Y}}(t) = \tilde{G}(t, \tilde{Y}(t), \widetilde{\tilde{X}}(t-\tau)) = \widetilde{\tilde{G}}(t, \tilde{Y}(t)), \quad \tau \leqslant t < 2\tau, \\ \tilde{Y}(t) = \widetilde{\tilde{X}}(t), \quad 0 \leqslant t < \tau \end{cases}$$

where $\tilde{Y}(t)$ and $\widetilde{\tilde{X}}$ are respectively the same vectors as $Y(t)$ and $\tilde{X}(t)$ when replacing $u_i^0(t)$ by $u_i^0(t) - \int_\tau^t S_i(\sigma)d\sigma$ (respectively $\varphi_i(t)$ by $\varphi_i(t) - \int_\tau^t S_i(\sigma)d\sigma$).

As we did previously, we easily show that $\widetilde{\tilde{G}}$ is a continuous function, and continuously differentiable with respect to the second variable. So, Cauchy-Lipschitz theorem gives the local existence and uniqueness of solutions on $[\tau, 2\tau)$ for the above problem. That implies the local existence of solution to system (43). To prove that the solution is global we investigate again the positivity and the finite bounds of $Y(t) = {}^{\mathbf{t}}\big(u_1^0(t), u_2^0(t), u_{a,1}(t), u_{a,2}(t), p_c(t), p_{ol}(t), C_1(t), C_2(t)\big)$. For that, we begin

with the relation

$$\dot{p_c}(t) = -(\delta_1 u_1^0(t) + \delta_2 u_2^0(t))p_c(t) \Longrightarrow p_c(t) = p_c(\tau)\exp\left(-\int_\tau^t \delta_1 u_1^0(s) + \delta_2 u_2^0(s)ds\right),$$

which is positive or null for all t in $[\tau, 2\tau)$, as $p_c(\tau) = \varphi_{p_c}(\tau)$ is greater or equal to 0. For the non-negativity of $u_i^0(t)$, $i = 1, 2$ for all t in $[\tau, +2\tau)$, we have

$$\dot{u_i^0}(t) \geqslant -\gamma_i u_i^0(t) - \delta_i u_i^0(t)p_c(t) \implies u_i^0(t) \geqslant u_i^0(\tau)\exp\left(-\int_0^t [\gamma_i + \delta_i p_c(s)]ds\right)$$

that induces $u_i^0(t) \geq 0$ for all $t \in (\tau, 2\tau)$ because $u_i^0(\tau) \geq 0$.

Knowing that $u_i^0(t) \geq 0$ it's straightforward that $p_c(t) \leq \varphi_{p_c}(\tau) < +\infty$.

For the upper bound of u_i^0 one can remark that $\dot{u}_i^0(t) \leq S_i(t) + \delta_i p_c(t-\tau)u_i^0(t-\tau)$. Knowing that $t \in [\tau, 2\tau)$ that implies $t_\tau = t - \tau \in [0, \tau]$ so $u_i^0(t_\tau)$ is known and correspond to the initial function φ_i which is already bounded. Then a simple integration on $[\tau, t]$ with $t < 2\tau$ achieves the proof that u_i^0 is bounded.

Given the non-negativity of p_c, u_1^0 and u_2^0, we have, for all t in $[\tau, 2\tau)$:

$$\dot{u}_{a,i}(t) \geqslant 0 \implies u_{a,i}(t) \geqslant u_{a,i}(\tau) \geqslant 0, \quad i = 1, 2,$$
$$\dot{p_{ol}}(t) \geqslant 0 \implies p_{ol}(t) \geqslant p_{sc}(\tau) = 0.$$

In addition, it is straightforward to verify that $u_{a,i}$ and p_{sc} are bounded.

We finally consider functions C_i:

$$\begin{aligned}
\dot{C}_i(t) &= \delta_i u_i^0(t)p_c(t) - \delta_i u_i^0(t-\tau)p_c(t-\tau),\\
C_i(t) &= C_i(\tau) + \delta_i \int_\tau^t u_i^0(s)p_c(s)ds - \delta_i \int_\tau^t u_i^0(s-\tau)p_c(s-\tau)ds,\\
&= \delta_i \int_0^\tau u_i^0(s)p_c(s)ds + \delta_i \int_\tau^t u_i^0(s)p_c(s)ds - \delta_i \int_0^{t-\tau} u_i^0(s)p_c(s)ds,\\
&= \delta_i \int_{t-\tau}^t u_i^0(s)p_c(s)ds, \quad \tau \leq t < 2\tau.
\end{aligned}$$

Thanks to non-negativity of u_i^0 and p_c, this proves that C_i, $i = 1, 2$ is non-negative on $[\tau, 2\tau)$ and obviously bounded.

That achieves the global existence solution on $[\tau, 2\tau)$. We then iterate this process on intervals $[n\tau, (n+1)\tau)$, $n \geq 2$ and $n \in \mathbb{N}^*$, and obtain existence and uniqueness of solutions of system (II) on $[0, T]$.

6. **Numerical simulations.** In this section, we give illustrations of the dynamics of our model, through numerical simulations, using only one type of Aβ . The numerical scheme is based on a finite volumes method for the size discretization of the advection-reaction equations combined with a second order Runge-Kutta time discretization. We use the Van Leer flux limiters for the advection part which is known to be of order two. So, the numerical solutions of our model are TVD (Total Variation Diminishing) and of order two.

We neglect any difficulties due to truncation of the computational domain and introduce the regular mesh with constant size step $\Delta x > 0$: the cells are the intervals $[x_{k-1}, x_k]$, $k \in \mathbb{N}$ with $x_k = (k + 1/2)\Delta x$ and $x_{-1} = 0$. We denote by F_k^n on of the numerical unknown (it can be the fibrils or the proto-oligomers or the fibrils inside the plaque). In the particular case where $F = f$, f_k^n is intended to be an

approximation of $\frac{1}{\Delta x}\int_{x_{k-1}}^{x_k} f(t^{(n)},z)dz$, where $t^{(0)}=0<t^{(1)}<\cdots<t^{(n)}<t^{(n+1)}$ defines the time-discretization, with possibly variable step $\Delta t^{(n)}=t^{(n+1)}-t^{(n)}$ in order to adapt the velocity time variation. For instance the numerical scheme for fibrils size-density (see equation (2)) is defined by the relation

$$f_k^* = f_k^n + \Delta t^{(n)}\left(-\frac{flux_{k+1}^n - flux_k^n}{\Delta x} + \mu(i)m^n - \gamma_f f_k^n\right), \tag{44}$$

$$f_k^{(n+1)} = \frac{1}{2}(f_k^n + f_k^*) + \frac{\Delta t^{(n)}}{2}\left(-\frac{flux_{k+1}^* - flux_k^*}{\Delta x} + \mu(i)m^* - \gamma_f f_k^*\right). \tag{45}$$

The interface fluxes, $flux_k^n = (vf)_k^n$ and $flux_k^* = (v^*f^*)_k^n$ are computed by using Van Leer approximation respectively with vf evaluated at time $t^{(n)}$ and at intermediate time t^* thanks to the second order Runge-Kutta method. Here $m^{(n)}$ and m^* are the numerical approximations of the monomers concentration respectively at first and second stage of the Runge-Kutta method based on the equation (4).

