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# Q-WELL-POSEDNESS OF AN A $\beta$-PROTEIN POLYMERIZATION MODEL 

Cheikh Gueye ${ }^{1,2}$, Sorin I. Ciuperca ${ }^{3}$, Laurent Pujo-Menjouet ${ }^{1,2}$ and Léon Matar Tine ${ }^{1,2}$


#### Abstract

In this work, we consider a Becker-Döring-like mathematical interaction model between $\mathrm{A} \beta$-monomers and $\mathrm{A} \beta$ proto-oligomers playing an important role in Alzheimer's disease. In this context, the clustering process where two or more $\mathrm{A} \beta$-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 $\mu$ from measured data at different times.


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

## 1. Introduction: a focus on the $\mathrm{A} \beta$ 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 $\mathrm{A} \beta$-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 $A D$, we consider only here the $\mathrm{A} \beta$ activity, leaving the even more complex coupling interactions with the Tau protein for future work. We remind here that $\mathrm{A} \beta$ 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]

[^0](Part I, Chapter 2).


Figure 1. Production of $\mathrm{A} \beta$ oligomers from the neurons (1), their polymerization into proto-oligomers (2) and eventually to $\mathrm{A} \beta$ oligomers (3) able to regulate the neuronal activity or kill them (4).

It is well known now that the $\mathrm{A} \beta$ 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 than fibrils during the early stages of $\mathrm{AD}[6,11,21,24,32]$. 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 $\mathrm{A} \beta$ 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 $\mathrm{A} \beta$ seeding and then accelerate the natural process, transforming it into a highly deterministic mechanism. The mechanism can be described as follows: $\mathrm{A} \beta$-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 $\mathrm{A} \beta$-oligomers in the brain results from a combination of several factors at different scales. Thus, understanding the complex formation and replication of $A \beta$-oligomers from $\mathrm{A} \beta$-monomers, 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 $\mathrm{A} \beta$-monomers leading to $\mathrm{A} \beta$ proto-oligomers. This polymerization mechanism is based on a gain and loss competition of $\mathrm{A} \beta$ 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 $\mathrm{A} \beta$ 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 $\{i\}+\{1\} \rightarrow\{i+1\}$. 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 $\{i\} \rightarrow\{i-1\}+1\}$.

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 $\mathrm{A} \beta$ 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 $\mathrm{A} \beta$ monomers characterized by its concentration $u_{1}(t)$ that can interact with a population of $\mathrm{A} \beta$ 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.

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 $\mathrm{A} \beta$-monomers and a population of $\mathrm{A} \beta$ 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


Figure 2. Detail of Fig. 1 when $\mathrm{A} \beta$ oligomers $u_{1}$ can form spontaneous clusters, of size $i$ named $u_{i}$ with a rate $\mu_{i}$ to start proto-oligomer dynamics. These protooligomers can polymerize with a size-dependent rate $r_{i}$ or depolymerize with a constant rate $b$.
of the system are given in Table 1.

| Variable | Definition |
| :---: | :--- |
| $u_{1}(t)$ | Concentration of $\mathrm{A} \beta$ monomers at time $t$ |
| $u_{i}(t)$, | Concentration of $\mathrm{A} \beta$ proto-oligomers of size $i=2, \cdots N$ at time $t$ |
| $\mu_{i}, i=2, \cdots, N$ | Nucleation rate for proto-oligomers of size $i$ |
| $r_{i} \geq 0, i=1, \ldots, N$ | Polymerization rate for proto-oligomers of size $i$ |
| $b>0$ | Depolymerization rate (taken as a constant) for proto-oligomers |
| $t \geq 0$ | the time |

TABLE 1. Description of the model variables and parameters.
(1) Monomers: $\mathrm{A} \beta$-monomers population by gain and loss of a single or a group of monomers is described as follows

$$
\frac{d u_{1}(t)}{d t}=-u_{1}(t) \sum_{i=1}^{N} r_{i} u_{i}(t)+b\left(2 u_{2}(t)+\sum_{i=3}^{N} u_{i}(t)\right)-u_{1}(t) \sum_{i=2}^{N} i \mu_{i} .
$$

The first term on the right-hand side stands for the loss of monomers when $\mathrm{A} \beta$ protooligomers 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 protooligomer of size $i$ with the rate $\mu_{i}$. The couple $\left(r_{i}, b\right), i \in\{2, \cdots, N\}$ is called kinetic coefficients of the model.
(2) Proto-oligomers: A $\beta$ proto-oligomers are structured in size ranging from $i=2$ to $i=N$ and their dynamics is given by

$$
\left\{\begin{array}{l}
\frac{d u_{2}(t)}{d t}=-\left(b+r_{2} u_{1}(t)\right) u_{2}(t)+b u_{3}(t)+u_{1}(t) \mu_{2} \\
\frac{d u_{i}(t)}{d t}=r_{i-1} u_{1}(t) u_{i-1}(t)-\left(b+r_{i} u_{1}(t)\right) u_{i}(t)+b u_{i+1}(t)+u_{1}(t) \mu_{i}, \quad i=3, . ., N-1 \\
\frac{d u_{N}(t)}{d t}=r_{N-1} u_{1}(t) u_{N-1}(t)-\left(b+r_{N} u_{1}(t)\right) u_{N}(t)+u_{1}(t) \mu_{N}
\end{array}\right.
$$

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 $\mu$ depending on the size of the proto-oligomers.
Let us denote $u(t)=\left(u_{1}(t), \cdots, u_{N}(t)\right)^{T}$ 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 $\mu=\left(\mu_{2}, \cdots, \mu_{N}\right)^{T} \in \mathbb{R}^{N-1}$. Thus, for $0<t_{1}<\cdots<t_{p} \leq T$ and measures $\left(Y^{(1)}, \cdots, Y^{(p)}\right) \in \mathbb{R}^{N p}$ we look for $\mu \in \mathbb{R}_{+}^{N-1}$ such that

$$
\begin{equation*}
u\left(t_{k}\right)=Y^{(k)}, \quad \forall k=1, \cdots, p, \tag{2.1}
\end{equation*}
$$

with $u\left(t_{k}\right)$ the solution evaluated at time $t_{k}$.
Let us denote $Y=\left(Y^{(1)}, \cdots, Y^{(p)}\right)^{T}$ and we define $F: \mathbb{R}^{N-1} \longrightarrow \mathbb{R}^{N p}$ such that $F(\mu)=$ $\left(u\left(t_{1}\right), \cdots, u(t p)\right)^{T} \in \mathbb{R}^{N p}$, then we are looking for $\mu \in \mathbb{R}_{+}^{N-1}$ such that $F(\mu)=Y$.
We introduce the function $G=\left(G_{1}, \cdots, G_{N}\right)^{T}: \mathbb{R}^{N} \longrightarrow \mathbb{R}^{N}$ such that for all $v=\left(v_{1}, \cdots, v_{N}\right)^{T} \in$ $\mathbb{R}^{N}$ we put

$$
\begin{aligned}
G_{1}(v) & =-v_{1} \sum_{i=1}^{N} r_{i} v_{i}+b\left(2 v_{2}+\sum_{i=3}^{N} v_{i}\right)-v_{1} \sum_{i=2}^{N} i \mu_{i} \\
G_{2}(v) & =-b v_{2}+b v_{3}+\mu_{2} v_{1} \\
\vdots & \vdots \\
G_{N-1}(v) & =v_{1}\left(r_{N-2} v_{N-2}-r_{N-1} v_{N-1}+\mu_{N-1}\right)+b\left(v_{N}-v_{N-1}\right) \\
G_{N}(v) & \left.=v_{1}\left(r_{N-1} v_{N-1}-r_{N} v_{N}+\mu_{N}\right)-b v_{N}\right),
\end{aligned}
$$

and rewrite the interaction model between $\mathrm{A} \beta$-monomers and $\mathrm{A} \beta$ proto-oligomers as follow

$$
\left\{\begin{align*}
\frac{d u(t)}{d t} & =G(u(t)),  \tag{2.2}\\
u(0) & =u^{0}
\end{align*}\right.
$$

where $u^{0}=\left(u_{1}^{0}, \cdots, u_{N}^{0}\right)^{T} \in \mathbb{R}_{+}^{N}$.

