Math. Model. Nat. Phenom. 19 (2024) 19
https://doi.org/10.1051/mmnp/2023028

Mathematical Modelling of Natural Phenomena
www.mmnp-journal.org

Q-WELL-POSEDNESS OF AN Aβ-PROTEIN POLYMERIZATION MODEL

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Abstract. In this work, we consider a Becker-Döring-like mathematical interaction model between Aβ-monomers and Aβ proto-oligomers playing an important role in Alzheimer's disease. In this context, the clustering process where two or more Aβ-monomers spontaneously aggregate and form a seed of proto-oligomers is highlighted. We prove the quadratic well-posedness [4] of the problem associated with the estimation of clustering rate μ from measured data at different times.

Mathematics Subject Classification. 65L09, 65J22, 92B05.

Received March 9, 2023. Accepted September 7, 2023.

1. Introduction: a focus on the Aβ protein

Alzheimer's disease (AD) is an age-related neurodegenerative disease that consists of gradual neuron loss. It is characterized by the presence of neurofibrillary tangles and neuritic plaques in postmortem brain tissue [26]. On the one hand, tangles are intraneuronal accumulations due to a microtubule-binding protein called Tau protein, which is insoluble and hyperphosphorylated. Plaques, on the other hand, are extracellular aggregates of Aβ-peptides derived from the cleavage of the amyloid precursor protein (APP) with inflammation and astrogliosis phenomena [13, 27]. From these two main hypotheses explaining the cause and mechanism of AD, we consider only here the Aβ activity, leaving the even more complex coupling interactions with the Tau protein for future work. We remind here that Aβ proteins can adopt various stable conformations. When pathological, these misconformations lead to the creation of structured assemblies that can be used as biological markers of the disease [11, 17, 18]. Other mechanisms like oxidative stress, inflammation and altered cholesterol homeostasis are also involved in AD. We do not consider them either in our mathematical modelling approach. However, more details on the amyloid cascade hypothesis can be found in [25] (Part I, Chap. 2).

It is well known now that the Aβ self-assembly leads to different types of structures: first, the proto-oligomers that may create two types of elements. On the one hand, the fibrils, long linear polymeric structures that can coalesce, break or depolymerize to form the so-called amyloid plaques which constitute the visible deposits observed in most of the latest stages of AD patients. Oligomers, on the other hand, appear like smaller structures

Keywords and phrases: Q well-posedness, parameter estimation, inverse problem, polymerization process, Aβ-protein, Alzheimer' disease.

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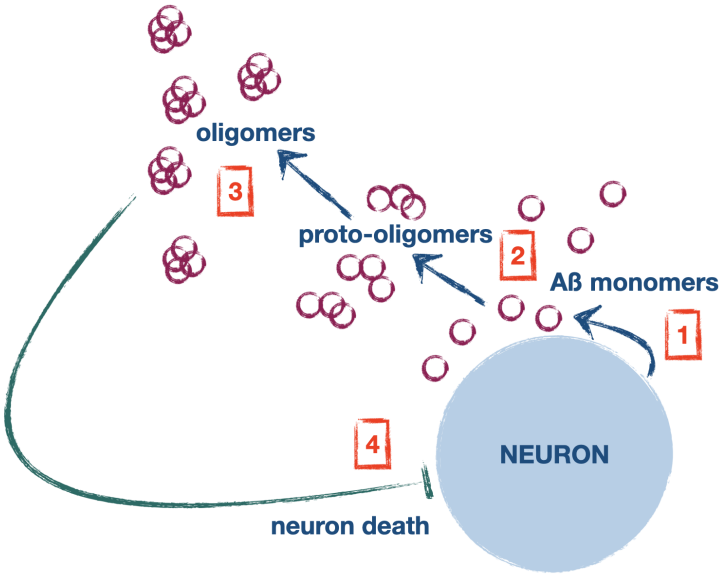

FIGURE 1. Production of Aβ oligomers from the neurons (1), their polymerization into proto-oligomers (2) and eventually to Aβ oligomers (3) able to regulate the neuronal activity or kill them (4).

than fibrils during the early stages of AD [6, 11, 21, 24, 32]. They are also able to join the amyloid plaque but this is not their major role in the pathology. Indeed, oligomers are the most armful characters. They can stress the neuron by stopping its activity. This process, called UPR (unfolded protein response) [1], is a way to save it temporarily (see Fig. 1). But with a repeated amount of stress, this latter may be killed. Repeated millions of times in the brain, this mechanism is at the origin of the memory impairment of the patient but also the fatal issue of the disease.

Here also, to simplify our model, we focus our attention on the early stage when only oligomers, the most dangerous elements of the disease, are formed. Indeed, even if fibrils play an important role in the disease, they appear not to be as dangerous as oligomers.

One of the most essential phenomena described and studied in this work relies on the ability of misfolded Aβ monomer to accidentally form clusters of proto-oligomers of any size lower than oligomers. Triggering this event in normal conditions is often highly stochastic, eventually driven by mutations or co-factors. However, during the laboratory experiments, it can be initiated by inoculation of pathological Aβ seeding and then accelerate the natural process, transforming it into a highly deterministic mechanism. The mechanism can be described as follows: Aβ-monomers can spontaneously change conformation and assemble into small structures called proto-oligomers. Once a proto-oligomer is formed, it has the ability to change size either by aggregating other monomers (polymerizing) or releasing a monomer(depolymerizing). Repeating this alternating gain and loss of monomers, the proto-oligomers can reach a certain given size and then become oligomers (stable structure, that is unable to polymerize or depolymerize) [2, 7].

Recent discoveries show that oligomers play a very determining role in the progression of Alzheimer's disease, more precisely in neuronal death. Indeed, the membrane of neurons is believed to be damaged by the presence of amyloid protein aggregates.

So, the propagation of Aβ-oligomers in the brain results from a combination of several factors at different scales. Thus, understanding the complex formation and replication of Aβ-oligomers from Aβ-monomers,

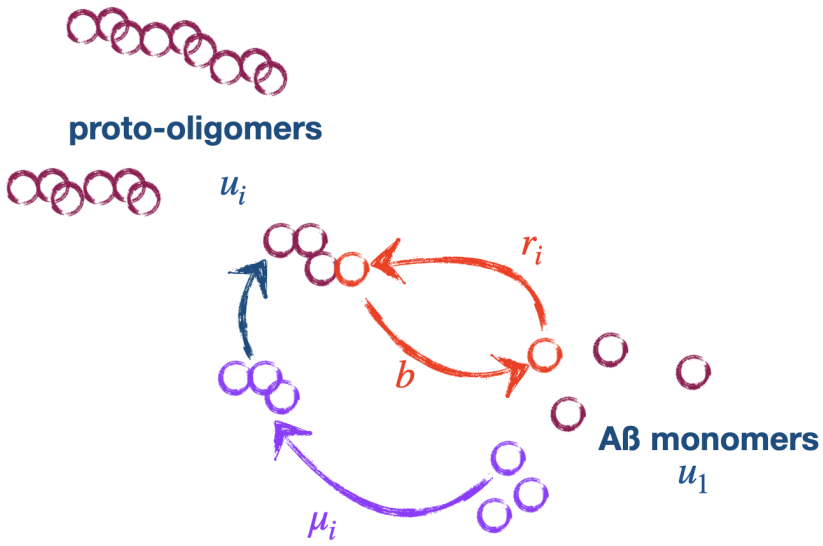

FIGURE 2. Detail of Fig. 1 when Aβ oligomers u_1 can form spontaneous clusters, of size i named u_i with a rate μ_i to start proto-oligomer dynamics. These proto-oligomers can polymerize with a size-dependent rate r_i or depolymerize with a constant rate b.

especially at the initial stage of the disease, is of paramount importance for us to develop therapeutic strategies before the first symptoms of dementia appear [9, 11, 22, 23, 26, 28].

In this paper, we focus then our modelling approach to this initial stage of the disease, by describing and analysing the polymerization mechanism of Aβ-monomers leading to Aβ proto-oligomers. This polymerization mechanism is based on a gain and loss competition of Aβ monomers with given kinetic rates. Consequently, when there are no proto-oligomers, the polymerization process cannot start. In experimental conditions, one needs at least a seed of Aβ proto-oligomer to trigger the disease that is when two or more monomers suddenly aggregate and forms a proto-oligomer of size i (i is the number of aggregated monomers).

The real cause from the clinical point of view of this triggering event is for the moment unknown, but once the very first nuclei of proto-oligomers are formed, then the process of proto-oligomerization starts. With a size-dependent rate, a proto-oligomer goes from size i to size $i+1$ by a gain of a monomer $\{i\}+\{1\} \to \{i+1\}$. On the other hand, it can depolymerize, that is going from size i to size $i-1$ by loss of a monomer with a constant (size-independent) rate $\{i\} \to \{i-1\}+1\}$.

This mechanism of gain and loss of monomers causes the appearance of proto-oligomer size distribution. By progressively lengthening, each of the oligomers reaches its maximum size and then becomes Aβ oligomers very harmful to neurons [12] and one of the causes of neuronal death [3, 16, 30, 31]. Many mathematical models have already studied polymerization leading to the formation of oligomers and also their strong relationship with the development of Alzheimer's disease. For more details, one can refer to [5, 8, 10, 14, 15, 19, 20, 29].