For the flux with Van Leer limiter method, we compute:

$$\text{if } v_k^n > 0 \quad \begin{cases} \theta & = \dfrac{f_{k-1}^n - f_{k-2}^n}{\epsilon + f_k^n - f_{k-1}^n}, \\ flux_k^n & = v_k^n\left(f_{k-1}^n + (f_k^n - f_{k-1}^n)\phi(\theta)\right), \end{cases} \quad \text{with} \quad \epsilon = 1.0e^{-12}$$

$$\text{else} \quad \begin{cases} \theta & = \dfrac{f_k^n - f_{k-1}^n}{\epsilon + f_{k+1}^n - f_k^n}, \\ flux_k^n & = v_k^n\left(f_k^n - (f_k^n - f_{k-1}^n)\phi(\dfrac{1}{\theta+\epsilon_1})\right), \end{cases} \quad \text{with} \quad \epsilon_1 = 1.0e^{-10}$$

where the limiter function ϕ given by $\phi(\theta) = \frac{1}{2}\left(\frac{|\theta|+\theta}{1+|\theta|}\right)$.

We apply this scheme for the part of the model dealing with partial differential equations. For the other part of the model dealing with ordinary differential equation, the approximation is done thanks to the second order Runge-Kutta method. Boundaries conditions are taken into account thanks to fictious mesh added at the domain.

For the parameters of the simulations we consider the followings: $g_f(x) = g(x) = x^{1/3}$, $b_f = b_a = b = 1$, $\gamma_f = \gamma = \delta = 0.1$, $\tau = 3$, $x_0 = 5$. For all the simulations we take initial conditions for the quantities involved in the prion catalysis process as follow $u^0(t=0) = 0$, $p_c(t=0) = 1$, $p_{sc}(t=0) = 0$, $C(t=0) = 0$, $u_a(t=0) = 0$,

$$\mu(x) = \begin{cases} \exp\left(\dfrac{1}{(x-0.9)^2 - 1.2}\right)\left(1 - \dfrac{x}{2}\right)^{10} & \text{if } 0 < x < 1.9, \\ 0 \text{ elsewhere.} \end{cases}$$

6.1. **Results with free initial size-density repartition for fibrils, proto-oligomers and plaque.** We first consider the case where there are only Aβ monomers and prions PrP^c initially, which corresponds to what can be done experimentally. In terms of initial conditions, we therefore have: $f^{in}(x) = 0$, $f_a^{in}(x) = 0$ and $u^{in}(x) = 0$. Figure 2 displays the evolution in time of the size density repartition of fibrils, proto-oligomers and fibrils in plaque, as well as the evolution of the total mass, which remains constant as expected. One can observe the creation of fibrils and proto-oligomers is only due to function μ, which allows to create small polymers. In this case, there are very few polymers with a large size. Evolutions of

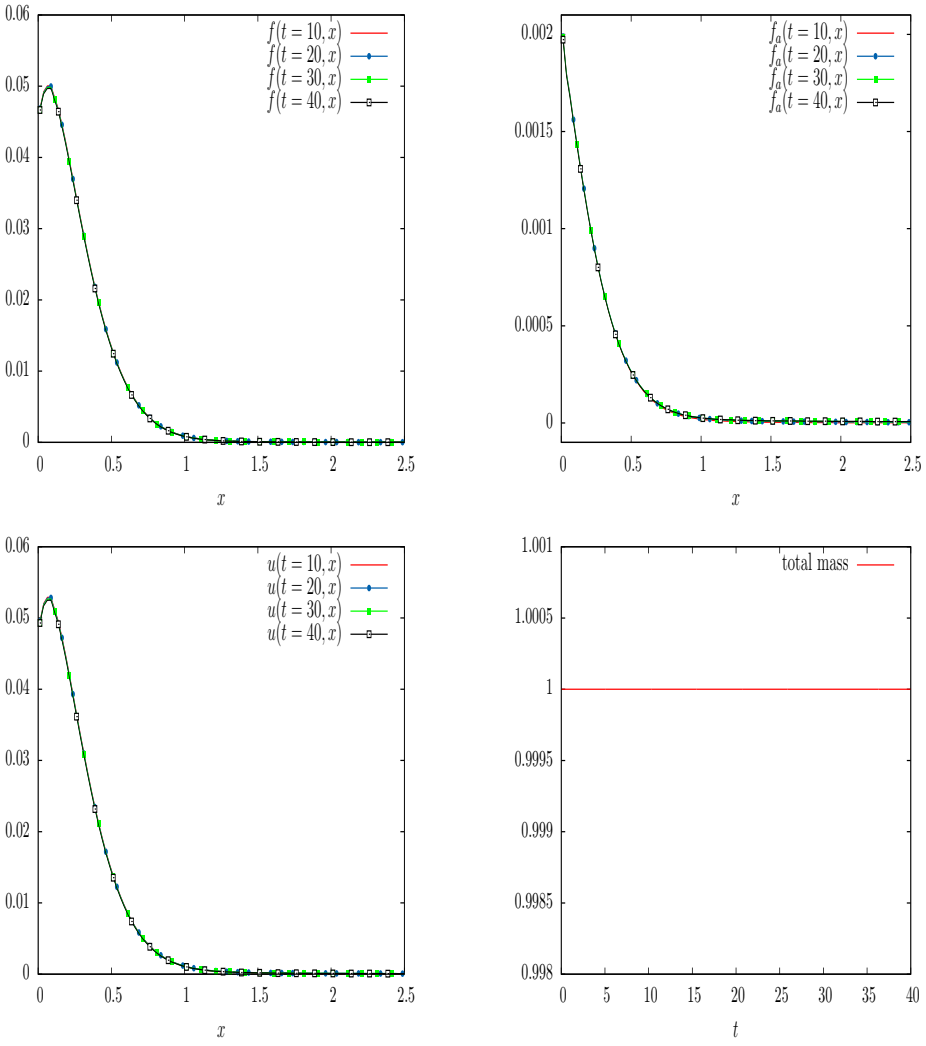

Figure 2. Evolution of size density repartition of fibrils $f(t,x)$, proto-oligomers $u(t,x)$ and fibrils in plaque $f_a(t,x)$ for different times ($t = 10, 20, 30, 40$). The last figure displays the evolution of the total mass.

concentration of Aβ monomers, oligomers, oligomers in plaque, PrP^c, PrP^{ol} and complexes are presented in Figure 3. One can note that, because there is no polymer initially, few oligomers are created and thus, the emergence of PrP^{ol} prions remains quite slow.