Equality in (2.1) is needed to be true in the least squares sense, which means we are looking for $\mu^{*}=\left(\mu_{2}^{*}, \cdots, \mu_{N}^{*}\right)^{T} \in \mathbb{R}^{N-1}$ that minimizes the function $J: \mathbb{R}^{N-1} \longrightarrow \mathbb{R}$ defined for all $\mu \in \mathbb{R}^{N-1}$ by $J(\mu)=\frac{1}{2} \sum_{k=1}^{p}\left|u\left(t_{k}\right)-Y^{(k)}\right|^{2}$ with $u$ solution of (2.2).
Denoting $Y=\left(Y^{(1)}, \cdots, Y^{(p)} \in \mathbb{R}^{N p}\right.$ we can write $J$ as follow

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

where $\|\cdot\|$ stands for the Euclidean norm in $\mathbb{R}^{N p}$.
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, $\Omega$ 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

$$
\begin{equation*}
J_{Z}(\mu)=\frac{1}{2}\|\varphi(\mu)-Z\|_{E_{2}}^{2}, \quad \forall \mu \in \Omega \tag{2.3}
\end{equation*}
$$

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

$$
\left\{\begin{array}{l}
\hat{\mu} \in U  \tag{2.4}\\
J_{Z}(\hat{\mu}) \leq J_{Z}(\mu) \quad \forall \mu \in \Omega
\end{array}\right.
$$

This is the identification problem of $\mu$ from a measure, $Z$, of $\varphi(\mu)$. We have the following definitions (for more details see [4])

Definition 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. The problem (2.4) is said to be identifiable on a subset $U_{1}$ of $\Omega$ if $\varphi$ is injective on $U_{1}$.

Let $\mu^{0}, \mu^{1} \in \Omega$ such that the segment $\left\{(1-s) \mu^{0}+s \mu^{1}, s \in[0,1]\right\}$ is included $\Omega$. We introduce the function $P_{\mu^{0}, \mu^{1}}:[0,1] \longrightarrow E_{2}$ such that $P_{\mu^{0}, \mu^{1}}(s)=\varphi\left((1-s) \mu^{0}+s \mu^{1}\right) \forall s \in[0,1]$. For simplicity we denote $P_{\mu^{0}, \mu^{1}}$ by $P$.
We can see the function $P$ as a curve in $E_{2}$; the tangent to $P$ at $s$ is given by $P^{\prime}(s)$. We have

$$
P^{\prime}(s)=D \varphi\left((1-s) \mu^{0}+s \mu^{1}\right)\left(\mu_{1}-\mu_{0}\right) \in E_{2} .
$$

Definition 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 $P^{\prime}(s)=0 \Rightarrow \mu^{0}=\mu^{1}$.
In the case where $\varphi$ is linear and continuous then the identifiability is equivalent to the L.I
Definition 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

$$
\alpha_{m}\left\|\mu_{0}-\mu_{1}\right\| \leq \int_{0}^{1}\left\|P^{\prime}(s)\right\| d s, \quad \forall \mu_{0}, \mu_{1} \in U_{1}
$$

Definition 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

$$
\Theta\left(P, s_{0}, s_{1}\right)=\arccos \left(\left\langle\frac{P^{\prime}\left(s_{0}\right)}{\left\|P^{\prime}\left(s_{0}\right)\right\|}, \frac{P^{\prime}\left(s_{1}\right)}{\left\|P^{\prime}\left(s_{1}\right)\right\|}\right\rangle\right) \in[0, \pi]
$$

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

$$
\Theta(P)=\sup _{s_{0}, s_{1} \in[0,1]} \Theta\left(P, s_{0}, s_{1}\right)
$$

Definition 6. Suppose that the problem (2.4) is L.I. on $U_{1} \subset \Omega$. We call deflection on $(\varphi, U)$ the number $\Theta\left(\varphi, U_{1}\right) \in[0, \pi]$ given by

$$
\Theta\left(\varphi, U_{1}\right)=\sup _{\mu^{0}, \mu^{1} \in U_{1}, \mu^{0} \neq \mu^{1}} \Theta\left(P_{\mu^{0}, \mu^{1}}\right)
$$

Definition 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

$$
\begin{equation*}
\left\|P^{\prime \prime}(s)\right\| \leq \frac{1}{R}\left\|P^{\prime}(s)\right\|^{2}, \quad \forall s \in[0,1], \quad \forall \mu^{0}, \mu^{1} \in U_{1}, \mu^{0} \neq \mu^{1} \tag{2.5}
\end{equation*}
$$

Definition 8. Let $U_{1} \subset \Omega$ and suppose that the problem (2.4) is L.I. and $F C$ on $U_{1}$. Then we say that (2.4) is a FC/LD problem (finite curvature/limited deflected problem) on $U_{1}$ if

$$
\Theta\left(\varphi, U_{1}\right) \leq \frac{\pi}{2}
$$

For simplicity we recall here the following result which is in fact Theorem 4.4.1 page 177 of [4]:
Proposition 1. Suppose that the problem (2.4) is linearly stable and $F C / L D$ on $U$. Then it is $Q$ well posed with the neighbourhood $V_{0}$ given by

$$
V_{0}=\left\{z \in E_{2}, \quad \operatorname{dist}(z, \varphi(U))<R\right\}
$$

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

$$
\operatorname{dist}(z, \varphi(U))=\inf _{y \in \varphi(U)}\|z-y\|
$$

Now we can state the main result of this section:
Theorem 1. Let assume
(1) $\operatorname{dim}\left(E_{1}\right)<+\infty$
(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

$$
\begin{equation*}
\left\langle P^{\prime}\left(s_{1}\right), P^{\prime}\left(s_{2}\right)\right\rangle \geq 0, \forall s_{1}, s_{2} \in[0,1] . \tag{2.6}
\end{equation*}
$$

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 1 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

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

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 $\mu$ denoted $G_{0}$ and another one depending on $\mu$. So, $G\left(v_{1}, \cdots, v_{N}\right)=$ $G_{0}\left(v_{1}, \cdots, v_{N}\right)+[M \mu] v_{1}$ with $G_{0}: \mathbb{R}^{N} \longrightarrow \mathbb{R}^{N}$

$$
G_{0}\left(v_{1}, \cdots, v_{N}\right)=\left(\begin{array}{c}
G_{01}\left(v_{1}, \cdots, v_{N}\right) \\
G_{02}\left(v_{1}, \cdots, v_{N}\right) \\
\vdots \\
G_{0 N}\left(v_{1}, \cdots, v_{N}\right)
\end{array}\right)
$$

where

$$
\begin{aligned}
G_{01}\left(v_{1}, \cdots, v_{N}\right) & =-v_{1} \sum_{i=1}^{N} r_{i} v_{i}+b\left(2 v_{2}+\sum_{i=3}^{N} v_{i}\right) \\
G_{02}\left(v_{1}, \cdots, v_{N}\right) & =-b v_{2}+b v_{3} \\
G_{03}\left(v_{1}, \cdots, v_{N}\right) & =-r_{3} v_{1} v_{3}-b v_{3}+b v_{4} \\
\vdots & \vdots \\
G_{0 N-1}\left(v_{1}, \ldots, v_{N}\right) & =v_{1}\left(r_{N-2} v_{N-2}-r_{N-1} v_{N-1}\right)+b\left(v_{N}-v_{N-1}\right) \\
G_{0 N}\left(v_{1}, \ldots, v_{N}\right) & =v_{1}\left(r_{N-1} v_{N-1}-r_{N} v_{N}\right)-b v_{N}
\end{aligned}
$$

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

$$
M=\left(\begin{array}{ccccccc}
-2 & -3 & -4 & -5 & \cdots & -(N-1) & -N \\
1 & 0 & 0 & 0 & \cdots & 0 & 0 \\
0 & 1 & 0 & 0 & \cdots & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \cdots & \vdots & \vdots \\
0 & 0 & 0 & 0 & \cdots & 1 & 0
\end{array}\right)
$$

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

$$
\left\{\begin{align*}
\frac{\partial u}{\partial t} & =G_{0}(u(t))+[M \mu] u_{1}(t)  \tag{2.7}\\
u(0) & =u^{0}
\end{align*}\right.
$$

and we state the main result of this paper
Theorem 2. Let $U \subset \mathbb{R}^{N-1}$ a compact and convex subset of (] $0,+\infty[)^{N-1}$ 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 1.