This paper is part of this momentum. With a simple size-structured model we highlight the very beginning of the polymerization process where monomers interact with proto-oligomers. So, we consider a population of Aβ monomers characterized by its concentration $u_1(t)$ that can interact with a population of Aβ proto-oligomers characterized by its concentration $u_i(t)$ where $i \in \{2, \cdots, N\}$, $N \in \mathbb{N}$ (see Fig. 2). The interest in taking into account the effect of spontaneous clustering is to be able to estimate its rate using temporal data on the concentrations of monomers and proto-oligomers. Indeed, this rate is an essential parameter in the early stage of the disease. Consequently, analyzing a model able to estimate appears to us as a big step in understanding AD.

TABLE 1. Description of the model variables and parameters.

Variable	Definition
$u_1(t)$	Concentration of Aβ monomers at time t
$u_i(t)$,	Concentration of Aβproto-oligomers of size $i = 2, \cdots N$ at time t
μ_i, $i = 2, \cdots, N$	Nucleation rate for proto-oligomers of size i
$r_i \geq 0$, $i = 2, ..., N$	Polymerization rate for proto-oligomers of size i
$b > 0$	Depolymerization rate (taken as a constant) for proto-oligomers
$t \geq 0$	the time

The paper is organized as follows, section 2 is devoted to the description of the model and the importance of the spontaneous clustering process in the context of Alzheimer's disease. In section 3, we analyze the quadratic well-posedness of the model. Section 4 is left for the conclusion and perspectives.

2. Model description

Our model describes the interaction dynamics between a population of Aβ-monomers and a population of Aβ proto-oligomers. This interaction is governed by a process of gain and loss of monomers which we refer to as the polymerization/depolymerization process. By polymerization we mean the gain of monomers by proto-oligomers and by depolymerization we mean the loss of monomers from proto-oligomers. The system is assumed to occur in a homogeneous domain and the main variables of the system are given in Table 1.

1. **Monomers**: Aβ-monomers population by gain and loss of a single or a group of monomers is described as follows

$$\frac{\mathrm{d}u_1(t)}{\mathrm{d}t} = -u_1(t)\sum_{i=2}^{N} r_i u_i(t) + b\Big(2u_2(t) + \sum_{i=3}^{N} u_i(t)\Big) - u_1(t)\sum_{i=2}^{N} i\mu_i.$$

   The first term on the right-hand side stands for the loss of monomers when Aβ proto-oligomers of all sizes polymerize. The second term on the right-hand side describes the gain of monomers when two or more proto-oligomers depolymerize. The last term stands for the multi-monomeric nucleation when i-monomers merge and spontaneously form a proto-oligomer of size i with the rate μ_i. The couple (r_i, b), $i \in \{2, \cdots, N\}$ is called kinetic coefficients of the model.
2. **Proto-oligomers**: Aβ proto-oligomers are structured in size ranging from $i = 2$ to $i = N$ and their dynamics is given by

$$\begin{cases} \dfrac{\mathrm{d}u_2(t)}{\mathrm{d}t} = -\big(b + r_2 u_1(t)\big)u_2(t) + bu_3(t) + u_1(t)\mu_2, \\ \dfrac{\mathrm{d}u_i(t)}{\mathrm{d}t} = r_{i-1}u_1(t)u_{i-1}(t) - \big(b + r_i u_1(t)\big)u_i(t) + bu_{i+1}(t) + u_1(t)\mu_i, \quad i = 3, .., N-1, \\ \dfrac{\mathrm{d}u_N(t)}{\mathrm{d}t} = r_{N-1}u_1(t)u_{N-1}(t) - \big(b + r_N u_1(t)\big)u_N(t) + u_1(t)\mu_N. \end{cases}$$

   The first equation of the system is for the dynamics of proto-oligomers of size $i = 2$. So, the model loses the proto-oligomers that either depolymerize and become monomers or polymerize to give proto-oligomer of size $i = 3$. The second equation is for proto-oligomers of size $2 < i < N$. It balances between what is gained or lost by the polymerization of proto-oligomers of size $i - 1$ and i itself and by depolymerization of proto-oligomers of size $i + 1$ and i itself. The third equation models the dynamics of the proto-oligomers of the maximal size N. For these proto-oligomers of size N, the concentration increases when those of size $N - 1$ gain monomers by polymerization while it decreases when they polymerize or depolymerize.

Either for monomers or proto-oligomers, the nucleation process is integrated into each equation of the model with a rate μ depending on the size of the proto-oligomers.

Let us denote $u(t) = (u_1(t), \cdots, u_N(t))^T$ the vector of unknowns. Knowing a sequence of measures (approximations) of $u(t)$ at given times $t_1, \cdots, t_p$, $p \in \mathbb{N}$, we would like to estimate the nucleation parameter $\mu = (\mu_2, \cdots, \mu_N)^T \in \mathbb{R}^{N-1}$. Thus, for $0 < t_1 < \cdots < t_p \leq T$ and measures $(Y^{(1)}, \cdots, Y^{(p)}) \in \mathbb{R}^{Np}$ we look for $\mu \in \mathbb{R}_+^{N-1}$ such that

$$u(t_k) = Y^{(k)}, \quad \forall k = 1, \cdots, p, \tag{2.1}$$

with $u(t_k)$ the solution evaluated at time t_k.

Let us denote $Y = (Y^{(1)}, \cdots, Y^{(p)})^T$ and we define $F : \mathbb{R}^{N-1} \longrightarrow \mathbb{R}^{Np}$ such that $F(\mu) = (u(t_1), \cdots, u(tp))^T \in \mathbb{R}^{Np}$, then we are looking for $\mu \in \mathbb{R}_+^{N-1}$ such that $F(\mu) = Y$.

We introduce the function $G = (G_1, \cdots, G_N)^T : \mathbb{R}^N \longrightarrow \mathbb{R}^N$ such that for all $v = (v_1, \cdots, v_N)^T \in \mathbb{R}^N$ we put

$$\begin{aligned}
G_1(v) &= -v_1 \sum_{i=2}^{N} r_i v_i + b(2v_2 + \sum_{i=3}^{N} v_i) - v_1 \sum_{i=2}^{N} i\mu_i \\
G_2(v) &= -bv_2 + bv_3 + \mu_2 v_1 \\
&\vdots \\
G_{N-1}(v) &= v_1(r_{N-2}v_{N-2} - r_{N-1}v_{N-1} + \mu_{N-1}) + b(v_N - v_{N-1}) \\
G_N(v) &= v_1(r_{N-1}v_{N-1} - r_N v_N + \mu_N) - bv_N),
\end{aligned}$$

and rewrite the interaction model between Aβ-monomers and Aβ proto-oligomers as follow

$$\left\{ \begin{array}{rcll} \dfrac{\mathrm{d}u(t)}{\mathrm{d}t} & = & G(u(t)), & t \in (0, T_f], \\ u(0) & = & u^0, & \end{array} \right. \tag{2.2}$$

where $u^0 = (u_1^0, \cdots, u_N^0)^T \in \mathbb{R}_+^N$.

Equality in (2.1) is needed to be true in the least squares sense, which means we are looking for $\mu^* = (\mu_2^*, \cdots, \mu_N^*)^T \in \mathbb{R}^{N-1}$ that minimizes the function $J : \mathbb{R}^{N-1} \longrightarrow \mathbb{R}$ defined for all $\mu \in \mathbb{R}^{N-1}$ by $J(\mu) = \dfrac{1}{2} \displaystyle\sum_{k=1}^{p} |u(t_k) - Y^{(k)}|^2$ with u solution of (2.2).

Denoting $Y = (Y^{(1)}, \cdots, Y^{(p)}) \in \mathbb{R}^{Np}$ we can write J as follow

$$J(\mu) = \frac{1}{2} \|F(\mu) - Y\|^2,$$

where $\|\cdot\|$ stands for the Euclidean norm in $\mathbb{R}^{Np}$.

In the following, we recall the general framework of what is called "Q well-posed" problems.

2.1. Reminder on Q well-posed problems (see [4])

Let E_1 be a Banach space, E_2 an Hilbert one, Ω an open subset of E_1 and $\varphi : \Omega \longrightarrow E_2$ a C^2 regular function. Let $U \subset \Omega$ be a convex and closed set. For all $Z \in E_2$, we introduce the function $J_Z : \Omega \longrightarrow \mathbb{R}$ such that

$$J_Z(\mu) = \frac{1}{2} \|\varphi(\mu) - Z\|_{E_2}^2, \quad \forall \mu \in \Omega. \tag{2.3}$$

We are looking for $\hat{\mu} \in U$ that minimizes J_Z means

$$\begin{cases} \hat{\mu} \in U \\ J_Z(\hat{\mu}) \leq J_Z(\mu) \quad \forall \mu \in \Omega. \end{cases} \tag{2.4}$$

This is the identification problem of μ from a measure, Z, of $\varphi(\mu)$.

We have the following definitions (for more details see [4])

Definition 2.1. The problem (2.4) is said to be "Q well-posed" (Quadradically well-posed) if there exists a neighborhood V_0 of $\varphi(\mu)$ in E_2 such that

1. For all $Z \in V_0$ the problem (2.4) has a unique solution $\hat{u} \in U$.
2. For all $Z \in V_0$ the function J_Z has no parasitic stationary points.
3. The function $Z \in V_0 \longrightarrow \hat{\mu} \in U$ is locally Lipschitz continuous.