6.2. **Results with gaussian initial distribution for fibrils, proto-oligomers and plaque.** We now assume that proto-oligomers and fibrils are present initially with monomers and PrP^c. Initial conditions are given by:

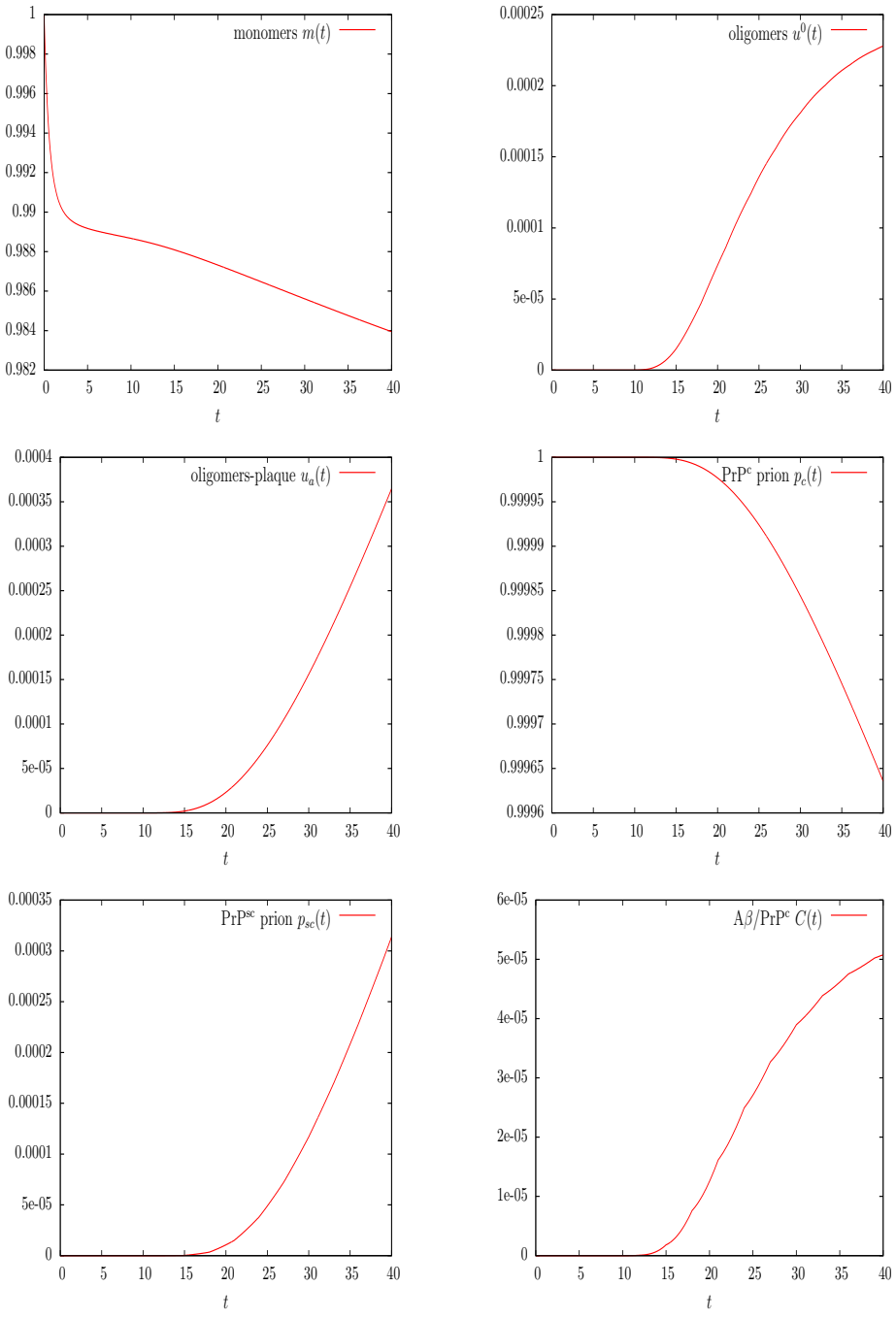

Figure 3. Evolution with time of Aβ monomers, Aβ oligomers, oligomers in plaque, prions PrP^c, prions PrP^{ol} and complexes, with only monomers and PrP^c initially.

$$f^{in}(x) = \begin{cases} \dfrac{\exp(-\frac{5(x-1.5)^2}{2})}{\sqrt{0.4\pi}}, \end{cases} \qquad u^{in}(x) = \begin{cases} \dfrac{\exp(-\frac{5(x-1)^2}{2})}{\sqrt{0.4\pi}} \text{ if } 1 \le x \le x_0, \\ 0 \text{ elsewhere,} \end{cases}$$

$$f_a^{in}(x) = \begin{cases} \dfrac{\exp(-\frac{5(x-1.75)^2}{2})}{\sqrt{0.4\pi}}. \end{cases}$$

Figure 4 displays the evolutions of monomer concentration, oligomers, oligomers in plaque, prions PrP^c and PrP^{ol} and complexes. As expected, the total mass remains constant.

In a first time we observe an increase in monomers, meaning that proto-oligomers and fibrils initially depolymerize. Then monomer concentration decreases, which corresponds to the formation of larger polymers. Oligomers appear after a certain time, and their concentration decreases after a while, meaning that proto-oligomers do not reach the size x_0. With the increase of Aβ oligomers, we notice the emergence of Aβ / PrP^c complexes and of PrP^{ol}.

Figures 5 and 6 display the evolution of size density repartition of fibrils $f(t,x)$, proto-oligomers $u(t,x)$ and fibrils in plaque $f_a(t,x)$ for given times. One observes that fibrils become larger with time, but after a certain time there are more small fibrils due to the spontaneous term μ than large ones. Likewise, because fibrils in plaque only depolymerize, we notice a larger concentration of small ones. For proto-oligomers, we observe the impact of μ function as small proto-oligomers rapidly appear. Some proto-oligomers finally reach the maximal size x_0 and become oligomers.

7. **Discussion.** The role of Aβ oligomers and PrP^c prions in Alzheimer's disease remains to be fully understood. Recent evidence suggests that Aβ oligomers can interact with PrP^c to induce cytotoxic damages to neurons, increasing their apoptosis. Moreover, this interaction could misfold PrP^c into pathogenic prions PrP^{sc}, potentially leading to the emergence of prion diseases such as Creutzfeldt-Jakob disease. Mathematical modelling can help to qualitatively explain polymerization kinetics and evolution of polymer length that are involved in the emergence of AD. In this work, we propose a mathematical model to describe the polymerization of Aβ monomers, and the interactions between Aβ oligomers and PrP^c. Polymerization process is modelled with partial differential equations, based on Lifshitz-Slyozov equations [28]. One can note that in our model, we study the evolution of three different species (proto-oligomers, fibrils and fibrils in plaque) through advection-reaction equations, making the analysis more complex. PrP^{ol} catalysis, through interactions with Aβ oligomers, is described using ordinary and delayed differential equations. These two submodels are linked through the source term of oligomers coming from proto-oligomers, and can be studied one at a time. For the first one, we use Schauder fixed point theorem to prove existence and uniqueness of mild solutions, even in the case of singular polymerization rates. Existence and uniqueness of solutions for the second sub-model are obtained with Cauchy-Lipschitz theorem. Numerical simulations with different initial conditions are given to illustrate the different profiles that can be obtained with this model. Because we have no experimental data available yet, we only provide simulations with one type of Aβ .