### 2.2.1. Proof of hypothesis 3 of Theorem 1

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 $P^{\prime}(s)=0$ and we will end up with a contradiction.

We have $P(s)=F\left((1-s) \mu^{0}+s \mu^{1}\right)=u\left(t_{1}, s\right)$, where $u\left(t_{1}, s\right)$ is solution of

$$
\left\{\begin{align*}
\frac{\partial u}{\partial t} & =G_{0}\left(u\left(t_{1}, s\right)\right)+u_{1}\left(t_{1}, s\right) M\left((1-s) \mu^{0}+s \mu^{1}\right)  \tag{2.8}\\
u(0, s) & =u^{0}
\end{align*}\right.
$$

We have $P^{\prime}(s)=\frac{\partial u}{\partial s}\left(t_{1}, s\right)$. Let put $V(t, s)=\frac{\partial u}{\partial s}(t, s)$ that satisfies the following system obtained by derivation with respect to $s$ of system (2.8)

$$
\left\{\begin{align*}
\frac{\partial V}{\partial t}(t, s) & =\sum_{k=1}^{N} \frac{\partial G_{0}}{\partial u_{k}}(u(t, s)) \frac{\partial u_{k}}{\partial s}+V_{1}(t, s) M\left((1-s) \mu^{0}+s \mu^{1}\right)+u_{1}(t, s) M\left(\mu^{1}-\mu^{0}\right)  \tag{2.9}\\
V(0, s) & =0
\end{align*}\right.
$$

Denoting $\delta=M\left(\mu^{1}-\mu^{0}\right)$ then the system (2.9) becomes thanks to the relation $P^{\prime}(s)=0$,

$$
\begin{cases}\frac{\partial V}{\partial t}(t, s) & =D G_{0}(u(t, s)) V(t, s)+V_{1}(t, s) M\left((1-s) \mu^{0}+s \mu^{1}\right)+u_{1}(t, s) \delta  \tag{2.10}\\ V(0, s) & =0 \\ V\left(t_{1}, s\right) & =0\end{cases}
$$

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

$$
\left\{\begin{aligned}
\frac{\partial V}{\partial t} \frac{1}{\|\delta\|_{\infty}} & =D G_{0}(u) \frac{V}{\|\delta\|_{\infty}}+\frac{V_{1}}{\|\delta\|_{\infty}} M\left((1-s) \mu^{0}+s \mu^{1}\right)+u_{1} \frac{1}{\|\delta\|_{\infty}} \delta \\
V(0, s) & =0 \\
V\left(t_{1}, s\right) & =0
\end{aligned}\right.
$$

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

The proof of our result will follow several steps.
Step 1 Let state that $u, \frac{\partial u}{\partial t}$ and $D G_{0}(u)$ are bounded
Proposition 2. There exists $C_{1} \geq 0, C_{2} \geq 0, L \geq 0$ depending on $u^{0}$ such that
$0 \leq u_{i}(t) \leq C_{1}, \forall i=1, \cdots, N ;\left\|\frac{\partial u}{\partial t}(t, s)\right\| \leq L ;\left\|D G_{0}(u(t))\right\| \leq C_{2} \quad \forall t \in[0, T], \forall s \in[0,1]$.
Proof. The total mass of the interaction system between monomers and proto-oligomers is given by $\rho(t)=\sum_{i=1}^{N} i u_{i}(t)=u_{1}(t)+\sum_{i=2}^{N} i u_{i}(t)$. 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 oligomers of size $N$ are not longer considered in the model
when they gain monomers. So, denoting $K=\sum_{i=1}^{N} i u_{i}^{0}$ 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

$$
\begin{equation*}
\left\|\frac{\partial u}{\partial t}(t, s)\right\| \leq L \forall t \in[0, T], \forall s \in[0,1] \tag{2.11}
\end{equation*}
$$

From the continuity of $D G_{0}$ and the fact that $u$ belongs to a compact of $\mathbb{R}^{N}$ we deduce the existence of $C_{2} \geq 0$ such that

$$
\begin{equation*}
\left\|D G_{0}(u(t))\right\| \leq C_{2}, \forall t \in[0, T], \forall s \in[0,1] \tag{2.12}
\end{equation*}
$$

Step 2 Let state that $V$ and $\frac{\partial V}{\partial t}$ are bounded
Proposition 3. There exists $C_{3} \geq 0, C_{4} \geq 0$ such that $\|V\| \leq C_{3}$ and $\left\|\frac{\partial V}{\partial t}\right\| \leq C_{4} \forall t \in[0, T]$, $\forall s \in[0,1]$.
Proof. Let multiply the equation (2.10) by $V$ and get the relation

$$
\frac{1}{2} \frac{\partial\left(\|V\|^{2}\right)}{\partial t}=D G_{0}(u) V \cdot V+M\left((1-s) \mu^{0}+s \mu^{1}\right) V_{1} \cdot V+u_{1} \delta \cdot V
$$

From the estimations $\left\|D G_{0}(u(t))\right\| \leq C_{2} ;\left\|M\left((1-s) \mu^{0}+s \mu^{1}\right)\right\| \leq A_{0}$ with $A_{0}$ constant; $\left\|V_{1}\right\| \leq\|V\| ;$ $\left\|u_{1}\right\| \leq C_{1}$ and $\|\delta\|_{\infty}=1$, we deduce the inéquality

$$
\left.\left.\frac{1}{2} \frac{\partial\left(\|V\|^{2}\right)}{\partial t} \leq\left(C_{2}+A_{0}\right)\|V\|^{2}+C_{1}\|V\|, \text { pour tout } t \in\right] 0, T\right]
$$

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

$$
\begin{equation*}
\left.\left.\frac{\partial\left(\|V\|^{2}\right)}{\partial t} \leq\left(2 C_{2}+2 A_{0}+1\right)\|V\|^{2}+C_{1}^{2}, \text { pour tout } \quad t \in\right] 0, T\right] \tag{2.13}
\end{equation*}
$$

Using Gronwall lemma we deduce in one hand

$$
\|V\|^{2} \leq\|V(0, s)\|^{2} e^{\left(2 C_{2}+2 A_{0}+1\right) t}+\frac{C_{1}^{2}}{2 C_{2}+2 A_{0}+1} e^{\left(2 C_{2}+2 A_{0}+1\right) t}=\frac{C_{1}^{2}}{2 C_{2}+2 A_{0}+1} e^{\left(2 C_{2}+2 A_{0}+1\right) t}
$$

So, denoting $C_{3}=C_{1} \sqrt{\frac{e^{\left(2 C_{2}+2 A_{0}+1\right) T}}{2 C_{2}+2 A_{0}+1}}$ we get $\|V\| \leq C_{3}$.
In other hand, from the time evolution equation of $V$ we have

$$
\left.\left.\left\|\frac{\partial V}{\partial t}\right\| \leq\left\|D G_{0}(u)\right\|\|V\|+\left\|V_{1}\right\|\left\|M\left((1-s) \mu^{0}+s \mu^{1}\right)\right\|+\left\|u_{1}\right\|\|\delta\|, \quad \forall t \in\right] 0, T\right]
$$

Knowing that $\left\|D G_{0}(u)\right\| \leq C_{2},\left\|M\left((1-s) \mu^{0}+s \mu^{1}\right)\right\| \leq A_{0},\left\|u_{1}\right\| \leq C_{1},\|\delta\|_{\infty}=1$ and $\|V\| \leq C_{3}$, then we deduce

$$
\begin{equation*}
\left\|\frac{\partial V}{\partial t}\right\| \leq C_{4} \tag{2.14}
\end{equation*}
$$

with $C_{4}=\left(C_{2}+A_{0}\right) C_{3}+C_{1}$.