Definition 2.2. The problem (2.4) is said to be identifiable on a subset U_1 of Ω if φ is injective on U_1.

Let $\mu^0, \mu^1 \in \Omega$ such that the segment $\{(1-s)\mu^0 + s\mu^1, s \in [0,1]\}$ is included Ω. We introduce the function $P_{\mu^0,\mu^1} : [0,1] \longrightarrow E_2$ such that $P_{\mu^0,\mu^1}(s) = \varphi((1-s)\mu^0 + s\mu^1) \ \ \forall s \in [0,1]$. For simplicity we denote P_{μ^0,μ^1} by P.

We can see the function P as a curve in E_2; the tangent to P at s is given by $P'(s)$. We have

$$P'(s) = D\varphi((1-s)\mu^0 + s\mu^1)(\mu_1 - \mu_0) \in E_2.$$

Definition 2.3. The problem (2.4) is said to be linearly identifiable (L.I) on a subset $U_1 \subset \Omega$ if for all $\mu^0, \mu^1 \in U_1$, for all $s \in [0,1]$ we have $P'(s) = 0 \Rightarrow \mu^0 = \mu^1$.

In the case where φ is linear and continuous then the identifiability is equivalent to the L.I

Definition 2.4. The problem (2.4) is said to be **linearly stable** on a subset $U_1 \subset \Omega$ if there exists $\alpha_m > 0$ such that

$$\alpha_m \|\mu_0 - \mu_1\| \leq \int_0^1 \|P'(s)\| \, \mathrm{d}s, \quad \forall \ \mu_0, \mu_1 \in U_1.$$

Definition 2.5. Suppose that the problem (2.4) is L.I. on $U_1 \subset \Omega$ and consider $\mu_0, \mu_1 \in U_1$ with $\mu_0 \neq \mu_1$.
i) We call **deflection on** P **between** s_0 **and** s_1 with $s_0, s_1 \in [0,1]$ the number

$$\Theta(P, s_0, s_1) = \arccos\left(\langle \frac{P'(s_0)}{\|P'(s_0)\|}, \frac{P'(s_1)}{\|P'(s_1)\|} \rangle\right) \in [0, \pi]$$

where $\langle \cdot, \cdot \rangle$ is the scalar product on E_2 (this number is the angle between tangent vectors on P in s_0 and s_1 respectively).
ii) We call **deflection on** P the number

$$\Theta(P) = \sup_{s_0, s_1 \in [0,1]} \Theta(P, s_0, s_1)$$

Definition 2.6. Suppose that the problem (2.4) is L.I. on $U_1 \subset \Omega$. We call **deflection on** (φ, U) the number $\Theta(\varphi, U_1) \in [0, \pi]$ given by

$$\Theta(\varphi, U_1) = \sup_{\mu^0, \mu^1 \in U_1, \mu^0 \neq \mu^1} \Theta(P_{\mu^0,\mu^1})$$

Definition 2.7. The problem (2.4) is said to be a **FC problem** (finitely curvature problem) on $U_1 \subset \Omega$ if there exist $R > 0$ such that

$$\|P''(s)\| \leq \frac{1}{R}\|P'(s)\|^2, \quad \forall\, s \in [0,1], \quad \forall\, \mu^0, \mu^1 \in U_1,\ \mu^0 \neq \mu^1. \tag{2.5}$$

Definition 2.8. Let $U_1 \subset \Omega$ and suppose that the problem (2.4) is L.I. and FC on U_1. Then we say that (2.4) is a **FC/LD problem** (finite curvature/limited deflected problem) on U_1 if

$$\Theta(\varphi, U_1) \leq \frac{\pi}{2}.$$

For simplicity we recall here the following result which is in fact Theorem 4.4.1 page 177 of [4]:

Proposition 2.9. *Suppose that the problem (2.4) is linearly stable and FC/LD on U. Then it is Q - well posed with the neighbourhood V_0 given by*

$$V_0 = \{z \in E_2,\ \ dist(z, \varphi(U)) < R\}$$

where $R > 0$ satisfies the inequality (2.5) and

$$dist(z, \varphi(U)) = \inf_{y \in \varphi(U)} \|z - y\|.$$

Now we can state the main result of this section:

Theorem 2.10. *Let assume*

1. *$dim(E_1) < +\infty$*
2. *U is bounded (which implies that U is convex and compact)*
3. *The problem (2.4) is (L.I) on an open neighborhood U_1 of U*
4. *For all $\mu^0, \mu^1 \in U$ with $\mu^0 \neq \mu^1$, we have*

$$\langle P'(s_1), P'(s_2)\rangle \geq 0, \quad \forall s_1, s_2 \in [0,1]. \tag{2.6}$$

Then the problem (2.4) is Q well-posed.

Proof. From Theorem 4.5.1 page 180 of [4] we deduce that the problem (2.4) is linearly stable and a FC problem on U. Moreover from (2.6) we deduce that $\Theta(\varphi, U) \leq \frac{\pi}{2}$ which implies that (2.4) is a FC/LD problem on U. Then Proposition 2.9 gives us the result. □

2.2. Main result of the paper

For our problem of parameter identification, let assume $p = 1$. So, the function F is recasted as follow

$$\begin{aligned} F:\ & \mathbb{R}^{N-1} \longrightarrow \mathbb{R}^N \\ & \mu \longrightarrow F(\mu) = u(t_1) \end{aligned}$$

where u is the unique solution of the interaction system between monomers and proto-oligomers.

We apply the general framework described in Section 2.1 with $E_1 = \mathbb{R}^{N-1}$, $E_2 = \mathbb{R}^N$, $\varphi = F$ and $Z = Y^{(1)}$.

We consider U as a convex and compact subset of $\mathbb{R}^{N-1}$. We split the G function in (2.2) in two parts: one not depending on μ denoted G_0 and another one depending on μ. So, $G(v_1, \cdots, v_N) = G_0(v_1, \cdots, v_N) + \big[M\mu\big]v_1$ with $G_0 : \mathbb{R}^N \longrightarrow \mathbb{R}^N$

$$G_0(v_1,\cdots,v_N)=\begin{pmatrix} G_{01}(v_1,\cdots,v_N)\\ G_{02}(v_1,\cdots,v_N)\\ \vdots\\ G_{0N}(v_1,\cdots,v_N)\end{pmatrix},$$

where

$$\begin{aligned}
G_{01}(v_1,\cdots,v_N)&=-v_1\sum_{i=2}^{N}r_iv_i+b\Big(2v_2+\sum_{i=3}^{N}v_i\Big)\\
G_{02}(v_1,\cdots,v_N)&=-bv_2+bv_3\\
G_{03}(v_1,\cdots,v_N)&=-r_3v_1v_3-bv_3+bv_4\\
&\vdots\ \vdots\ \vdots\\
G_{0N-1}(v_1,...,v_N)&=v_1(r_{N-2}v_{N-2}-r_{N-1}v_{N-1})+b(v_N-v_{N-1})\\
G_{0N}(v_1,...,v_N)&=v_1(r_{N-1}v_{N-1}-r_Nv_N)-bv_N
\end{aligned}$$

and the matrix $M\in\mathcal{M}_{N,N-1}(\mathbb{R})$ is given by

$$M=\begin{pmatrix} -2 & -3 & -4 & -5 & \cdots & -(N-1) & -N\\ 1 & 0 & 0 & 0 & \cdots & 0 & 0\\ 0 & 1 & 0 & 0 & \cdots & 0 & 0\\ \vdots & \vdots & \vdots & \vdots & \cdots & \vdots & \vdots\\ 0 & 0 & 0 & 0 & \cdots & 0 & 1\end{pmatrix}.$$

From this, we rewrite our system (2.2) as follow

$$\begin{cases}\dfrac{\partial u}{\partial t}=G_0\big(u(t)\big)+\big[M\mu\big]u_1(t),\\ u(0)=u^0\end{cases}\tag{2.7}$$

and we state the main result of this paper

Theorem 2.11. *Let $U\subset\mathbb{R}^{N-1}$ a compact and convex subset of $\Big((0,+\infty)\Big)^{N-1}$ and let assume $u_1^0>0$. Then there exits $r>0$ depending on U and u^0 such that for all t_1 satisfying $0<t_1<r$, the problem (2.4) is $Q-$well posed.*

To prove this result we just need to fulfill the hypothesis 3 and 4 of Theorem 2.10.

2.2.1. Proof of hypothesis 3 of Theorem 2.10

We consider an open and bounded neighborhood U_1 of U with $U_1\subset\Omega$ and we prove the expected result by contradiction method, means we assume $\mu^0\in U_1$, $\mu^1\in U_1$ with $\mu^0\neq\mu^1$ and $s\in[0,1]$ such that $P'(s)=0$ and we will end up with a contradiction.