Note that even we decided to keep only one Aβ population for the simulations in section 6, it was for clarity of the paper. One question may be asked then: why

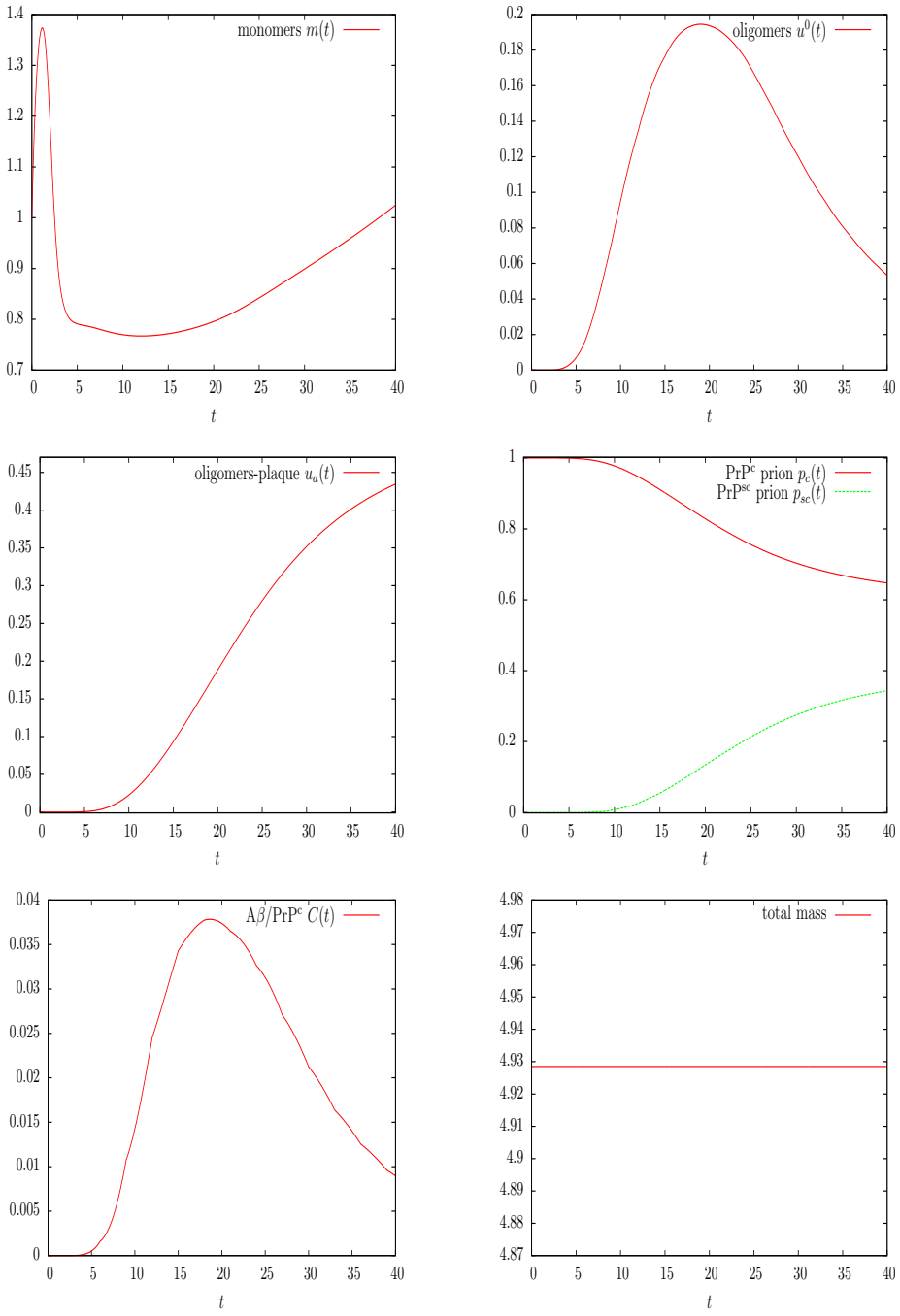

Figure 4. Time evolution of the concentrations of Aβ monomers, oligomers, oligomers in plaque, PrP^c and PrP^{sc}, Aβ / PrP^c complexes and total mass.