## Step 3

In one hand for small time interval $\left[0, t_{1}\right]$, 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

$$
\begin{equation*}
\|V\| \leq C_{4} t, \quad \forall \quad t \in\left[0, t_{1}\right] . \tag{2.15}
\end{equation*}
$$

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 we deduce $u_{1}(t, s) \geq u_{1}^{0}-L t, \forall t>0$. Choosing $\tau_{1}>0$ such that $\tau_{1}<\frac{u_{1}^{0}}{2 L}$ we write the estimation

$$
\begin{equation*}
u_{1}(t, s) \geq \frac{u_{1}^{0}}{2}, \quad \forall \quad t \in\left[0, \tau_{1}\right] . \tag{2.16}
\end{equation*}
$$

We consider $0<t_{1} \leq \tau_{1}$ and assume there exists an index $i_{0}$ such that $\left|\delta_{i_{0}}\right|=1$. Then the component $i_{0}$ of equation (2.10) is

$$
\left.\left.\frac{\partial V_{i_{0}}}{d t}=\left[D G_{0}(u) V\right]_{i_{0}}+\left[\left[M\left((1-s) \mu^{0}+s \mu^{1}\right)\right] V_{1}\right]_{i_{0}}+u_{1} \delta_{i_{0}} . \quad t \in\right] 0, T\right]
$$

From Rolle's theorem and knowing that $V_{i_{0}}(0)=V_{i_{0}}\left(t_{1}\right)$, then there exists at least $\tau \in\left(0, t_{1}\right)$ such that $\frac{\partial v_{i_{0}}(\tau)}{d t}=0$. So,

$$
u_{1}(\tau, s) \delta_{i_{0}}=-\left(\left[D G_{0}(u(\tau, s)) V(\tau, s)\right]_{i_{0}}+\left[M\left((1-s) \mu^{0}+s \mu^{1}\right)\right]_{i_{0}} V_{1}(\tau, s)\right)
$$

The hypothesis $\left|\delta_{i_{0}}\right|=1$ implies $\frac{u_{1}^{0}}{2} \leq\left|\left[D G_{0}(u) V(\tau)\right]_{i_{0}}+\left[M\left((1-s) \mu^{0}+s \mu^{1}\right)\right]_{i_{0}} V_{1}(\tau)\right|$. Thanks to (2.15), we deduce the existence of $C_{5}>0$ such that $\frac{u_{1}^{0}}{2}\left|\delta_{i_{0}}\right|<C_{5} t_{1}$. Then $\left|\delta_{i_{0}}\right| \leq \frac{2 C_{5}}{u_{1}^{0}} t_{1}$.

One can choose $r=\frac{1}{2} \min \left(\frac{u_{1}^{0}}{L}, \frac{u_{1}^{0}}{2 C_{5}}\right)$, then if $0<t_{1}<r$ we have $\left|\delta_{i_{0}}\right|<1$ which contradicts the fact that $\left|\delta_{i_{0}}\right|=1$. That achieves the proof of the linear identifiability of our problem.

### 2.2.2. Proof of hypothesis 4 of Theorem 1

Let consider $E(t)=V\left(t, s_{1}\right) V\left(t, s_{2}\right)$. We then obtain in one hand $E(0)=V\left(0, s_{1}\right) V\left(0, s_{2}\right)=0$ and in other hand, from the expansion

$$
E^{\prime}(t)=\frac{\partial V\left(t, s_{1}\right)}{\partial t} V\left(t, s_{2}\right)+\frac{\partial V\left(t, s_{2}\right)}{\partial t} V\left(t, s_{1}\right)
$$

we deduce at $t=0$ the relation $E^{\prime}(0)=0$ because $V\left(0, s_{1}\right)=V\left(0, s_{2}\right)=0$. Now we need to evaluate $E^{\prime \prime}(0)$. For this let use notations $V^{\prime}, V^{\prime \prime}$ and $v^{\prime \prime \prime}$ as respectively the first, second and third derivatives with respect to $t$. So we have

$$
E^{\prime \prime}(t)=V^{\prime \prime}\left(t, s_{1}\right) V\left(t, s_{2}\right)+V^{\prime \prime}\left(t, s_{2}\right) V\left(t, s_{1}\right)+2 V^{\prime}\left(t, s_{2}\right) V^{\prime}\left(t, s_{1}\right)
$$

Taking $t=0$ we get $E^{\prime \prime}(0)=2 V^{\prime}\left(0, s_{2}\right) V^{\prime}\left(0, s_{1}\right)$,. From this, we can state the following result on $E^{\prime \prime}(0)$

Lemma 1. There is $\lambda_{M}>0$ such that

$$
E^{\prime \prime}(0) \geq 2 \lambda_{M}\left(u_{1}^{0}\right)^{2}\|\alpha\|^{2}, \quad \text { where } \alpha=\mu^{1}-\mu^{0}
$$

Proof. Let remind the equation satisfied by $V\left(t, s_{1}\right)$ :
$\frac{\partial V}{\partial t}\left(t, s_{1}\right)=D G_{0}\left(u\left(t, s_{1}\right)\right) V\left(t, s_{1}\right)+V_{1}\left(t, s_{1}\right) M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)+u_{1}\left(t, s_{1}\right) M\left(\mu^{1}-\mu^{0}\right) \quad \forall s_{1} \in[0,1]$.
Taking $t=0$, we obtain

$$
V^{\prime}\left(0, s_{1}\right)=u_{1}\left(0, s_{1}\right)\left(\mu^{1}-\mu^{0}\right)=u_{1}^{0} M\left(\mu^{1}-\mu^{0}\right)
$$

Doing the same with $s_{2}$ we obtain

$$
V^{\prime}\left(0, s_{2}\right)=u_{1}\left(0, s_{2}\right)\left(\mu^{1}-\mu^{0}\right)=u_{1}^{0} M\left(\mu^{1}-\mu^{0}\right)
$$

Since $E^{\prime \prime}(0)=2 V^{\prime}\left(0, s_{1}\right) V^{\prime}\left(0, s_{2}\right)$ we have

$$
E^{\prime \prime}(0)=2\left(u_{1}^{0}\right)^{2}(M \cdot \alpha)(M \cdot \alpha)=2\left(u_{1}^{0}\right)^{2}\left(M^{T} M \alpha \cdot \alpha\right) .
$$

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

Now assume that $u_{1}^{0}>0$ and $\alpha \neq 0$, then $E^{\prime \prime}(0)>0$. Since $E$ is of class $C^{2}$ so we have the Taylor expansion $E(t)=E(0)+E^{\prime}(0) t+\frac{t^{2}}{2} E^{\prime \prime}(0)+o\left(t^{2}\right)$. As $E(0)=E^{\prime}(0)=0$ then $E(t)=\frac{t^{2}}{2} E^{\prime \prime}(0)+o\left(t^{2}\right)$. So, if $t$ is small enough we get $E(t) \geq 0$, but the interval for which $E(t) \geq 0$ depends on $\alpha$ and we need an non-dependent interval. So the key point is to use the Taylor expansion with integral remainder

$$
E(t)=E(0)+E^{\prime}(0) t+\frac{t^{2}}{2} E^{\prime \prime}(0)+\frac{t^{3}}{2} \int_{0}^{1}(1-r)^{2} E^{(3)}(r t) d r
$$

Since $E(0)=E^{\prime}(0)=0$ then the previous expansion becomes

$$
\begin{equation*}
E(t)=\frac{t^{2}}{2} E^{\prime \prime}(0)+\frac{t^{3}}{2} \int_{0}^{1}(1-r)^{2} E^{(3)}(r t) d r \tag{2.17}
\end{equation*}
$$

From (2.17) we can state the following result
Lemma 2. There exists a constant $C_{5}$ that does not depend on $\alpha$ such that

$$
\left|E^{(3)}(t)\right| \leq C_{5}\|\alpha\|^{2}, \forall t \in[0,1]
$$

Proof. We have

$$
E^{(3)}(t)=V^{\prime \prime \prime}\left(t, s_{1}\right) \cdot V\left(t, s_{2}\right)+3 V^{\prime \prime}\left(t, s_{1}\right) \cdot V^{\prime}\left(t, s_{2}\right)+3 V^{\prime}\left(t, s_{1}\right) \cdot V^{\prime \prime}\left(t, s_{2}\right)+V\left(t, s_{1}\right) \cdot V^{\prime \prime \prime}\left(t, s_{2}\right)
$$