We have $P(s) = F\Big((1-s)\mu^0 + s\mu^1\Big) = u(t_1, s)$, where $u(t_1, s)$ is solution of

$$\begin{cases} \dfrac{\partial u}{\partial t} = G_0\Big(u(t_1, s)\Big) + u_1(t_1, s)M\Big((1-s)\mu^0 + s\mu^1\Big), \\ u(0, s) = u^0. \end{cases} \tag{2.8}$$

We have $P'(s) = \dfrac{\partial u}{\partial s}(t_1, s)$. Let put $V(t, s) = \dfrac{\partial u}{\partial s}(t, s)$ that satisfies the following system obtained by derivation with respect to s of system (2.8)

$$\begin{cases} \dfrac{\partial V}{\partial t}(t, s) & = \displaystyle\sum_{k=1}^{N} \frac{\partial G_0}{\partial u_k}\Big(u(t, s)\Big)\frac{\partial u_k}{\partial s} + V_1(t, s)M\Big((1-s)\mu^0 + s\mu^1\Big) + u_1(t, s)M\big(\mu^1 - \mu^0\big), \\ V(0, s) & = 0. \end{cases} \tag{2.9}$$

Denoting $\delta = M\big(\mu^1 - \mu^0\big)$ then the system (2.9) becomes thanks to the relation $P'(s) = 0$,

$$\begin{cases} \dfrac{\partial V}{\partial t}(t, s) & = DG_0\Big(u(t, s)\Big)V(t, s) + V_1(t, s)M\Big((1-s)\mu^0 + s\mu^1\Big) + u_1(t, s)\delta, \\ V(0, s) & = 0, \\ V(t_1, s) & = 0. \end{cases} \tag{2.10}$$

The hypothesis $\mu^{(0)} \neq \mu^{(1)}$ implies that $\delta \neq 0$ because the rank of matrix M is $N - 1$.

Now let divides by $\|\delta\|$ the system (2.10) then we get

$$\begin{cases} \dfrac{\partial V}{\partial t}\dfrac{1}{\|\delta\|_\infty} = DG_0(u)\dfrac{V}{\|\delta\|_\infty} + \dfrac{V_1}{\|\delta\|_\infty}M\Big((1-s)\mu^0 + s\mu^1\Big) + u_1\dfrac{1}{\|\delta\|_\infty}\delta, \\ V(0, s) = 0, \\ V(t_1, s) = 0. \end{cases}$$

Let use again the notation δ for $\dfrac{\delta}{\|\delta\|_\infty}$ and V for $\dfrac{V}{\|\delta\|_\infty}$. We can then assume that V and δ satisfy (2.10) with $\|\delta\|_\infty = 1$.

The proof of our result will follow several steps.

Step 1 Let state that u, $\dfrac{\partial u}{\partial t}$ and $DG_0(u)$ are bounded

Proposition 2.12. *There exists $C_1 \geq 0, C_2 \geq 0, L \geq 0$ depending on u^0 such that $0 \leq u_i(t) \leq C_1, \forall i = 1, \cdots, N$; $\|\dfrac{\partial u}{\partial t}(t, s)\| \leq L$; $\|DG_0(u(t))\| \leq C_2 \quad \forall t \in [0, T]$, $\forall s \in [0, 1]$.*

Proof. The total mass of the interaction system between monomers and proto-oligomers is given by $\rho(t) = \sum_{i=1}^{N} iu_i(t) = u_1(t) + \sum_{i=2}^{N} iu_i(t)$. We have $\rho(t) \leq \rho(0)$, $\forall t \geq 0$. This inequality, that we prove in the appendix, is due to the fact that proto-oligomers of size N are not longer considered in the model when they gain monomers. So, denoting $K = \sum_{i=1}^{N} iu_i^0$ we can write $\forall\, t \in [0, T]$, $\forall\, s \in [0, 1]$,

$$0 \leq u_i(t, s) \leq \frac{K}{i} \leq C_1.$$

Knowing that u belongs to a bounded subset, we deduce that there exists $L \geq 0$ such that

$$\|\frac{\partial u}{\partial t}(t,s)\| \leq L \ \ \forall\, t \in [0,T], \forall\, s \in [0,1]. \tag{2.11}$$

From the continuity of DG_0 and the fact that u belongs to a compact of $\mathbb{R}^N$ we deduce the existence of $C_2 \geq 0$ such that

$$\|DG_0(u(t))\| \leq C_2, \ \forall\, t \in [0,T], \forall\, s \in [0,1]. \tag{2.12}$$

□

Step 2 Let state that V and $\dfrac{\partial V}{\partial t}$ are bounded

Proposition 2.13. *There exists $C_3 \geq 0, C_4 \geq 0$ such that $\|V\| \leq C_3$ and $\|\dfrac{\partial V}{\partial t}\| \leq C_4$ $\forall\, t \in [0,T]$, $\forall\, s \in [0,1]$.*

Proof. Let multiply the equation (2.10) by V and get the relation

$$\frac{1}{2}\frac{\partial\Big(\|V\|^2\Big)}{\partial t} = DG_0(u)V \cdot V + M\Big((1-s)\mu^0 + s\mu^1\Big)V_1 \cdot V + u_1\delta \cdot V.$$

From the estimations $\|DG_0(u(t))\| \leq C_2$; $\|M\Big((1-s)\mu^0+s\mu^1\Big)\| \leq A_0$ with A_0 constant; $\|V_1\| \leq \|V\|$; $\|u_1\| \leq C_1$ and $\|\delta\|_\infty = 1$, we deduce the inéquality

$$\frac{1}{2}\frac{\partial\Big(\|V\|^2\Big)}{\partial t} \leq \big(C_2 + A_0\big)\big\|V\big\|^2 + C_1\big\|V\big\|, \ \text{for all } t \in (0,T].$$

Applying Young inequality to the last term at the left hand side of the previous relation, we deduce the estimate

$$\frac{\partial\Big(\|V\|^2\Big)}{\partial t} \leq \big(2C_2 + 2A_0 + 1\big)\big\|V\big\|^2 + C_1^2, \ \text{for all} \quad t \in (0,T], \tag{2.13}$$

Using Gronwall lemma we deduce in one hand

$$\big\|V\big\|^2 \leq \big\|V(0,s)\big\|^2 \mathrm{e}^{(2C_2+2A_0+1)t} + \frac{C_1^2}{2C_2+2A_0+1}\mathrm{e}^{(2C_2+2A_0+1)t} = \frac{C_1^2}{2C_2+2A_0+1}\mathrm{e}^{(2C_2+2A_0+1)t}.$$

So, denoting $C_3 = C_1\sqrt{\dfrac{\mathrm{e}^{(2C_2+2A_0+1)T}}{2C_2+2A_0+1}}$ we get $\|V\| \leq C_3$.

In other hand, from the time evolution equation of V we have

$$\|\frac{\partial V}{\partial t}\| \leq \|DG_0(u)\|\|V\| + \|V_1\|\|M\big((1-s)\mu^0 + s\mu^1\big)\| + \|u_1\|\|\delta\|, \quad \forall\, t \in]0,T].$$

Knowing that $\|DG_0(u)\| \leq C_2$, $\|M\big((1-s)\mu^0 + s\mu^1\big)\| \leq A_0$, $\|u_1\| \leq C_1$, $\|\delta\|_\infty = 1$ and $\|V\| \leq C_3$, then we deduce

$$\|\frac{\partial V}{\partial t}\| \leq C_4 \tag{2.14}$$

with $C_4 = (C_2 + A_0)C_3 + C_1$. □

Step 3

In one hand for small time interval $[0, t_1]$, it is easy to see that V is under linear in time. Indeed, we have $V(t) = V(0,s) + \int_0^t \frac{\partial V}{\partial t} d\tau = \int_0^t \frac{\partial V}{\partial t} d\tau$ which gives us, thanks to (2.14), the expected result

$$\|V\| \leq C_4 t, \quad \forall \quad t \in [0, t_1]. \tag{2.15}$$

In other hand, we have $u_1(t,s) = u_1^0 + \int_0^t \frac{\partial u_1}{\partial t} d\tau$, then $u_1(t,s) \geq u_1^0 - \int_0^t \left|\frac{\partial u_1}{\partial t}\right| d\tau$.

Using the result proved in Proposition 2.12 we deduce $u_1(t,s) \geq u_1^0 - Lt$, $\forall \quad t > 0$. Choosing $\tau_1 > 0$ such that $\tau_1 < \frac{u_1^0}{2L}$ we write the estimation

$$u_1(t,s) \geq \frac{u_1^0}{2}, \quad \forall \quad t \in [0, \tau_1]. \tag{2.16}$$

We consider $0 < t_1 \leq \tau_1$ and assume there exists an index i_0 such that $|\delta_{i_0}| = 1$. Then the component i_0 of equation (2.10) is

$$\frac{\partial V_{i_0}}{\partial t} = \Big[DG_0(u)V\Big]_{i_0} + \Big[\big[M\Big((1-s)\mu^0 + s\mu^1\Big)\big]V_1\Big]_{i_0} + u_1\delta_{i_0}, \qquad t \in (0, T].$$

From Rolle's theorem and knowing that $V_{i_0}(0) = V_{i_0}(t_1)$, then there exists at least $\tau \in (0, t_1)$ such that $\frac{\partial V_{i_0}(\tau)}{\partial t} = 0$. So,

$$u_1(\tau, s)\delta_{i_0} = -\Big(\big[DG_0(u(\tau,s))V(\tau,s)\big]_{i_0} + \big[M\big((1-s)\mu^0 + s\mu^1\big)\big]_{i_0} V_1(\tau, s)\Big).$$

The hypothesis $|\delta_{i_0}| = 1$ implies $\frac{u_1^0}{2} \leq \Big|[DG_0(u)V(\tau)]_{i_0} + [M\big((1-s)\mu^0 + s\mu^1\big)]_{i_0} V_1(\tau)\Big|$. Thanks to (2.15), we deduce the existence of $C_5 > 0$ such that $\frac{u_1^0}{2}|\delta_{i_0}| < C_5 t_1$. Then $|\delta_{i_0}| \leq \frac{2C_5}{u_1^0} t_1$.