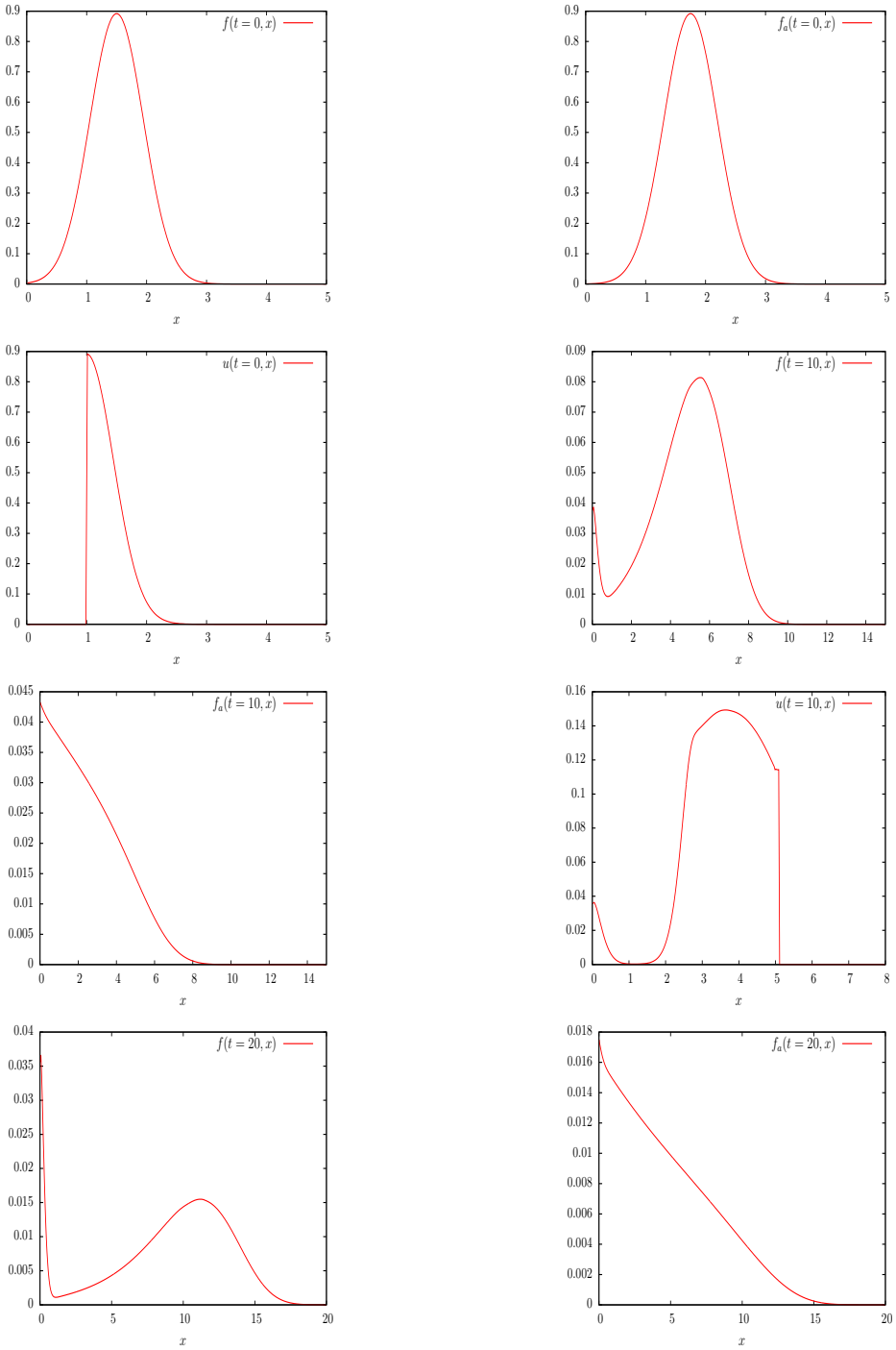

Figure 5. Evolution of size density repartition of fibrils $f(t,x)$, proto-oligomers $u(t,x)$ and fibrils in plaque $f_a(t,x)$ for different times ($t = 0, 10, 20$)

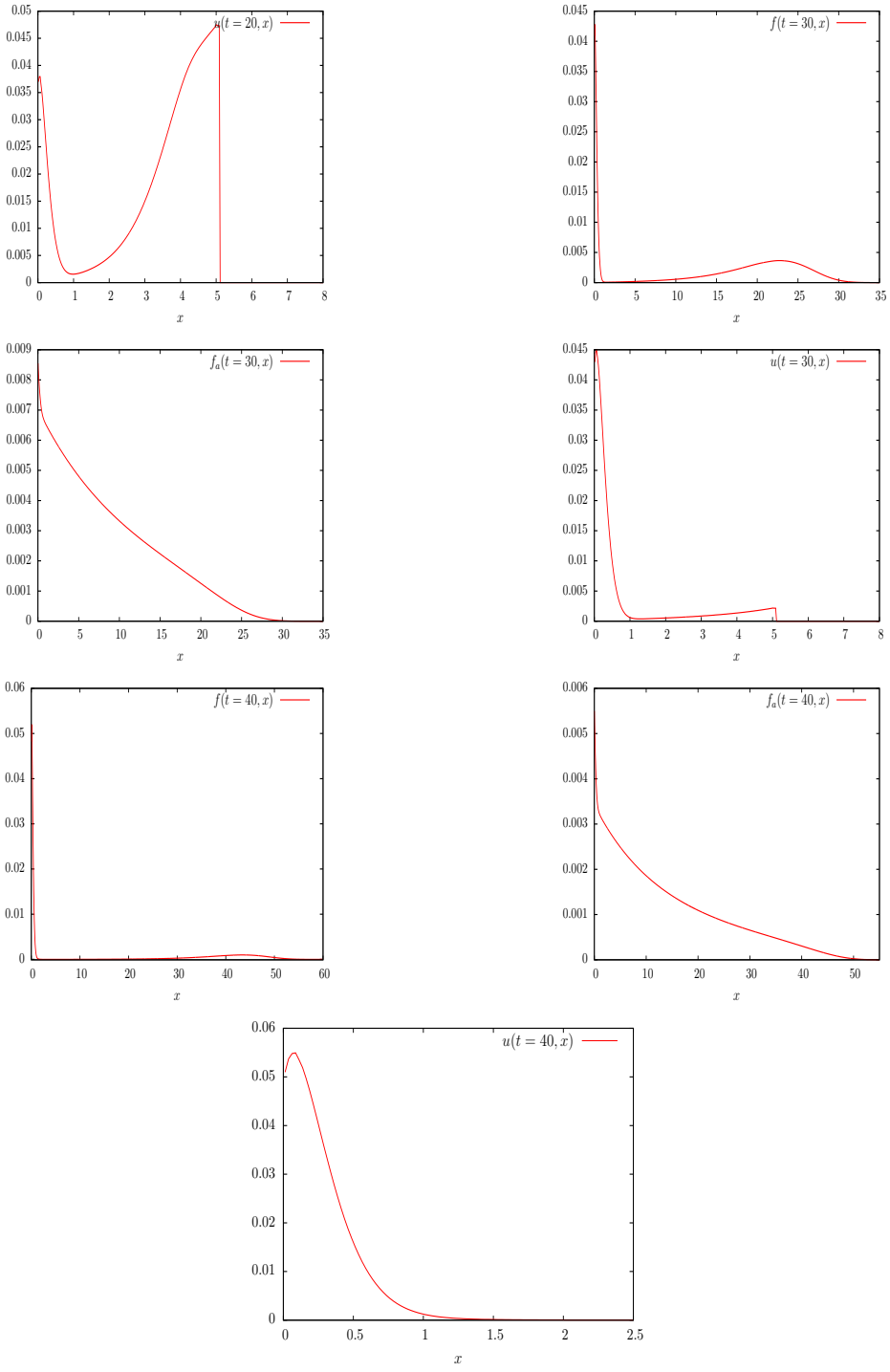

Figure 6. Evolution of size density repartition of fibrils $f(t,x)$, proto-oligomers $u(t,x)$ and fibrils in plaque $f_a(t,x)$ for different times ($t = 20, 30, 40$).

should not consider only one Aβ type in the model then? There are two answers to this question:

1. first, adding two types of Aβ in our model did not bring much difficulty for the theory, and it was biologically supported by [6] and [23],

2. adding the Aβ-42 population in our simulations following the ratio given in [23] change the results. For instance, in Figure 7 (top left) we added simulations of fibrils formation at time $t = 10$ to compare with Figure 3 (top left).

   In Figure 7 (top right) we gave oligomers consisting of Aβ-42 formation within the same time lapse as in Figure 4 (top right). The result shows that with 10% of the Aβ-40 population, and with the same kinetic parameters, no oligomers are formed within the same period of time. Experimental results, not yet provided, should show some early onset of Aβ-42, and thus encourage us to increase their kinetic parameter values in comparison to the Aβ-40 (see Figure 7, bottom with $g(x) = x^{1/2}$). One of our future work is to proceed to a sensitivity analysis and estimate of parameters by comparing our simulations with real biological data.

To the best of our knowledge, this is the first model describing both Aβ polymerization process and interactions with PrP^c. However, because it is developed in an *in vitro* context, some *in vivo* processes are not included in the model. For instance, one could add the production of Aβ monomers on diseased neuronal membranes, as proposed in [1, 5]. Neurons could also be damaged due to the binding of Aβ oligomers to PrP^c , as done in [21]. Astrocytes play also a role in cleaning the surroundings of the neurons by bringing oligomers and fibrils into amyloid plaques in their neighbourhood. Thus spatial structure should also bee taken into account.