So, it is sufficient to show that

$$
\begin{equation*}
\left|V^{(k)}\left(t, s_{j}\right)\right| \leq C\|\alpha\|, \forall k=0,1,2,3, \ldots \text { and } \forall j=1,2 . \tag{2.18}
\end{equation*}
$$

Since $\mu^{0}$ and $\mu^{1}$ are in the bounded set $U$, then there exists a constant $\bar{\mu}>0$ such that $\left|\mu^{0}\right| \leq \bar{\mu}$ and $\left|\mu^{1}\right| \leq \bar{\mu}$. So we have $\left|(1-s) \mu^{0}+s \mu^{1}\right| \leq \bar{\mu}$ 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

$$
\left\{\begin{array}{l}
V^{\prime}\left(t, s_{1}\right)=D G_{0}\left(u\left(t, s_{1}\right)\right) V\left(t, s_{1}\right)+V_{1}\left(t, s_{1}\right) M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)+u_{1}\left(t, s_{1}\right) M \alpha, \forall s_{1} \in[0,1]  \tag{2.19}\\
V\left(0, s_{1}\right)=0
\end{array}\right.
$$

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

$$
\left\{\begin{aligned}
\frac{1}{2} \frac{\partial\left(\|V\|^{2}\right)}{\partial t} & =D G_{0}(u) V \cdot V+M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right) V_{1} \cdot V+u_{1} M \alpha \cdot V \\
V\left(0, s_{1}\right) & =0
\end{aligned}\right.
$$

which gives

$$
\left\{\begin{aligned}
\frac{1}{2} \frac{\partial\left(\|V\|^{2}\right)}{\partial t} & \leq\left\|D G_{0}(u)\right\|\|V\|^{2}+\left\|M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)\right\|\left\|V_{1}\right\|\|V\|+\left\|u_{1}\right\|\|M \alpha\|\|V\| \\
V\left(0, s_{1}\right) & =0
\end{aligned}\right.
$$

as $\left\|D G_{0}(u)\right\| C_{2},\left\|M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)\right\| \leq\|M\| \bar{\mu},\left\|V_{1}\right\| \leq\|V\|,\left\|u_{1}\right\| \leq C_{1}$ and $\|M \alpha\| \leq\|M\|\|\alpha\|$ then the previous inequality becomes

$$
\left\{\begin{align*}
\frac{1}{2} \frac{\partial\left(\|V\|^{2}\right)}{\partial t} & \leq C_{2}\|V\|^{2}+\|M\| \bar{\mu}\|V\|^{2}+C_{1}\|M\|\|\alpha\|\|V\|  \tag{2.20}\\
V\left(0, s_{1}\right) & =0
\end{align*}\right.
$$

By setting $\alpha_{0}=C_{1}\|M\|\|\alpha\|$ we get

$$
\left\{\begin{align*}
\frac{1}{2} \frac{\partial\left(\|V\|^{2}\right)}{\partial t} & \leq\left(C_{2}+\|M\| \bar{\mu}\right)\|V\|^{2}+\alpha_{0}\|V\|,  \tag{2.21}\\
V\left(0, s_{1}\right) & =0
\end{align*}\right.
$$

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

$$
\left\{\begin{align*}
\frac{\partial\left(\|V\|^{2}\right)}{\partial t} & \leq\left(2 C_{2}+2\|M\| \bar{\mu}+1\right)\|V\|^{2}+\alpha_{0}^{2}  \tag{2.22}\\
V\left(0, s_{1}\right) & =0
\end{align*}\right.
$$

From Gronwall's lemma one deduces

$$
\|V\|^{2} \leq\left\|V\left(0, s_{1}\right)\right\| e^{\left(2 C_{2}+2\|M\| \bar{\mu}+1\right) t}+\frac{\alpha_{0}^{2}\left(e^{\left(2 C_{2}+2\|M\| \bar{\mu}+1\right) t}\right)}{2 C_{2}+2\|M\| \bar{\mu}+1} \leq \frac{\alpha_{0}^{2}\left(e^{\left(2 C_{2}+2\|M\| \bar{\mu}+1\right) t}\right)}{2 C_{2}+2\|M\| \bar{\mu}+1} \forall t \in[0, T]
$$

We set $C_{6}=C_{1}\|M\| \sqrt{\frac{e^{\left(2 C_{2}+2\|M\| \bar{\mu}+1\right) t}}{2 C_{2}+2\|M\| \bar{\mu}+1}}$, hence the estimate of $V\left(t, s_{1}\right)$ is given by

$$
\begin{equation*}
\left\|V\left(t, s_{1}\right)\right\| \leq C_{6}\|\alpha\| \quad \forall t \in[0, T] \tag{2.23}
\end{equation*}
$$

Now, from (2.19) one deduces

$$
\left\|V^{\prime}\left(t, s_{1}\right)\right\| \leq\left\|D G_{0}(u)\right\|\|V\|+\left\|V_{1}\right\|\left\|M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)\right\|+\left\|u_{1}\right\|\|M \alpha\|
$$

which gives

$$
\left\|V^{\prime}\left(t, s_{1}\right)\right\| \leq C_{2}\left\|V\left(t, s_{1}\right)\right\|+\left\|V\left(t, s_{1}\right)\right\|\|M\| \bar{\mu}+C_{1}\|M\|\|\alpha\| .
$$

We then obtain

$$
\begin{equation*}
\left\|V^{\prime}\left(t, s_{1}\right)\right\| \leq C_{7}\|\alpha\| \quad \forall t \in[0, T] \tag{2.24}
\end{equation*}
$$

with $C_{7}=C_{2} C_{6}+C_{6}\|M\| \bar{\mu}+C_{1}\|M\|$.
Step 2: $k=2$
Deriving the equation (2.19) with respect to time variable $t$, we get

$$
\begin{equation*}
V^{\prime \prime}\left(t, s_{1}\right)=D^{2} G_{0}(u) u^{\prime} V+D G_{0}(u) V^{\prime}+V_{1}^{\prime} M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)+u_{1}^{\prime} M \alpha \tag{2.25}
\end{equation*}
$$

This previous relation implies

$$
\left\|V^{\prime \prime}\left(t, s_{1}\right)\right\| \leq\left\|D^{2} G_{0}(u)\right\|\left\|u^{\prime}\right\|\|V\|+\left\|D G_{0}(u)\right\|\left\|V^{\prime}\right\|+\left\|V_{1}^{\prime}\right\|\left\|M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)\right\|+\left\|u_{1}^{\prime}\right\|\|M \alpha\|
$$

From (2.11), (2.23), (2.24), $\left\|M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)\right\| \leq\|M\| \bar{\mu}$ and $\left\|D^{2} G_{0}(u)\right\| \leq C_{2_{1}}$ (see (2.10) we obtain

$$
\begin{equation*}
\left\|V^{\prime \prime}\left(t, s_{1}\right)\right\| \leq C_{9}\|\alpha\| \quad \forall t \in[0, T] \tag{2.26}
\end{equation*}
$$

with $C_{9}=C_{2} L C_{6}+C_{2} C_{6}+C_{7}\|M\| \bar{\mu}+C_{1}\|M\|$.
Step 3: $k=3$
We derive the equation (2.25) with respect of $t$ and get

$$
\begin{align*}
V^{\prime \prime \prime}\left(t, s_{1}\right) & =D^{3} G_{0}\left(u\left(t, s_{1}\right)\right) u^{\prime}\left(t, s_{1}\right) u^{\prime}\left(t, s_{1}\right) V\left(t, s_{1}\right)+D^{2} G_{0}\left(u\left(t, s_{1}\right)\right) u^{\prime \prime}\left(t, s_{1}\right) V\left(t, s_{1}\right) \\
& +2 D^{2} G_{0}\left(u\left(t, s_{1}\right)\right) u^{\prime}\left(t, s_{1}\right) V^{\prime}\left(t, s_{1}\right)+D G_{0}\left(u\left(t, s_{1}\right)\right) V^{\prime \prime}\left(t, s_{1}\right)  \tag{2.27}\\
& +V_{1}^{\prime \prime}\left(t, s_{1}\right) M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)+u_{1}^{\prime \prime}\left(t, s_{1}\right) M \alpha
\end{align*}
$$