One can choose $r = \frac{1}{2}\min(\frac{u_1^0}{L}, \frac{u_1^0}{2C_5})$, then if $0 < t_1 < r$ we have $|\delta_{i_0}| < 1$ which contradicts the fact that $|\delta_{i_0}| = 1$. That achieves the proof of the linear identifiability of our problem.

2.2.2. Proof of hypothesis 4 of Theorem 2.10

Let consider $E(t) = V(t, s_1)V(t, s_2)$. We then obtain in one hand $E(0) = V(0, s_1)V(0, s_2) = 0$ and in other hand, from the expansion

$$E'(t) = \frac{\partial V(t, s_1)}{\partial t} V(t, s_2) + \frac{\partial V(t, s_2)}{\partial t} V(t, s_1)$$

we deduce at $t = 0$ the relation $E'(0) = 0$ because $V(0, s_1) = V(0, s_2) = 0$. Now we need to evaluate $E''(0)$. For this let use notations V', V'' and v''' as respectively the first, second and third derivatives with respect to t. So we have

$$E''(t) = V''(t, s_1)V(t, s_2) + V''(t, s_2)V(t, s_1) + 2V'(t, s_2)V'(t, s_1).$$

Taking $t=0$ we get $E''(0)=2V'(0,s_2)V'(0,s_1)$. From this, we can state the following result on $E''(0)$

Lemma 2.14. *There is $\lambda_M>0$ such that*

$$E''(0)\geq 2\lambda_M(u_1^0)^2\|\alpha\|^2,\quad \textit{where } \alpha=\mu^1-\mu^0.$$

Proof. Let remind the equation satisfied by $V(t,s_1)$:

$$\frac{\partial V}{\partial t}(t,s_1)=DG_0\Big(u(t,s_1)\Big)V(t,s_1)+V_1(t,s_1)M\Big((1-s_1)\mu^0+s_1\mu^1\Big)+u_1(t,s_1)M(\mu^1-\mu^0)\quad \forall\, s_1\in[0,1].$$

Taking $t=0$, we obtain

$$V'(0,s_1)=u_1(0,s_1)(\mu^1-\mu^0)=u_1^0M(\mu^1-\mu^0).$$

Doing the same with s_2 we obtain

$$V'(0,s_2)=u_1(0,s_2)(\mu^1-\mu^0)=u_1^0M(\mu^1-\mu^0).$$

Since $E''(0)=2V'(0,s_1)V'(0,s_2)$ we have

$$E''(0)=2(u_1^0)^2(M\cdot\alpha)(M\cdot\alpha)=2(u_1^0)^2(M^TM\alpha\cdot\alpha).$$

The matrix M^TM is a positive defined and symmetric matrix because the $rank(M)=N-1$. So there exists $\lambda_M>0$ (the smallest eigenvalue of M^TM) such that $M^TM\alpha\cdot\alpha\geq\lambda_M\|\alpha\|^2$ which achieves the proof of the lemma. □

Now assume that $u_1^0>0$ and $\alpha\neq 0$, then $E''(0)>0$. Since E is of class C^2 so we have the Taylor expansion $E(t)=E(0)+E'(0)t+\frac{t^2}{2}E''(0)+o(t^2)$. As $E(0)=E'(0)=0$ then $E(t)=\frac{t^2}{2}E''(0)+o(t^2)$. So, if t is small enough we get $E(t)\geq 0$, but the interval for which $E(t)\geq 0$ depends on α and we need an non-dependent interval. So the key point is to use the Taylor expansion with integral remainder

$$E(t)=E(0)+E'(0)t+\frac{t^2}{2}E''(0)+\frac{t^3}{2}\int_0^1(1-r)^2E^{(3)}(rt)\mathrm{d}r.$$

Since $E(0)=E'(0)=0$ then the previous expansion becomes

$$E(t)=\frac{t^2}{2}E''(0)+\frac{t^3}{2}\int_0^1(1-r)^2E^{(3)}(rt)\mathrm{d}r. \tag{2.17}$$

From (2.17) we can state the following result

Lemma 2.15. *There exists a constant C_5 that does not depend on α such that*

$$|E^{(3)}(t)|\leq C_5\|\alpha\|^2,\ \forall\, t\in[0,1].$$

Proof. We have

$$E^{(3)}(t)=V'''(t,s_1)\cdot V(t,s_2)+3V''(t,s_1)\cdot V'(t,s_2)+3V'(t,s_1)\cdot V''(t,s_2)+V(t,s_1)\cdot V'''(t,s_2).$$

So, it is sufficient to show that

$$|V^{(k)}(t,s_j)| \leq C\|\alpha\|, \ \forall\, k=0,1,2,3,\dots \text{ and } \forall\, j=1,2. \tag{2.18}$$

Since μ^0 and μ^1 are in the bounded set U, then there exists a constant $\bar{\mu}>0$ such that $|\mu^0| \leq \bar{\mu}$ and $|\mu^1| \leq \bar{\mu}$. So we have $|(1-s)\mu^0 + s\mu^1| \leq \bar{\mu}$ and $|\alpha| \leq 2\bar{\mu}$. We will prove (2.18) in the case $j=1$ and it will be the same reasoning for $j=2$.

Step 1 : $k=0$ or $k=1$

We have

$$\begin{cases} V'(t,s_1) = DG_0(u(t,s_1))V(t,s_1) + V_1(t,s_1)M\Big((1-s_1)\mu^0 + s_1\mu^1\Big) + u_1(t,s_1)M\alpha, \ \forall\, s_1 \in [0,1] \\ V(0,s_1) = 0. \end{cases} \tag{2.19}$$

Dropping the arguments to simplify notation, we then multiply (2.19) by V and get

$$\begin{cases} \dfrac{1}{2}\dfrac{\partial(\|V\|^2)}{\partial t} = DG_0(u)V\cdot V + M\Big((1-s_1)\mu^0 + s_1\mu^1\Big)V_1\cdot V + u_1 M\alpha\cdot V, \\ V(0,s_1) = 0, \end{cases}$$

which gives

$$\begin{cases} \dfrac{1}{2}\dfrac{\partial(\|V\|^2)}{\partial t} \leq \|DG_0(u)\|\|V\|^2 + \|M\Big((1-s_1)\mu^0 + s_1\mu^1\Big)\|\|V_1\|\|V\| + \|u_1\|\|M\alpha\|\|V\|, \\ V(0,s_1) = 0, \end{cases}$$

as $\|DG_0(u)\| C_2$, $\|M\Big((1-s_1)\mu^0 + s_1\mu^1\Big)\| \leq \|M\|\bar{\mu}$, $\|V_1\| \leq \|V\|$, $\|u_1\| \leq C_1$ and $\|M\alpha\| \leq \|M\|\|\alpha\|$ then the previous inequality becomes

$$\begin{cases} \dfrac{1}{2}\dfrac{\partial(\|V\|^2)}{\partial t} \leq C_2\|V\|^2 + \|M\|\bar{\mu}\|V\|^2 + C_1\|M\|\|\alpha\|\|V\|, \\ V(0,s_1) = 0. \end{cases} \tag{2.20}$$

By setting $\alpha_0 = C_1\|M\|\|\alpha\|$ we get

$$\begin{cases} \dfrac{1}{2}\dfrac{\partial(\|V\|^2)}{\partial t} \leq (C_2 + \|M\|\bar{\mu})\|V\|^2 + \alpha_0\|V\|, \\ V(0,s_1) = 0. \end{cases} \tag{2.21}$$

Applying Young's inequality to the last term at the right hand side we write $\alpha_0\|V\| \leq \frac{\alpha_0^2}{2} + \frac{\|V\|^2}{2}$.
Hence the inequality (2.21) becomes

$$\begin{cases} \dfrac{\partial(\|V\|^2)}{\partial t} \leq (2C_2 + 2\|M\|\bar{\mu} + 1)\|V\|^2 + \alpha_0^2, \\ V(0,s_1) = 0. \end{cases} \tag{2.22}$$

From Gronwall's lemma one deduces

$$\|V\|^2 \leq \|V(0,s_1)\|e^{(2C_2+2\|M\|\bar{\mu}+1)t} + \frac{\alpha_0^2\big(e^{(2C_2+2\|M\|\bar{\mu}+1)t}\big)}{2C_2+2\|M\|\bar{\mu}+1} \leq \frac{\alpha_0^2\big(e^{(2C_2+2\|M\|\bar{\mu}+1)t}\big)}{2C_2+2\|M\|\bar{\mu}+1} \ \forall\, t\in[0,T].$$

We set $C_6 = C_1\|M\|\sqrt{\dfrac{e^{(2C_2+2\|M\|\bar{\mu}+1)t}}{2C_2+2\|M\|\bar{\mu}+1}}$, hence the estimate of $V(t,s_1)$ is given by

$$\|V(t,s_1)\| \leq C_6\|\alpha\| \qquad \forall\, t\in[0,T]. \tag{2.23}$$

Now, from (2.19) one deduces

$$\|V'(t,s_1)\| \leq \|DG_0(u)\|\|V\| + \|V_1\|\|M\big((1-s_1)\mu^0+s_1\mu^1\big)\| + \|u_1\|\|M\alpha\|,$$

which gives

$$\|V'(t,s_1)\| \leq C_2\|V(t,s_1)\| + \|V(t,s_1)\|\|M\|\bar{\mu} + C_1\|M\|\|\alpha\|.$$

We then obtain

$$\|V'(t,s_1)\| \leq C_7\|\alpha\| \qquad \forall\, t\in[0,T], \tag{2.24}$$

with $C_7 = C_2C_6 + C_6\|M\|\bar{\mu} + C_1\|M\|$.