Furthermore, since the delay term τ representing the time duration in which the PrP^c and Aβ form a complex seem quite small (order of 30 to 40 minutes) in comparison with the experimental times (order of several days). It seemed first not necessary to us to add it into our system (numerical simulations not shown here). This would have lead to non-linear ordinary differential equations only. However, we decided to keep this delay for three reasons. The first one is a biological reason: this delay brings a lag time that seems negligible here, but is relevant for biologists. Second, from a theoretical point of view, our delay differential equation are quite standard and did not bring any extra-difficulty to our study. Third, if one speculate a new therapy involving a molecule that would keep this Aβ / PrP^c complex for days instead of minutes, the whole dynamics could be modified then, and thanks to this model, we could qualitatively and quantitatively bring the impact of this strategy to the spread of the disease.

Nevertheless, we believe that our model gives insights on Aβ polymerization and on the interactions between Aβ and PrP^c. It remains to compare our numerical simulations to experimental data and to find optimal parameter estimates. This can help to highlight differences between Aβ -40 and Aβ -42 and to identify new possible therapeutic targets to slow down or even avoid the emergence of Alzheimer's disease or prion diseases.

Appendix A. **Measurability of $\bar{s}(t,x)$.** In this appendix, we aim to show the measurability of the function $\bar{s}(t,x)$ introduced in the proof of lemma 1. Let us consider the set $Q = [0,T] \times (0,x_0)$. For all (t,x) in Q let $\bar{s}(t,x)$ be defined as:

$$\bar{s}(t,x) = \sup\{s \in [0,t], X(s;t,x) = x_0\}, \tag{46}$$

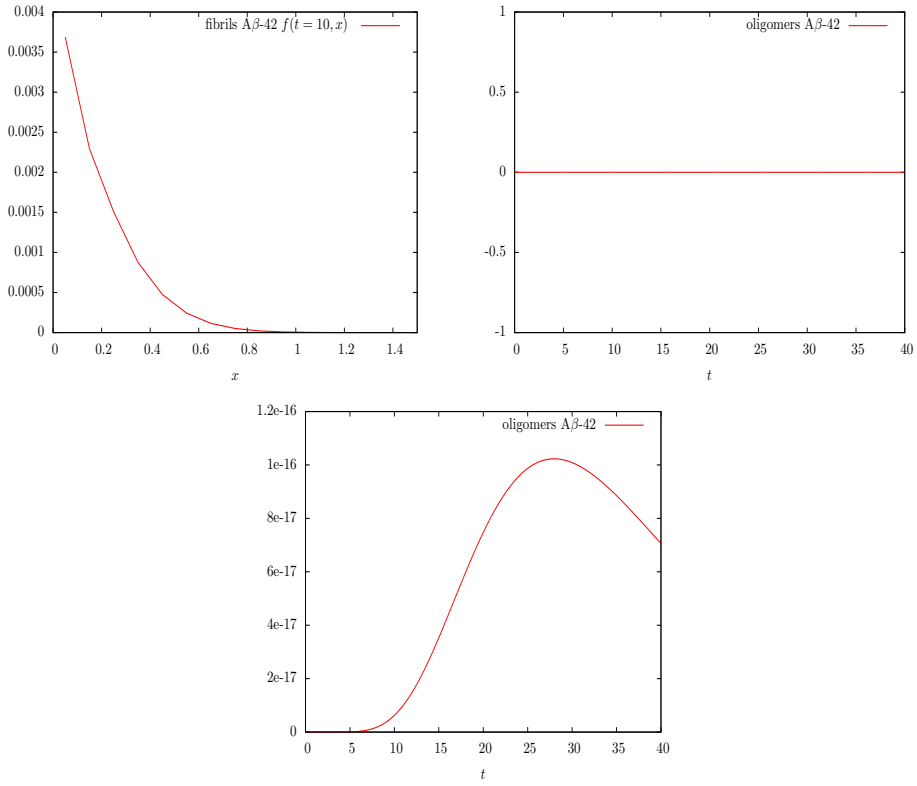

Figure 7. Evolution of Aβ-42 type of species fibrils (after a time period of 10 units) (top left) and oligomers (top right) taking into account the same assumptions as in section 6 and oligomers with a faster kinetics (bottom). Here we consider the ratio of 10% of Aβ-40 type species proposed in [23] with the same kinetics and then a faster kinetics for oligomers ($g(x) = x^{1/2}$).

where we understand that $\bar{s}(t,x) = 0$ if $X(s;t,x) < x_0$ for any s in $[0,t]$.

For α in $\mathbb{R}$, we consider the following set:

$$A_\alpha = \{(t,x) \in Q, \bar{s}(t,x) \geqslant \alpha\}. \tag{47}$$

We want to show that A_α is measurable. Let us note that if α is lower or equal to 0, then A_α is exactly Q and if α is greater or equal to T, A_α is the empty set. We then assume that α is in $(0,T)$.

Proposition 1. *With these notations, we have $A_\alpha = B_\alpha$, where*

$$B_\alpha = \{(t, X(t;s,x_0)), (t,s) \in F_\alpha\} \cap Q,$$

with

$$F_\alpha = \{(t,s) \in \mathbb{R}^2, 0 \leqslant s \leqslant t \leqslant T\}.$$

Proof. 1. $A_\alpha \subseteq B_\alpha$

Let us take (t,x) in A_α. We have (t,x) in Q and $X(\bar{s}(t,x);t,x) = x_0$, which is equivalent to $x = X(t;\bar{s}(t,x),x_0)$. We also have $\alpha \leqslant \bar{s}(t,x) \leqslant t \leqslant T$, whence $(t,\bar{s}(t,x))$ is in F_α. Therefore (t,x), which is equal to $(t, X(t;\bar{s}(t,x),x_0))$, is in B_α.

2. $B_\alpha \subseteq A_\alpha$

Let us consider $(t,x) = (t, X(t; s_1, x_0))$ in B_α. Then we have $0 < x = X(t; s_1, x_0) < x_0$ and $\alpha \leqslant s_1 \leqslant t \leqslant T$. Then necessarily $\bar{s}(t,x) \geqslant s_1$, so $\bar{s}(t,x) \geqslant \alpha$, that is (t,x) is in A_α. □

We can note that the set $\{(t, X(t; s, x_0)), (t,s) \in F_\alpha\}$ is the image of the compact set F_α by a continuous function, so it is a compact set. It follows that it is a closed set, and then a measurable set. Q is also measurable, and therefore so is B_α. As B_α is exactly A_α by proposition 1, A_α is measurable. Finally, the function $\bar{s}$ from Q to $\mathbb{R}$ is measurable.

Appendix B. **Proof of lemma 6.** We provide here the proof of lemma 6 introduced in section 4.2, to prove that $h(\Sigma_T)$ is a relatively compact subspace of $C_b^0([0,T])$.