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

$$
u^{\prime \prime}\left(t, s_{1}\right)=D G_{0}\left(u\left(t, s_{1}\right)\right) u^{\prime}\left(t, s_{1}\right)+u_{1}^{\prime}\left(t, s_{1}\right) M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)
$$

Triangular inequality yields

$$
\begin{equation*}
\left\|u^{\prime \prime}\left(t, s_{1}\right)\right\| \leq\left\|D G_{0}\left(u\left(t, s_{1}\right)\right)\right\|\left\|u^{\prime}\left(t, s_{1}\right)\right\|+\left\|u_{1}^{\prime}\left(t, s_{1}\right)\right\|\left\|M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)\right\| \tag{2.28}
\end{equation*}
$$

Using (2.12), $\left\|M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)\right\| \leq\|M\| \bar{\mu},\left\|u^{\prime}\right\| \leq C_{8}$ and $\left\|u_{1}^{\prime}\right\| \leq C_{1}$ the previous relation reads

$$
\begin{equation*}
\left\|u^{\prime \prime}\left(t, s_{1}\right)\right\| \leq C_{10} \tag{2.29}
\end{equation*}
$$

with $C_{10}=C_{2} L+L\|M\| \bar{\mu}$.
Let us apply the triangular inequality to (2.27),
$\left\|V^{\prime \prime \prime}\left(t, s_{1}\right)\right\| \leq\left\|D^{3} G_{0}\left(u\left(t, s_{1}\right)\right)\right\|\left\|u^{\prime}\left(t, s_{1}\right)\right\|\left\|u^{\prime}\left(t, s_{1}\right)\right\|\left\|V\left(t, s_{1}\right)\right\|+\left\|D^{2} G_{0}\left(u\left(t, s_{1}\right)\right)\right\|\left\|u^{\prime \prime}\left(t, s_{1}\right)\right\|\left\|V\left(t, s_{1}\right)\right\|$ $+\left\|2 D^{2} G_{0}\left(u\left(t, s_{1}\right)\right)\right\|\left\|u^{\prime}\left(t, s_{1}\right)\right\|\left\|V^{\prime}\left(t, s_{1}\right)\right\|+\left\|D^{2} G_{0}\left(u\left(t, s_{1}\right)\right)\right\|\left\|V^{\prime \prime}\left(t, s_{1}\right)\right\|$
$+\left\|V_{1}^{\prime \prime}\left(t, s_{1}\right)\right\|\left\|M\left(\left(1-s_{1}\right) \mu^{0}+s_{1} \mu^{1}\right)\right\|+\left\|u_{1}^{\prime \prime}\left(t, s_{1}\right)\right\|\|M \alpha\|$.

We now have $\left\|D^{3} G_{0}(u)\right\| \leq C_{2_{2}}$ from (2.12), then using (2.22), (2.29), (2.11), (2.23), (2.24), (2.26) we easily get

$$
\begin{equation*}
\left\|V^{\prime \prime \prime}\left(t, s_{1}\right)\right\| \leq C_{11}\|\alpha\| \tag{2.31}
\end{equation*}
$$

with $C_{11}=C_{2_{2}} L^{2} C_{6}+C_{2_{1}} C_{10} C_{6}+2 C_{2_{1}} L C_{7}+C_{2_{1}} C_{9}+C_{9}\|M\| \bar{\mu}+C_{10}\|M\|$.
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.

Now, to end the proof of Theorem 2, let recall the equation (2.17)

$$
E(t)=\frac{t^{2}}{2} E^{\prime \prime}(0)+\frac{t^{3}}{2} \int_{0}^{1}(1-r)^{2} E^{(3)}(r t) d r
$$

From Lemma 2 we have

$$
\left|\int_{0}^{1}(1-r) E^{(3)}(r t) d r\right| \leq \int_{0}^{1}(1-r)^{2} C_{5}\|\alpha\|^{2} d r=\frac{1}{3} C_{5}\|\alpha\|^{2}
$$

which gives

$$
\begin{equation*}
\frac{t^{3}}{2} \int_{0}^{1}(1-r) E^{(3)}(r t) d r \geq-\frac{t^{3}}{6} C_{5}\|\alpha\|^{2} \tag{2.32}
\end{equation*}
$$

According to Lemma 1 we get

$$
\begin{equation*}
\frac{t^{2}}{2} E^{\prime \prime}(0) \geq t^{2} \lambda_{M}\left(u_{1}^{0}\right)^{2}\|\alpha\|^{2} \tag{2.33}
\end{equation*}
$$

From (2.32) and (2.33) we deduce

$$
\begin{equation*}
E(t)=\frac{t^{2}}{2} E^{\prime \prime}(0)+\frac{t^{3}}{2} \int_{0}^{1}(1-r)^{2} E^{(3)}(r t) d r \geq\left(\lambda_{M}\left(u_{1}^{0}\right)^{2}-C_{5} \frac{t}{6}\right) t^{2}\|\alpha\|^{2} \tag{2.34}
\end{equation*}
$$

We choose $t_{1}>0$ such that $\frac{C_{5} t_{1}}{6} \leq \lambda_{M}\left(u_{1}^{0}\right)^{2}$ (for instance we set $t_{1}=\frac{6 \lambda_{M}\left(u_{1}^{0}\right)^{2}}{C_{5}}$ ) and this gives from (2.34)

$$
E(t) \geq 0, \quad \forall t \in\left(0, t_{1}\right)
$$

Then the hypothesis of Theorem 1 are verified which ends the proof of Theorem 2.

## 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 $\mu^{*}$.
We recall below the considered structured model with maximal size $N$ where $u=\left(u_{1}, \cdots, u_{N}\right)^{T} \in$ $\mathbb{R}_{+}^{N}$ is the unknowns vector.

$$
\left\{\begin{align*}
\frac{d u_{1}(t)}{d t} & =-u_{1}(t) \sum_{i=1}^{N} r_{i} u_{i}(t)+b\left(2 u_{2}(t)+\sum_{i=3}^{N} u_{i}(t)\right)-u_{1}(t) \sum_{i=2}^{N} i \mu_{i}  \tag{3.35}\\
\frac{d u_{i}(t)}{d t} & =r_{i-1} u_{1}(t) u_{i-1}(t)-\left(b+r_{i} u_{1}(t)\right) u_{i}(t)+b u_{i+1}(t)+u_{1}(t) \mu_{i} \\
i & =2, \ldots, N-1 \\
\frac{d u_{N}(t)}{d t} & =r_{N-1} u_{1}(t) u_{N-1}(t)-\left(b+r_{N} u_{1}(t)\right) u_{N}(t)+u_{1}(t) \mu_{N} \\
u(0) & =u^{0}
\end{align*}\right.
$$

where $u^{0}=\left(u_{1}^{0}, \ldots, u_{N}^{0}\right)^{T} \in \mathbb{R}_{+}^{N}$.
For the notation, the nucleation parameter $\mu=\left(\mu_{2}, \ldots, \mu_{N}\right)^{T} \in \mathbb{R}_{+}^{N-1}$ 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 (3.35) 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

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

with $u$ depending on $\mu$ i.e. $u=F(\mu)$ solution of (3.35) taken at $t_{1}$. So we write

$$
\begin{equation*}
\varphi(\mu)=\frac{1}{2}\|F(\mu)-\hat{u}\|_{\mathbb{R}^{N}}^{2}, \tag{3.36}
\end{equation*}
$$

where

$$
F(\mu)=\left(\begin{array}{c}
u_{1}^{\mu}\left(t_{1}\right) \\
u_{2}^{\mu}\left(t_{1}\right) \\
\vdots \\
u_{N}^{\mu}\left(t_{1}\right)
\end{array}\right) \in \mathbb{R}^{N} \text { and } \hat{u}=\left(\begin{array}{c}
\hat{u}_{1}\left(t_{1}\right) \\
\hat{u}_{2}\left(t_{1}\right) \\
\vdots \\
\hat{u}_{N}\left(t_{1}\right)
\end{array}\right) \in \mathbb{R}^{N} .
$$