Step 2 : $k=2$

Deriving the equation (2.19) with respect to time variable t, we get

$$V''(t,s_1) = D^2G_0(u)u'V + DG_0(u)V' + V_1'M\big((1-s_1)\mu^0+s_1\mu^1\big) + u_1'M\alpha. \tag{2.25}$$

This previous relation implies

$$\|V''(t,s_1)\| \leq \|D^2G_0(u)\|\|u'\|\|V\| + \|DG_0(u)\|\|V'\| + \|V_1'\|\|M\big((1-s_1)\mu^0+s_1\mu^1\big)\| + \|u_1'\|\|M\alpha\|.$$

From (2.11), (2.23), (2.24), $\|M\big((1-s_1)\mu^0+s_1\mu^1\big)\| \leq \|M\|\bar{\mu}$ and $\|D^2G_0(u)\| \leq C_{2_1}$ (see (2.10)) we obtain

$$\|V''(t,s_1)\| \leq C_9\|\alpha\| \qquad \forall t\in[0,T], \tag{2.26}$$

with $C_9 = C_2LC_6 + C_2C_6 + C_7\|M\|\bar{\mu} + C_1\|M\|$.

Step 3 : $k=3$

We derive the equation (2.25) with respect of t and get

$$\begin{aligned} V'''(t,s_1) &= D^3G_0(u(t,s_1))u'(t,s_1)u'(t,s_1)V(t,s_1) + D^2G_0(u(t,s_1))u''(t,s_1)V(t,s_1) \\ &\quad + 2D^2G_0(u(t,s_1))u'(t,s_1)V'(t,s_1) + DG_0(u(t,s_1))V''(t,s_1) \\ &\quad + V_1''(t,s_1)M\big((1-s_1)\mu^0+s_1\mu^1\big) + u_1''(t,s_1)M\alpha. \end{aligned} \tag{2.27}$$

We also derive the equation (2.8) with respect of t and get

$$u''(t,s_1) = DG_0(u(t,s_1))u'(t,s_1) + u_1'(t,s_1)M\big((1-s_1)\mu^0 + s_1\mu^1\big)$$

Triangular inequality yields

$$\|u''(t,s_1)\| \leq \|DG_0(u(t,s_1))\|\|u'(t,s_1)\| + \|u_1'(t,s_1)\|\|M\big((1-s_1)\mu^0 + s_1\mu^1\big)\|. \tag{2.28}$$

Using (2.12), $\|M\big((1-s_1)\mu^0 + s_1\mu^1\big)\| \leq \|M\|\bar{\mu}$, $\|u'\| \leq C_8$ and $\|u_1'\| \leq C_1$ the previous relation reads

$$\|u''(t,s_1)\| \leq C_{10}, \tag{2.29}$$

with $C_{10} = C_2 L + L\|M\|\bar{\mu}$.

Let us apply the triangular inequality to (2.27),

$$\begin{aligned}\|V'''(t,s_1)\| \leq{}& \|D^3G_0(u(t,s_1))\|\|u'(t,s_1)\|\|u'(t,s_1)\|\|V(t,s_1)\| + \|D^2G_0(u(t,s_1))\|\|u''(t,s_1)\|\|V(t,s_1)\| \\ &+ \|2D^2G_0(u(t,s_1))\|\|u'(t,s_1)\|\|V'(t,s_1)\| + \|D^2G_0(u(t,s_1))\|\|V''(t,s_1)\| \\ &+ \|V_1''(t,s_1)\|\|M\big((1-s_1)\mu^0 + s_1\mu^1\big)\| + \|u_1''(t,s_1)\|\|M\alpha\|.\end{aligned} \tag{2.30}$$

We now have $\|D^3G_0(u)\| \leq C_{2_2}$ from (2.12), then using (2.22), (2.29), (2.11), (2.23), (2.24), (2.26) we easily get

$$\|V'''(t,s_1)\| \leq C_{11}\|\alpha\| \tag{2.31}$$

with $C_{11} = C_{2_2}L^2C_6 + C_{2_1}C_{10}C_6 + 2C_{2_1}LC_7 + C_{2_1}C_9 + C_9\|M\|\bar{\mu} + C_{10}\|M\|$.

Using the same reasoning, we finally obtain the same inequalities with s_2 in place of s_1 which gives the result of Lemma 2.15.

□

Now, to end the proof of Theorem 2.11, let recall the equation (2.17)

$$E(t) = \frac{t^2}{2}E''(0) + \frac{t^3}{2}\int_0^1 (1-r)^2E^{(3)}(rt)\mathrm{d}r.$$

From Lemma 2.15 we have

$$\Big|\int_0^1 (1-r)E^{(3)}(rt)\mathrm{d}r\Big| \leq \int_0^1 (1-r)^2C_5\|\alpha\|^2\mathrm{d}r = \frac{1}{3}C_5\|\alpha\|^2$$

which gives

$$\frac{t^3}{2}\int_0^1 (1-r)E^{(3)}(rt)\mathrm{d}r \geq -\frac{t^3}{6}C_5\|\alpha\|^2. \tag{2.32}$$

According to Lemma 2.14 we get

$$\frac{t^2}{2}E''(0) \geq t^2\lambda_M(u_1^0)^2\|\alpha\|^2. \tag{2.33}$$

From (2.32) and (2.33) we deduce

$$E(t) = \frac{t^2}{2}E''(0) + \frac{t^3}{2}\int_0^1 (1-r)^2 E^{(3)}(rt)\mathrm{d}r \geq \big(\lambda_M(u_1^0)^2 - C_5\frac{t}{6}\big)t^2\|\alpha\|^2. \tag{2.34}$$

We choose $t_1 > 0$ such that $\frac{C_5 t_1}{6} \leq \lambda_M(u_1^0)^2$ (for instance we set $t_1 = \frac{6\lambda_M(u_1^0)^2}{C_5}$) and this gives from (2.34)

$$E(t) \geq 0, \qquad \forall\, t \in (0, t_1).$$

Then the hypothesis of Theorem 2.10 are verified which ends the proof of Theorem 2.11.

3. Numerical illustrations

To illustrate numerically the identification of the nucleation parameter $\mu \in \mathbb{R}^{N-1}$ from a given measurement of u at one small time $t_1 \in (0, T)$, we transform the inverse problem into an optimization problem by means of a function whose only minimum is μ^*.

We recall below the considered structured model with maximal size N where $u = (u_1, \cdots, u_N)^T \in \mathbb{R}_+^N$ is the unknowns vector.

$$\begin{cases} \dfrac{\mathrm{d}u_1(t)}{\mathrm{d}t} = -u_1(t)\displaystyle\sum_{i=2}^{N} r_i u_i(t) + b\Big(2u_2(t) + \sum_{i=3}^{N} u_i(t)\Big) - u_1(t)\sum_{i=2}^{N} i\mu_i, \\ \dfrac{\mathrm{d}u_2(t)}{\mathrm{d}t} = -\big(b + r_2 u_1(t)\big)u_2(t) + bu_3(t) + u_1(t)\mu_2, \\ \dfrac{\mathrm{d}u_i(t)}{\mathrm{d}t} = r_{i-1}u_1(t)u_{i-1}(t) - \big(b + r_i u_1(t)\big)u_i(t) + bu_{i+1}(t) + u_1(t)\mu_i, \\ \qquad i = 3, \ldots, N-1, \\ \dfrac{\mathrm{d}u_N(t)}{\mathrm{d}t} = r_{N-1}u_1(t)u_{N-1}(t) - \big(b + r_N u_1(t)\big)u_N(t) + u_1(t)\mu_N, \\ u(0) = u^0, \end{cases} \tag{3.1}$$

where $u^0 = \big(u_1^0, \ldots, u_N^0\big)^T \in \mathbb{R}_+^N$.

For the notation, the nucleation parameter $\mu = (\mu_2, \ldots, \mu_N)^T \in \mathbb{R}_+^{N-1}$ begin with the index 2 because one single monomer cannot form by nucleation a proto-oligomer.