Proof. According to equation (29), we have:

$$|A_m(t) - A_n(t)| \leqslant \underbrace{|\int_0^{+\infty} g_f(x)(f_m(t,x) - f_n(t,x))dx|}_{I_{A1}} + \underbrace{|\int_0^{x_0} g(x)(u_m(t,x) - u_n(t,x))dx|}_{I_{A2}}. \tag{48}$$

Let us focus on I_{A1}. We know that:

$$f_m(t,x) = f^{in}(X_m(0;t,x))\mathrm{e}^{-\gamma_f t} J_m(0;t,x) + \int_0^t \mu(X_m(s;t,x))\tilde{m}(s) \quad \mathrm{e}^{-\gamma_f(t-s)} J_m(s;t,x)ds,$$

and the same holds for $f_n(t,x)$.

Therefore, we have

$$I_{A1} \leqslant \mathrm{e}^{-\gamma_f t} \underbrace{|\int_0^{+\infty} g_f(x)\left(f^{in}(X_m(0;t,x))J_m(0;t,x) - f^{in}(X_n(0;t,x))J_n(0;t,x)\right)dx|}_{K_1}$$
$$\underbrace{+|\int_0^{+\infty}\int_0^t g_f(x)\mathrm{e}^{-\gamma_f(t-s)}\mu(X_m(s;t,x))\tilde{m}(s)J_m(s;t,x) - \mu(X_n(s;t,x))\tilde{n}(s)J_n(s;t,x)dsdx|}_{K_2}. \tag{49}$$

We compute term K_1 with integration by substitution, with $y = X_p(0;t,x)$, $p = m,n$. First, let us note that:

$$\lim_{x\to+\infty} X(s;t,x) = +\infty, \quad 0 \leqslant s \leqslant t,$$

and:

$$\text{if } x < +\infty, \text{ then } X(s;t,x) < \infty, \text{ for all } s,\ 0 \leqslant s \leqslant t.$$

We therefore have:

$$\begin{aligned}
K_1 &= |\int_{X_m(0;t,0)}^{+\infty} g_f(X_m(t;0,y))f^{in}(y)dy - \int_{X_n(0;t,0)}^{+\infty} g_f(X_n(t;0,y))f^{in}(y)dy|,\\
&= |\int_{X_m(0;t,0)}^{X_n(0;t,0)} g_f(X_m(t;0,y))f^{in}(y)dy + \int_{X_n(0;t,0)}^{+\infty} f^{in}(y)\Big(g_f(X_m(t;0,y))\\
&\quad - g_f(X_m(t;0,y))\Big)dy|,\\
&\leqslant \sup_{[X_m(0;t,0),X_n(0;t,0)]} (g_f(X_m(t;0,y))f^{in}(y))|X_n(0;t,0) - X_m(0;t,0)|\\
&\quad + \int_{X_n(0;t,0)}^{+\infty} G_f|X_m(t;0,y) - X_n(t;0,y)|f^{in}(y)dy, \qquad (50)
\end{aligned}$$

where G_f is the upper bound for the derivative of g_f, as stated in Hypothesis 1.

Let us now compute $|X_m(s;t,x) - X_n(s;t,x)|$.

Lemma 8. *For all s,t such as $0 \leqslant s,t \leqslant T$, there exists a constant C so that:*

$$|X_m(s;t,x) - X_n(s;t,x)| \leqslant C\sup_{[0,T]}|\tilde{m} - \tilde{n}|.$$

According to lemma 8, we obtain the existence of C_1 and C_2 such as:

$$K_1 \leqslant \sup_{[0,T]}|\tilde{m} - \tilde{n}|\left(\sup_{[X_m(0;t,0),X_n(0;t,0)]} (g_f(X_m(t;0,y))f^{in}(y))C_1 + G_fC_2||f^{in}||_{L^1}\right). \quad (51)$$

Let us now study term K_2 in equation (49):

$$\begin{aligned}
K_2 = |\int_0^t \mathrm{e}^{-\gamma_f(t-s)}(\tilde{m}(s)\int_0^{+\infty} g_f(x)\mu(X_m(s;t,x))J_m(s;t,x)dx\\
- \tilde{n}(s)\int_0^{+\infty} g_f(x)\mu(X_n(s;t,x))J_n(s;t,x)dx)ds|
\end{aligned}$$

Aβ / PrP^c with $y = X(s;t,x)$ gives us:

$$\begin{aligned}
&K_2\\
&=|\int_0^t \mathrm{e}^{-\gamma_f(t-s)}\left(\tilde{m}(s)\int_{X_m(s;t,0)}^{+\infty} g_f(X_m(t;s,y))\mu(y)dy - \tilde{n}(s)\int_{X_n(s;t,0)}^{+\infty} g_f(X_n(t;s,y))\mu(y)dy\right)ds|,\\
&K_2 = |\int_0^t \mathrm{e}^{-\gamma_f(t-s)}\tilde{m}(s)\int_{X_m(s;t,0)}^{X_n(s;t,0)} g_f(X_m(t;s,y))\mu(y)dyds\\
&\quad + \int_0^t \mathrm{e}^{-\gamma_f(t-s)}\tilde{m}(s)\int_{X_n(s;t,0)}^{+\infty} \mu(y)(g_f(X_m(t;s,y)) - g_f(X_n(t;s,y)))dyds\\
&\quad + \int_0^t \mathrm{e}^{-\gamma_f(t-s)}(\tilde{m}(s) - \tilde{n}(s))\int_{X_n(s;t,0)}^{+\infty} g_f(X_n(t;s,y))\mu(y)dyds|,
\end{aligned}$$

and finally

$$K_2 \leqslant \int_0^t M_T \sup_{[X_m(s;t,0),X_n(s;t,0)]} (g_f(X_m(t;s,y))\mu(y))|X_n(s;t,0) - X_m(s;t,0)|ds$$
$$+ \int_0^t M_T \int_{X_n(s;t,0)}^{+\infty} G_f\mu(y)|X_m(t;s,y) - X_n(t;s,y)|dyds$$
$$+ \int_0^t |\tilde{m}(s) - \tilde{n}(s)|||g\mu||_{L^1}ds.$$

Lemma 8 provides the existence of constants C_1 and C_2 such as:

$$K_2 \leqslant \sup_{[0,T]}|\tilde{m} - \tilde{n}| \tag{52}$$
$$\left(M_T C_1 T \sup_{[0,T]}\big(\sup(g_f(X_m(t;s,y))\mu(y))\big) + M_T G_f C_2 T||\mu||_{L^1} + T||g\mu||_{L^1}\right).$$

Combining relations (51) and (52) gives us the existence of a constant α_1 such as:

$$I_{A1} \leqslant \alpha_1 \sup_{[0,T]}|\tilde{m} - \tilde{n}|. \tag{53}$$

We perform the same analysis for I_{A2}, the second term in equation (48) and find the existence of a constant α_2 such as:

$$I_{A2} \leqslant \alpha_2 \sup_{[0,T]}|\tilde{m} - \tilde{n}|. \tag{54}$$

Relations (53) and (54) implies the existence of a constant α such as:

$$\sup_{[0,T]}|A_m(t) - A_n(t)| \leqslant \alpha \sup_{[0,T]}|\tilde{m}(t) - \tilde{n}(t)|. \tag{55}$$