We seek to solve the problem (3.36) in the least squares sense.
Our problem is to minimize $\varphi(\mu)$ :

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

where $F(\mu)=u$ is the solution of the ordinary differential equation for a fixed $\mu$.
In table 2 below we put the summary table of the parameters and unknowns of our model

### 3.1. Simulation of the direct problem

We simulate the direct problem (3.35) for a given vector of the nucleation parameter. Figure 3.1 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 $\mu$ involved in system (3.35) 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 $\mu_{f}$. The objective of the following tests is to forget this

| Parameter | Definition |
| :--- | :---: |
| $b=1$ | Depolymerization rate for proto-oligomers |
| $N=7$ | The maximum size of proto-oligomers |
| $\mu_{i}, i=2, \ldots, N$ | Nucleation rate for proto-oligomers of size $i$ |
| $T$ | Final time |
| $r_{0}=0.75$ and $b_{0}=0.5$ | Kinetic constants |
| $r_{i}=r_{0} \times i^{1 / 3}, i=1, \ldots, N$ | Polymerisation rate |
| $u_{i}(0)=(0.5 / \sqrt{2 \pi}) e^{\left(-0.5 \times(i-1)^{2}\right)}$ | The initial condition |
| $\mu_{f}=\mu_{i}=\frac{b_{0} \times i}{i+1}, i=2, \ldots, N$ | The given nucleation rate |
| $\mu_{r}$ | The estimated or reconstructed nucleation rate |
| $E r=\frac{\left\\|\mu_{r}-\mu_{f}\right\\|}{\left\\|\mu_{f}\right\\|}$ | Relative error for the estimation of $\mu$ |
| $\hat{u}$ | The measured data at a given time for the solution of $(3.35)$ |
| $\varepsilon_{p}$ | The perturbation parameter of the solution of the direct problem |
| $\varepsilon$ | The perturbation parameter of the nucleation rate $\mu_{f}$ |
| $\hat{u}_{p}$ | The perturbed solution |

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


Figure 3. Solution at time $T=1$ obtained with parameters taken from Table 2
dependency in $\mu_{f}$ 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 $\mu_{f}$.

We are interested in the case where we subtract a constant vector of value $\varepsilon$ from the reference nucleation parameter $\mu_{f}$. So, starting from this initial condition

$$
\mu^{i n, 0}=\mu_{f}-\varepsilon \times \operatorname{Ones}(N-1,1), \quad \text { where } \operatorname{Ones}(N-1,1)=(1, \cdots, 1)^{T}
$$

we find an estimation $\mu_{r}$ (value of $\mu$ reconstructed) using our minimization strategy. Of course if the algorithm converge then $\mu_{r}$ is expected to estimate $\mu_{f}$.

For various values of $\varepsilon$ and measured data taken at time $t_{1}=0.2$ we obtain

| $\mu_{f}$ | $\mu_{r}$ with $\varepsilon=0.1$ | $\mu_{r}$ with $\varepsilon=1$ | $\mu_{r}$ with $\varepsilon=10$ |
| :--- | :--- | :--- | :--- |
| $\mathbf{0 . 3 3 3 3 3 3 3 3 3 3 3 3 3 3}$ | 0.333349883502746 | 0.333368158686978 | 0.333360071687941 |
| $\mathbf{0 . 3 7 5 0 0 0 0 0 0 0 0 0 0 0 0}$ | 0.374975802656048 | 0.375014918722041 | 0.374976994055416 |
| $\mathbf{0 . 4 0 0 0 0 0 0 0 0 0 0 0 0 0 0}$ | 0.399966000229233 | 0.400001811533451 | 0.399990665024704 |
| $\mathbf{0 . 4 1 6 6 6 6 6 6 6 6 6 6 6 6 7}$ | 0.416676239871635 | 0.416670054947340 | 0.416641629407721 |
| $\mathbf{0 . 4 2 8 5 7 1 4 2 8 5 7 1 4 2 9}$ | 0.428571397045192 | 0.428567016101712 | 0.428533628763940 |
| $\mathbf{0 . 4 3 7 5 0 0 0 0 0 0 0 0 0 0 0}$ | 0.437532262391694 | 0.437477091332681 | 0.437552055817063 |

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

For this test, in the particular case where $\varepsilon=0.1$, the tool fminsearch converge after 430 iterations and gives the value $\varphi\left(\mu_{r}\right)=1.53774 e-12$. The corresponding relative error is $E_{r}=$ $5.725048933047261 e-05$.

### 3.3. Estimation with a random perturbation of $\mu_{f}$

Here we are interested in the case where a random perturbation is added to $\mu_{f}$. So, from initial conditions of the form:

$$
\mu^{i n, 0}=\mu_{f}-\varepsilon \times \operatorname{rand}(N, 1),
$$

where $\operatorname{rand}(n, m)$ : returns a matrix of $n$ rows and $m$ columns of random entries with values between 0 and 1.
For various values of $\varepsilon$ and measured data taken at time $t_{1}=0.2$ we obtain the results in the table 4 below

For this test, in the particular case where $\varepsilon=0.1$, the tool fminsearch converge after 223 iterations and gives the value $\varphi\left(\mu_{r}\right)=1.35969 e-12$. The corresponding relative error is $E_{r}=$ $6.689300069247282 e-05$.

| $\mu_{f}$ | $\mu_{r}$ with $\varepsilon=0.1$ | $\mu_{r}$ with $\varepsilon=1$ | $\mu_{r}$ with $\varepsilon=10$ |
| :--- | :--- | :--- | :--- |
| $\mathbf{0 . 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3}$ | 0.333305573630657 | 0.333333560732965 | 0.333334656165570 |
| $\mathbf{0 . 3 7 5 0 0 0 0 0 0 0 0 0 0 0 0}$ | 0.374988369081162 | 0.374999369462275 | 0.375000270956315 |
| $\mathbf{0 . 4 0 0 0 0 0 0 0 0 0 0 0 0 0 0}$ | 0.399964121775021 | 0.400000352426655 | 0.400000373413034 |
| $\mathbf{0 . 4 1 6 6 6 6 6 6 6 6 6 6 6 6 7}$ | 0.416686257711450 | 0.416666436408618 | 0.416667773479836 |
| $\mathbf{0 . 4 2 8 5 7 1 4 2 8 5 7 1 4 2 9}$ | 0.428610791605128 | 0.428571181230545 | 0.428571293138055 |
| $\mathbf{0 . 4 3 7 5 0 0 0 0 0 0 0 0 0 0 0}$ | 0.437486915154826 | 0.437500239323424 | 0.437498890474966 |

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

### 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 (3.35). So we consider as data the vector $\hat{u}_{p}$ defined by

$$
\hat{u}_{p}=\hat{u}-\varepsilon_{p} \times \operatorname{Ones}(N-1,1) .
$$

Thus, from a given initial condition $\mu^{i n, 0}=\mu_{f}-0.1 \times \operatorname{Ones}(N-1,1)$ we find an estimation sequence $\mu_{r}$ of $\mu_{f}$ using the our algorithm with the Matlab tool fminsearch.