Now we assume that we have $\hat{u} \in \mathbb{R}_+^N$ a vector measurement of the solution u of the system (3.1) at the given small time $t_1 \in (0, T)$. We propose to find numerically the vector of parameters $\mu \in \mathbb{R}^{N-1}$. To do this, we use the non-linear least squares method by introducing a function

$$\begin{array}{rccc} \varphi & : & \mathbb{R}^{N-1} & \longrightarrow & \mathbb{R} \\ & & \mu & \longmapsto & \varphi(\mu) = \frac{1}{2}\big|\big|u - \hat{u}\big|\big|^2, \end{array}$$

with u depending on μ *i.e.* $u = F(\mu)$ solution of (3.1) taken at t_1. So we write

$$\varphi(\mu) = \frac{1}{2}\Big\|F(\mu) - \hat{u}\Big\|_{\mathbb{R}^N}^2, \tag{3.2}$$

where

TABLE 2. Description of the parameters and unknowns of the model.

Parameter	Definition
$b = 1$	Depolymerization rate for proto-oligomers
$N = 7$	The maximum size of proto-oligomers
μ_i, $i = 2, \ldots, N$	Nucleation rate for proto-oligomers of size i
T	Final time
$r_0 = 0.75$ and $b_0 = 0.5$	Kinetic constants
$r_i = r_0 \times i^{1/3}$, $i = 2, \ldots, N$	Polymerisation rate
$u_i(0) = \left(0.5/\sqrt{2\pi}\right)\mathrm{e}^{(-0.5\times(i-1)^2)}$	The initial condition
$\mu_f = \mu_i = \frac{b_0\times i}{i+1}$, $i = 2, \ldots, N$	The given nucleation rate
μ_r	The estimated or reconstructed nucleation rate
$Er = \frac{\|\mu_r - \mu_f\|}{\|\mu_f\|}$	Relative error for the estimation of μ
$\hat{u}$	The measured data at a given time for the solution of (3.1)
ε_p	The perturbation parameter of the solution of the direct problem
ε	The perturbation parameter of the nucleation rate μ_f
$\hat{u}_p$	The perturbed solution

$$F(\mu)= \begin{pmatrix} u_1^{\mu}(t_1) \\ u_2^{\mu}(t_1) \\ \vdots \\ u_N^{\mu}(t_1) \end{pmatrix} \in \mathbb{R}^N \text{ and } \hat{u} = \begin{pmatrix} \hat{u}_1(t_1) \\ \hat{u}_2(t_1) \\ \vdots \\ \hat{u}_N(t_1) \end{pmatrix} \in \mathbb{R}^N.$$

We seek to solve the problem (3.2) in the least squares sense.

Our problem is to minimize $\varphi(\mu)$:

$$\min_{\mu\in\mathbb{R}^{N-1}} \left(\varphi(\mu) = \frac{1}{2}\left\|F(\mu) - \hat{u}\right\|^2\right),$$

where $F(\mu) = u$ is the solution of the ordinary differential equation for a fixed μ.

In Table 2 we put the summary of the parameters and unknowns of our model.

3.1. Simulation of the direct problem

We simulate the direct problem (3.1) for a given vector of the nucleation parameter. Figure 3 shows the time evolution for monomers u_1 and for proto-oligomers u_i, $i \in \{2, \cdots, 7\}$. The simulation is done with Matlab.

3.2. Simulations involving the estimation of the nucleation parameter

To estimate the nucleation parameter μ involved in system (3.1) we assume as measured data, $\hat{u}$ (synthesized here) the solution of the direct problem at time $t_1 \in (0, T)$. This synthesized solution is obtained with the nucleation parameter μ_f. The objective of the following tests is to forget this dependency in μ_f and to try to estimate this parameter through a minimization problem. We solve the minimization problem with the tool *fminsearch* of *Matlab*.

3.2.1. Estimation with a constant perturbation of μ_f.

We are interested in the case where we subtract a constant vector of value ε from the reference nucleation parameter μ_f. So, starting from this initial condition

$$\mu^{in,0} = \mu_f - \varepsilon \times Ones(N-1, 1), \quad \text{where } Ones(N-1, 1) = (1, \cdots, 1)^T$$

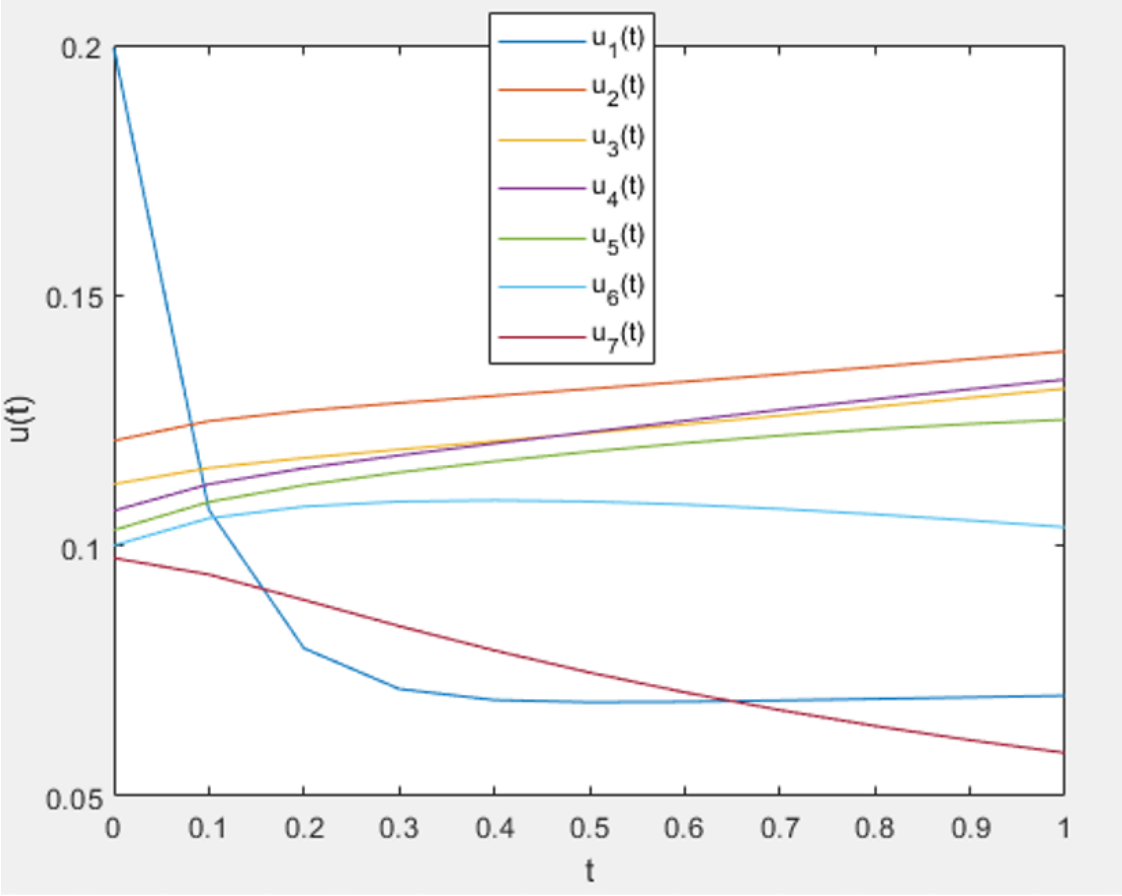

FIGURE 3. Solution at time $T = 1$ obtained with parameters taken from Table 2.

TABLE 3. Values of reconstructed nucleation parameter compared to the referenced one.

μ_f	μ_r with $\varepsilon = 0.1$	μ_r with $\varepsilon = 1$	μ_r with $\varepsilon = 10$
0.333333333333333	0.333349883502746	0.333368158686978	0.333360071687941
0.375000000000000	0.374975802656048	0.375014918722041	0.374976994055416
0.400000000000000	0.399966000229233	0.400001811533451	0.399990665024704
0.416666666666667	0.416676239871635	0.416670054947340	0.416641629407721
0.428571428571429	0.428571397045192	0.428567016101712	0.428533628763940
0.437500000000000	0.437532262391694	0.437477091332681	0.437552055817063

we find an estimation μ_r (value of μ reconstructed) using our minimization strategy. Of course if the algorithm converge then μ_r is expected to estimate μ_f.

For various values of ε and measured data taken at time $t_1 = 0.2$ we obtain the results in the Table 3.

For this test, in the particular case where $\varepsilon = 0.1$, the tool *fminsearch* converge after 430 iterations and gives the value $\varphi(\mu_r) = 1.53774e - 12$. The corresponding relative error is $E_r = 5.725048933047261e - 05$.

TABLE 4. Values of reconstructed nucleation parameter compared to the referenced one.

μ_f	μ_r with $\varepsilon = 0.1$	μ_r with $\varepsilon = 1$	μ_r with $\varepsilon = 10$
0.333333333333333	0.333305573630657	0.333333560732965	0.333334656165570
0.375000000000000	0.374988369081162	0.374999369462275	0.375000270956315
0.400000000000000	0.399964121775021	0.400000352426655	0.400000373413034
0.416666666666667	0.416686257711450	0.416666436408618	0.416667773479836
0.428571428571429	0.428610791605128	0.428571181230545	0.428571293138055
0.437500000000000	0.437486915154826	0.437500239323424	0.437498890474966

TABLE 5. Values of reconstructed nucleation parameter compared to the referenced one.