We now focus on $B_m(t) - B_n(t)$. According to equation (30), we have:

$$|B_m(t) - B_n(t)| \leqslant b(t)\underbrace{|\int_0^{+\infty} f_{a,m}(t,x) - f_{a,n}(t,x)dx|}_{I_{B1}} + b_f\underbrace{|\int_0^{+\infty} f_m(t,x) - f_n(t,x)dx|}_{I_{B2}}$$
$$+ b\underbrace{|\int_0^{x_0} u_m(t,x) - u_n(t,x)dx|}_{I_{B3}}. \tag{56}$$

We upper-bound I_{B2} and I_{B3} as we did previously for I_{A1} and I_{A2}, and finally find that there exist β_2 and β_3 such as:

$$I_{B2} \leqslant \beta_2 \sup_{[0,T]}|\tilde{m}(t) - \tilde{n}(t)|, \tag{57}$$
$$I_{B3} \leqslant \beta_3 \sup_{[0,T]}|\tilde{m}(t) - \tilde{n}(t)|. \tag{58}$$

We now have to study I_{B1}, the first term in equation (56):

$$\begin{aligned} I_{B1} &= \int_0^{+\infty} |f_{a,m}(t,x) - f_{a,n}(t,x)|dx, \\ &= \int_0^{+\infty} |f_a^{in}(X(0;t,x) + \gamma_f \int_0^t f_m(s, X(s;t,x))ds \\ &\quad - \left(f_a^{in}(X(0;t,x) + \gamma_f \int_0^t f_n(s, X(s;t,x)ds \right) |dx, \\ &= \gamma_f \int_0^t \underbrace{\int_0^{+\infty} |f_m(s, X(s;t,x) - f_n(s, X(s;t,x))|dx}_{I_{11}} ds. \end{aligned}$$

In I_{11}, we make the following substitution: $y = X(s;t,x)$ which can be written as $x = X(t;s,y)$. We then have:

$$\begin{aligned} I_{11} &= \int_{X(s;t,0)}^{+\infty} |f_m(s,y) - f_n(s,y)|J(t;s,y)dy, \\ &= \int_{X(s;t,0)}^{+\infty} |f_m(s,y) - f_n(s,y)| \exp(\int_s^t \frac{\partial v}{\partial x}(\sigma, X(\sigma;s,y))d\sigma)dy, \\ &= \int_{X(s;t,0)}^{+\infty} |f_m(s,y) - f_n(s,y)| \exp(\int_s^t m(\sigma)g'(X(\sigma;s,y))d\sigma)dy, \\ &\leqslant \int_{X(s;t,0)}^{+\infty} |f_m(s,y) - f_n(s,y)| \exp(M_T G(t-s))dy, \\ &\leqslant \mathrm{e}^{TGM_T} \int_0^{+\infty} |f_m(s,y) - f_n(s,y)|dy. \end{aligned}$$

According to (57), there exists β_2 such as:

$$I_{11} \leqslant \mathrm{e}^{TGM_T} \beta_2 \sup_{[0,T]} |\tilde{m}(t) - \tilde{n}(t)|.$$

We now go back to I_{B1}, and find that:

$$\begin{aligned} I_{B1} &\leqslant \gamma_f \int_0^t \mathrm{e}^{TGM_T} \beta_2 \sup_{[0,T]} |\tilde{m}(t) - \tilde{n}(t)|, \\ &\leqslant \gamma_f T \mathrm{e}^{TGM_T} \beta_2 \sup_{[0,T]} |\tilde{m}(t) - \tilde{n}(t)|. \end{aligned}$$

Therefore, there exists a constant β_1 such as:

$$I_{B1} \leqslant \beta_1 \sup_{[0,T]} |\tilde{m}(t) - \tilde{n}(t)|. \tag{59}$$

Combining relations (57)-(59) proves the existence of a constant β such as:

$$\sup_{[0,T]} |B_m(t) - B_n(t)| \leqslant \beta \sup_{[0,T]} |\tilde{m}(t) - \tilde{n}(t)|.$$

□

Proof. Proof of lemma 8. Let s, t such as $0 \leqslant s \leqslant t \leqslant T$.

$$\begin{aligned}
|X_m(s;t,x) - X_n(s;t,x)| = |&\int_s^t (g(X_m(\sigma;t,x))\tilde{m}(\sigma) - b)\, d\sigma \\
&- \int_s^t (g(X_n(\sigma;t,x))\tilde{n}(\sigma) - b)\, d\sigma|, \\
\leqslant &\int_s^t \tilde{m}(\sigma)|g(X_m(\sigma;t,x)) - g(X_n(\sigma;t,x))|d\sigma \\
&+ \int_t^s g(X_n(\sigma;t,x))|\tilde{m}(\sigma) - \tilde{n}(\sigma)|d\sigma, \\
\leqslant &\, GM_T \int_s^t \tilde{m}(\sigma)|X_m(\sigma;t,x) - X_n(\sigma;t,x)|d\sigma \\
&+ \left(\int_s^t (g(X_n(\sigma;t,x)))^2 d\sigma\right)^{1/2} \left(\int_s^t (\tilde{m}(\sigma) - \tilde{n}(\sigma))^2 d\sigma\right)^{1/2}
\end{aligned} \tag{60}$$

Because $g(0) = 0$ and $g'(x) \leqslant G$ for all x in $[0, +\infty)$, we have:

$$|g(X_n(s;t,x))| \leqslant GX_n(s;t,x),$$

and

$$\begin{aligned}
|X_n(s;t,x)| &= |x + \int_t^s (g(X_n(\sigma;t,x))\tilde{n}(\sigma) - b)\, d\sigma|, \\
&\leqslant x + \int_s^t b + GM_T|X_n(\sigma;t,x)|d\sigma.
\end{aligned}$$

Grönwall's inequality finally gives us the existence of a constant L_T such as

$$|X_n(s;t,x)| \leqslant L_T(2bT + x).$$

Let us now go back to relation (60):

$$\begin{aligned}
|X_m(s;t,x) - X_n(s;t,x)| \leqslant &\, GM_T \int_s^t |X_m(\sigma;t,x) - X_n(\sigma;t,x)|d\sigma \\
&+ GL_T(x + 2bT)T^{1/2} \left(\int_s^t (\tilde{m}(\sigma) - \tilde{n}(\sigma))^2 d\sigma\right)^{1/2}
\end{aligned}$$

We use Grönwall's inequality to obtain the following relation:

$$|X_m(s;t,x) - X_n(s;t,x)| \leqslant K(2bT + x)T \sup_{[0,T]} (\tilde{m}(t) - \tilde{n}(t)). \tag{61}$$

□

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