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Estimation of Nucleation Parameters Using a Linear Optimal Control Problem

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Abstract. In this paper, we consider a Becker-Doring-type mathematical interaction model between Aβ monomers and Aβ proto-oligomers, which play an important role in Alzheimer's disease, with a given initial condition, but where the nucleation parameter is unknown. All of this work revolves around estimating the nucleation rate, which is not accessible experimentally. This estimation is made using techniques related to solving optimal control problems. We then propose a necessary and sufficient condition to ensure the existence and uniqueness of the solution, which should make it possible to estimate this parameter.

1. Introduction

The formation of Aβ proto-oligomers occurs through the polymerization of Aβ monomers. This polymerization mechanism is based on a process of gaining and losing Aβ monomers at given rates. Thus, when there are initially no proto-oligomers, the polymerization process cannot start, so at least one Aβ proto-oligomer core is needed to trigger the process. This core is obtained by primary nucleation, where two or more monomers suddenly aggregate and form a proto-oligomer of size i (i is the number of aggregated monomers) [17].

This mechanism of monomer gain and loss causes the appearance of a multitude of proto-oligomers which, through elongation, reach their maximum size and then become Aβ oligomers. Oligomers are known to be very harmful to neurons and are thought to be one of the causes of neuronal death ([2], [3], [4], [5], [6]). Thus, many mathematical models focus on this polymerization phenomenon leading to the formation of oligomers and their involvement in Alzheimer's disease ([1], [15], [16], [17], [18], [19], [20], [21]).

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We consider the classical model of interaction between Aβ monomers and Aβ proto-oligomers by adding the concentration of Aβ oligomers [10] by making μ dependent on time, and we define an optimal control problem that minimizes a cost function dependent on a desired distribution of Aβ oligomers. The control thus considered is based on Pontryagin's maximum principle, which will allow us to establish the necessary conditions for optimality as a function of the set of admissible controls.

One of the first discrete models of fragmentation polymerization dates back to the 1930. Introduced by Becker-Doring in 1935, it aims to describe the polymerization and depolymerization of aggregates through the gain or loss of monomers. In other words, by choosing monomer C_1 as the reference unit for measuring the size of an aggregate, these polymerization and depolymerization reactions can be written as follows: for polymerization, we have $C_i + C_1 \xrightarrow{a_i} C_{i+1}$, where C_i is a cluster containing i elements C_1 and for depolymerization we have $C_i + C_1 \xleftarrow{b_i} C_{i+1}$ ([7], [8], [9]). The reaction rates are a_i for polymerization and b_i for depolymerization, respectively. Thanks to the mass law, these very simple kinetic schemes can be used to describe the flow of each aggregate of size i and thus the evolution of their concentrations for each size. In this interaction, the total mass, $\rho(t) = \sum_{i=1}^{\infty} iC_i$, is constant.

The Becker-Doring model is then represented by the following system:

$$\begin{cases} \dfrac{dC_1}{dt} = -2J_1 - \sum_{i=2}^{+\infty} J_i, \\ \dfrac{dC_i}{dt} = J_{i-1} - J_i, \quad for \quad i \geq 2, \end{cases}$$

where the flows are given for all $i \geq 1$ by $J_i = a_i C_i C_1 - b_i\, C_{i+1}$.

Optimal control theory has really taken off since the 1950s with the discovery of powerful tools such as R. Bellman's dynamic programming principle or Pontryagin's maximum principle ([24], [12]). These results play an essential role in the theory of optimal control of nonlinear systems and have given rise to two different approaches to optimal control problems.

From a mathematical point of view, a controlled system is a dynamic system whose state is described by an unknown function called a state function (or state variable), which verifies one or more laws of evolution (very often these are differential equations, but other types of equations can also be considered: integral equations, difference equations, stochastic equations, etc.). We will assume that we can act on the system (in fact, on the state of the system) via one or more functions called controls (or commands). Another type of problem that we may encounter, but which is mathematically equivalent, is the fact that the system itself is poorly understood, i.e., there are one or more parameters that are unknown, inaccessible, or difficult to measure directly. We then seek to deduce these parameters by viewing them as controls and observing the state of the system.

The paper is organized as follows: Section 2 is devoted to the formulation of our optimal control problem. In Section 3, we study the existence and uniqueness of the solution to the optimal

control problem and the optimality condition of the linear quadratic system. Section 4 presents the conclusion and future prospects.

2. Optimal control problem

2.1. **Position of the problem.** In this section, we add the oligomer population to our classical model of interaction between Aβ monomers and Aβ proto-oligomers [10].