For various constant noise $\varepsilon_{p}$ and $\hat{u}$ taken at time $t_{1}=0.2$ we obtain the following reconstructions

| $\mu_{f}$ | $\mu_{r}$ with $\varepsilon_{p}=10^{-4}$ | $\mu_{r}$ with $\varepsilon_{p}=10^{-3}$ | $\mu_{r}$ with $\varepsilon_{p}=10^{-2}$ |
| :--- | :--- | :--- | :--- |
| $\mathbf{0 . 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3}$ | 0.328640727168973 | 0.286286286618157 | 0.170758856257970 |
| $\mathbf{0 . 3 7 5 0 0 0 0 0 0 0 0 0 0 0 0}$ | 0.371815361198109 | 0.342858661869607 | 0.030984543696027 |
| $\mathbf{0 . 4 0 0 0 0 0 0 0 0 0 0 0 0 0 0}$ | 0.398490219045264 | 0.385120811338224 | 0.242704708094556 |
| $\mathbf{0 . 4 1 6 6 6 6 6 6 6 6 6 6 6 6 7}$ | 0.416757711871747 | 0.418023053611640 | 0.431381608326305 |
| $\mathbf{0 . 4 2 8 5 7 1 4 2 8 5 7 1 4 2 9}$ | 0.430279382129130 | 0.445560076787198 | 0.611233378024042 |
| $\mathbf{0 . 4 3 7 5 0 0 0 0 0 0 0 0 0 0 0}$ | 0.441501679429658 | 0.477483478408652 | 0.866321589124976 |

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

For this test, in the particular case where $\varepsilon_{p}=10^{-4}$, the tool fminsearch converges after 271 iterations and gives the value $\varphi\left(\mu_{r}\right)=8.42995 e-08$. 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

$$
\hat{u}_{p}=\hat{u}-\operatorname{rand}(N-1,1)
$$

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

| $\mu_{f}$ | $\mu_{r}$ |
| :--- | :--- |
| $\mathbf{0 . 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3}$ | 0.279499359432756 |
| $\mathbf{0 . 3 7 5 0 0 0 0 0 0 0 0 0 0 0 0}$ | 0.335029771112940 |
| $\mathbf{0 . 4 0 0 0 0 0 0 0 0 0 0 0 0 0 0}$ | 0.381304281712023 |
| $\mathbf{0 . 4 1 6 6 6 6 6 6 6 6 6 6 6 6 7}$ | 0.424035552157708 |
| $\mathbf{0 . 4 2 8 5 7 1 4 2 8 5 7 1 4 2 9}$ | 0.444535756902563 |
| $\mathbf{0 . 4 3 7 5 0 0 0 0 0 0 0 0 0 0 0}$ | 0.4565625455003123 |

Table 6. Values of reconstructed nucleation parameter compared to the referenced one for $\varepsilon_{p}=\operatorname{rand}(N-1,1)$

For this test, the tool fminsearch converge after 63 iterations and give the value $\varphi\left(\mu_{r}\right)=$ $1.11814 e-05$. 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 A $\beta$ proto-oligomers of any size $i \in\{2, \cdots, N\}$ by aggregating monomers or by a nucleation process where two or more $\mathrm{A} \beta$ 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.

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## Appendix

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

$$
\begin{equation*}
\rho(t)=\sum_{i=1}^{N} i u_{i}(t)=u_{1}(t)+\sum_{i=2}^{N} i u_{i}(t), \quad t \geq 0 \tag{4.37}
\end{equation*}
$$

Deriving (4.37) with respect to $t$ we write

$$
\begin{equation*}
\rho^{\prime}(t)=u_{1}^{\prime}(t)+\sum_{i=2}^{N-1} i u_{i}^{\prime}(t)+N u_{N}^{\prime}(t) . \tag{4.38}
\end{equation*}
$$

From the differential equations governing the considered system, the relation (4.38) is recasted as follow

$$
\begin{aligned}
\rho^{\prime}(\mathbf{t})= & -u_{1}(t) \sum_{i=1}^{N} r_{i} u_{i}(t)+b\left(2 u_{2}(t)+\sum_{i=3}^{N} u_{i}(t)\right)-u_{1}(t) \sum_{i=2}^{N} i \mu_{i}+u_{1}(t) \sum_{i=2}^{N-1} i\left(r_{i-1} u_{i-1}(t)-r_{i} u_{i}(t)\right) \\
& +b \sum_{i=2}^{N-1} i\left(u_{i+1}(t)-u_{i}(t)\right)+u_{1}(t) \sum_{i=2}^{N-1} i \mu_{i}+N r_{N-1} u_{1}(t) u_{N-1}(t)-N b u_{N}(t)-N r_{N} u_{1}(t) u_{N}(t)+N u_{1}(t) \mu_{N}
\end{aligned}
$$

Rearranging the terms leads to

$$
\begin{equation*}
\rho^{\prime}(\mathbf{t})=-u_{1} \sum_{i=1}^{N} r_{i} u_{i}+b\left(2 u_{2}+\sum_{i=3}^{N} u_{i}\right)+u_{1} A+b B-N b u_{N} \tag{4.39}
\end{equation*}
$$

where $A=\sum_{i=2}^{N} i\left(r_{i-1} u_{i-1}-r_{i} u_{i}\right)$ and $B=\sum_{i=2}^{N-1} i\left(u_{i+1}-u_{i}\right)$.
Computing $A$ and $B$ we obtain in one hand

$$
\begin{aligned}
A & =\sum_{i=2}^{N} i\left(r_{i-1} u_{i-1}-r_{i} u_{i}\right)=\sum_{i=2}^{N} i r_{i-1} u_{i-1}-\sum_{i=2}^{N} i r_{i} u_{i} \\
& =\sum_{i=1}^{N-1}(i+1) r_{i} u_{i}-\sum_{i=2}^{N} i r_{i} u_{i}=\sum_{i=1}^{N-1} i r_{i} u_{i}+\sum_{i=1}^{N-1} r_{i} u_{i}-\sum_{i=2}^{N} i r_{i} u_{i} \\
& =r_{1} u_{1}+\sum_{i=2}^{N-1} i r_{i} u_{i}+\sum_{i=1}^{N-1} r_{i} u_{i}-\sum_{i=2}^{N-1} i r_{i} u_{i}-N r_{N} u_{N} \\
& =\sum_{i=2}^{N-1} r_{i} u_{i}-N r_{N} u_{N}
\end{aligned}
$$

and in other hand

$$
\begin{aligned}
B & =\sum_{i=2}^{N-1} i\left(u_{i+1}-u_{i}\right)=\sum_{i=2}^{N-1} i u_{i+1}-\sum_{i=2}^{N-1} i u_{i}=\sum_{i=3}^{N}(i-1) u_{i}-\sum_{i=2}^{N-1} i u_{i} \\
& =\sum_{i=3}^{N-1}(i-1) u_{i}+(N-1) u_{N}-\sum_{i=2}^{N-1} i u_{i} \\
& =\sum_{i=3}^{N-1} i u_{i}-2 u_{2}-\sum_{i=3}^{N-1} i u_{i}-\sum_{i=3}^{N-1} u_{i}+(N-1) u_{N} \\
& =(N-1) u_{N}-2 u_{2}-\sum_{i=3}^{N-1} u_{i}
\end{aligned}
$$

Injecting the computed values of $A$ and $B$ in (4.39) we get

$$
\begin{aligned}
\rho^{\prime}(\mathbf{t}) & =-u_{1} \sum_{i=1}^{N} r_{i} u_{i}+b\left(2 u_{2}+\sum_{i=3}^{N} u_{i}\right)+u_{1}\left(\sum_{i=2}^{N-1} r_{i} u_{i}-N r_{N} u_{N}\right)+b\left((N-1) u_{N}-2 u_{2}-\sum_{i=3}^{N-1} u_{i}\right)-N b u_{N} \\
& =-u_{1} \sum_{i=1}^{N} r_{i} u_{i}+b \sum_{i=3}^{N} u_{i}+u_{1} \sum_{i=2}^{N-1} r_{i} u_{i}-N r_{N} u_{1} u_{N}-b \sum_{i=3}^{N} u_{i} \\
& =-u_{1} \sum_{i=1}^{N} r_{i} u_{i}+u_{1} \sum_{i=2}^{N-1} r_{i} u_{i}-N r_{N} u_{1} u_{N} \\
& =-u_{1} r_{1} u_{1}-u_{1} \sum_{i=2}^{N-1} r_{i} u_{i}-r_{N} u_{1} u_{N}+u_{1} \sum_{i=2}^{N-1} r_{i} u_{i}-N r_{N} u_{1} u_{N} \\
& =-u_{1} r_{1} u_{1}-r_{N} u_{1} u_{N}-N r_{N} u_{1} u_{N} \\
& =-\left(r_{1} u_{1}+r_{N} u_{N}+N r_{N} u_{N}\right) u_{1}
\end{aligned}
$$

which implies $\rho^{\prime}(t) \leq 0$ means $\rho(t) \leq \rho(0)=\rho_{0} \forall t>0$.

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