μ_f	μ_r with $\varepsilon_p = 10^{-4}$	μ_r with $\varepsilon_p = 10^{-3}$	μ_r with $\varepsilon_p = 10^{-2}$
0.333333333333333	0.328640727168973	0.286286286618157	0.170758856257970
0.375000000000000	0.371815361198109	0.342858661869607	0.030984543696027
0.400000000000000	0.398490219045264	0.385120811338224	0.242704708094556
0.416666666666667	0.416757711871747	0.418023053611640	0.431381608326305
0.428571428571429	0.430279382129130	0.445560076787198	0.611233378024042
0.437500000000000	0.441501679429658	0.477483478408652	0.866321589124976

3.3. Estimation with a random perturbation of μ_f

Here we are interested in the case where a random perturbation is added to μ_f. So, from initial conditions of the form:

$$\mu^{in,0} = \mu_f - \varepsilon \times rand(N, 1),$$

where $rand(n, m)$: returns a matrix of n rows and m columns of random entries with values between 0 and 1.

For various values of ε and measured data taken at time $t_1 = 0.2$ we obtain the results in the Table 4.

For this test, in the particular case where $\varepsilon = 0.1$, the tool *fminsearch* converge after 223 iterations and gives the value $\varphi(\mu_r) = 1.35969e - 12$. The corresponding relative error is $E_r = 6.689300069247282e - 05$.

3.4. Estimation with data taken as a constant perturbation of the solution

We are interested here in the case where we add a constant noise to the solution of the direct problem (3.1). So we consider as data the vector $\hat{u}_p$ defined by

$$\hat{u}_p = \hat{u} - \varepsilon_p \times Ones(N - 1, 1).$$

Thus, from a given initial condition $\mu^{in,0} = \mu_f - 0.1 \times Ones(N - 1, 1)$ we find an estimation sequence μ_r of μ_f using the our algorithm with the Matlab tool *fminsearch*.

For various constant noises ε_p and $\hat{u}$ taken at time $t_1 = 0.2$ we obtain the following reconstructions in the Table 5.

For this test, in the particular case where $\varepsilon_p = 10^{-4}$, the tool *fminsearch* converges after 271 iterations and gives the value $\varphi(\mu_r) = 8.42995e - 08$. The corresponding relative error is $E_r = 0.007455214811766$.

3.5. Estimation with data taken as a random perturbation of the solution

We consider the case where a random noise is added to the solution of the direct problem at time t_1 as follows

$$\hat{u}_p = \hat{u} - rand(N - 1, 1)$$

TABLE 6. Values of reconstructed nucleation parameter compared to the referenced one for $\varepsilon_p = rand(N-1,1)$.

μ_f	μ_r
0.333333333333333	0.279499359432756
0.375000000000000	0.335029771112940
0.400000000000000	0.381304281712023
0.416666666666667	0.424035552157708
0.428571428571429	0.444535756902563
0.437500000000000	0.4565625455003123

where the function $rand(N-1,1)$ gives a random vector of size $(N-1)\times 1$ and whose values are chosen in $[0,1]$. Thus from the initial condition $\mu^{in,0} = \mu_f - 0.02 \times Ones(N-1,1)$ we obtain the results in Table 6.

For this test, the tool *fminsearch* converge after 63 iterations and give the value $\varphi(\mu_r) = 1.11814e-05$. The relative error is $E_r = 0.087991219361796$.

4. Conclusion

In this paper we have investigated the inverse problem involved in the estimation of the nucleation parameter arising in a simplified model for early stage of Alzheimer's disease modeling. This simplified model describes the dynamics of formation of Aβ proto-oligomers of any size $i \in \{2,\cdots,N\}$ by aggregating monomers or by a nucleation process where two or more Aβ monomers spontaneously merge a form a proto-oligomer.

We analytically prove the Q well-posed of our identification parameter problem from a sequence of approximations of the expected solutions. We also provide some numerical illustrations by considering synthesized data as being the solutions at a given time of our direct problem (means the problem when the nucleation parameter is *a priori* known). The obtained results from different scenarios show a good consistency of our parameter reconstruction method.

Appendix A

Proof of the inequality $\rho(t) \leq \rho_0 \ \forall\ t > 0$

The total mass of the interaction system between monomers and proto-oligomers is

$$\rho(t) = \sum_{i=1}^{N} i u_i(t) = u_1(t) + \sum_{i=2}^{N} i u_i(t), \qquad t \geq 0. \tag{A.1}$$

Deriving (A.1) with respect to t we write

$$\rho'(t) = u_1'(t) + \sum_{i=2}^{N-1} i u_i'(t) + N u_N'(t). \tag{A.2}$$

For calculus convenience, let us define $r_1 = 0$. From the differential equations governing the considered system, the relation (A.2) is recasted as follow

$$\rho'(\mathbf{t}) = -u_1(t)\sum_{i=1}^{N} r_i u_i(t) + b\Big(2u_2(t) + \sum_{i=3}^{N} u_i(t)\Big) - u_1(t)\sum_{i=2}^{N} i\mu_i + u_1(t)\sum_{i=2}^{N-1} i\Big(r_{i-1}u_{i-1}(t) - r_i u_i(t)\Big)$$

$$+ b\sum_{i=2}^{N-1} i\Big(u_{i+1}(t) - u_i(t)\Big) + u_1(t)\sum_{i=2}^{N-1} i\mu_i + Nr_{N-1}u_1(t)u_{N-1}(t) - Nbu_N(t) - Nr_Nu_1(t)u_N(t) + Nu_1(t)\mu_N.$$

Rearranging the terms leads to

$$\rho'(\mathbf{t}) = -u_1\sum_{i=2}^{N} r_iu_i + b\Big(2u_2 + \sum_{i=3}^{N} u_i\Big) + u_1A + bB - Nbu_N, \tag{A.3}$$

where $A = \sum\limits_{i=2}^{N} i\Big(r_{i-1}u_{i-1} - r_iu_i\Big)$ and $B = \sum\limits_{i=2}^{N-1} i\Big(u_{i+1} - u_i\Big)$.

Computing A and B we obtain in one hand

$$\begin{aligned}
A &= \sum_{i=2}^{N} i\Big(r_{i-1}u_{i-1} - r_iu_i\Big) = \sum_{i=2}^{N} ir_{i-1}u_{i-1} - \sum_{i=2}^{N} ir_iu_i \\
&= \sum_{i=1}^{N-1} (i+1)r_iu_i - \sum_{i=2}^{N} ir_iu_i = \sum_{i=1}^{N-1} ir_iu_i + \sum_{i=1}^{N-1} r_iu_i - \sum_{i=2}^{N} ir_iu_i \\
&= r_1u_1 + \sum_{i=2}^{N-1} ir_iu_i + \sum_{i=1}^{N-1} r_iu_i - \sum_{i=2}^{N-1} ir_iu_i - Nr_Nu_N \\
&= \sum_{i=2}^{N-1} r_iu_i - Nr_Nu_N
\end{aligned}$$

and in other hand

$$\begin{aligned}
B &= \sum_{i=2}^{N-1} i\Big(u_{i+1} - u_i\Big) = \sum_{i=2}^{N-1} iu_{i+1} - \sum_{i=2}^{N-1} iu_i = \sum_{i=3}^{N} (i-1)u_i - \sum_{i=2}^{N-1} iu_i \\
&= \sum_{i=3}^{N-1} (i-1)u_i + (N-1)u_N - \sum_{i=2}^{N-1} iu_i \\
&= \sum_{i=3}^{N-1} iu_i - 2u_2 - \sum_{i=3}^{N-1} iu_i - \sum_{i=3}^{N-1} u_i + (N-1)u_N \\
&= (N-1)u_N - 2u_2 - \sum_{i=3}^{N-1} u_i
\end{aligned}$$

Injecting the computed values of A and B in (A.3) we get

$$\begin{aligned}
\rho'(\mathbf{t}) &= -u_1\sum_{i=1}^{N} r_iu_i + b\Big(2u_2 + \sum_{i=3}^{N} u_i\Big) + u_1\Big(\sum_{i=2}^{N-1} r_iu_i - Nr_Nu_N\Big) + b\Big((N-1)u_N - 2u_2 - \sum_{i=3}^{N-1} u_i\Big) - Nbu_N \\
&= -u_1\sum_{i=1}^{N} r_iu_i + b\sum_{i=3}^{N} u_i + u_1\sum_{i=2}^{N-1} r_iu_i - Nr_Nu_1u_N - b\sum_{i=3}^{N} u_i
\end{aligned}$$

$$
\begin{aligned}
&= -u_1 \sum_{i=1}^{N} r_i u_i + u_1 \sum_{i=2}^{N-1} r_i u_i - N r_N u_1 u_N \\
&= -u_1 r_1 u_1 - u_1 \sum_{i=2}^{N-1} r_i u_i - r_N u_1 u_N + u_1 \sum_{i=2}^{N-1} r_i u_i - N r_N u_1 u_N \\
&= -u_1 r_1 u_1 - r_N u_1 u_N - N r_N u_1 u_N \\
&= -\big(r_1 u_1 + r_N u_N + N r_N u_N\big) u_1,
\end{aligned}
$$

which implies $\rho'(t) \leq 0$ means $\rho(t) \leq \rho(0) = \rho_0 \; \forall \, t > 0$.

Acknowledgements

The authors are thankfull to the Agence National de la Recherche PrionDiff Project-ANR-21-CE15-0011 for his support.

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