The control problems we consider in this section will be of the following form:

$$\begin{cases} J(u,\mu) = \displaystyle\int_0^T L\Big(t,u(t),\mu(t)\Big)dt \longrightarrow \min_{\mu}, \\ \dfrac{du(t)}{dt} = F\Big(t,u(t),\mu(t)\Big), \\ u(0) = u_0, \\ \mu \in U, t \in I = [0,T], \end{cases} \tag{2.1}$$

where I is an interval of $\mathbb{R}$, $u(0) = u_0$ is the initial position of the Equation 2.1. In practice, the state of the system can represent velocity, position, temperature, and other measurable parameters. U is the set of measurable applications, locally bounded on I with values in $U \subset \mathbb{R}^m$.

The goal is to optimize the function described by the following formula:

$$J(u,\mu) = \int_0^T L\Big(t,u(t),\mu(t)\Big)dt.$$

We call $J(u,\mu)$ the control cost or objective function. The term involved in the objective function $\displaystyle\int_0^T L(t,u(t),\mu(t))dt$ depends on the state of the system throughout the trajectory of the solution, defined by the state variables. This trajectory also depends on time t but above all on the control variables $\mu(t)$.

The first question we usually ask ourselves when faced with a control problem 2.1 is what the optimal trajectories are in relation to the cost under consideration. Next, one of the related questions is the optimality condition, which is often based on Pontryagin's maximum principle.

2.2. **Description of our optimal control problem.** In this section, we introduce an optimal control problem on the total desired amount of oligomers that must not be exceeded from the polymerization and depolymerization process of proto-oligomers. This step constitutes a phase of predicting therapeutic strategies. Indeed, if we can control the nucleation rate $\mu(t) = \Big(\mu_2(t),\ldots,\mu_N(t)\Big)^T$ using, for example, medication, then it will be possible to evolve the system towards a desired stable state. Understanding this mechanism relies on knowledge of the nucleation rate, i.e., the rate at which a few Aβ monomers spontaneously group together to form a proto-oligomer. The lack of biological data on this nucleation rate, which is of paramount importance in the initiation of the pathology, motivates this study, in which we propose to estimate this nucleation rate through an optimal control problem.

The summary diagram is as follows:

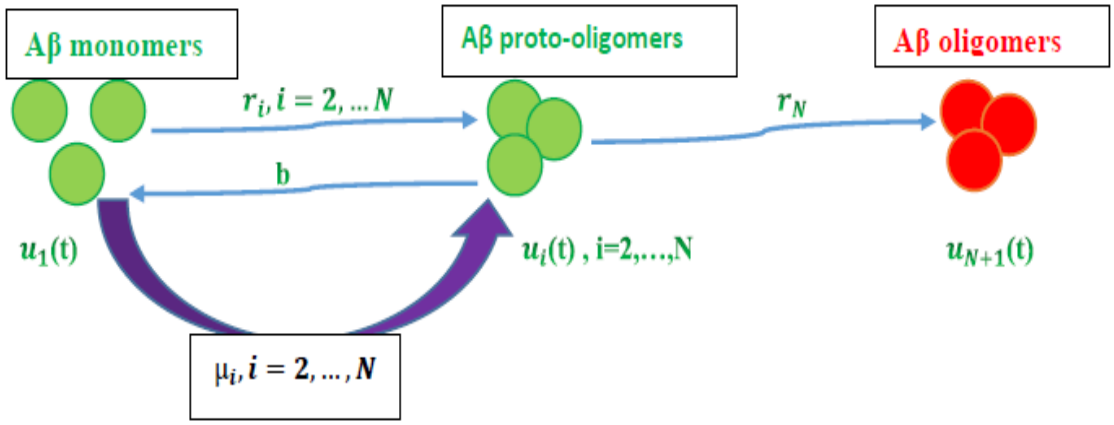

FIGURE 1. Representation of the polymerization process of monomers Aβ

We assume in Figure 1 that a proto-oligomer of size i, with $i \in \{2, \ldots, N\}$, reaches size $i+1$ through monomer gain at a rate r_i (polymerization rate). Similarly, it can reach size $i-1$ through monomer loss at a constant rate b (depolymerization rate). We will denote by $u_i(t)$ the concentration of proto-oligomers of size i with $i \in \{2, \ldots, N\}$ at time t and by $u_1(t)$ the concentration of monomers at time t. For this microscopic model, if there are no proto-oligomers at the start of the experiment, then the reaction does not start. This is why we introduce the parameter μ_i to take into account the effect of spontaneous nucleation for proto-oligomers of size i..

The system parameters are given in Table 1.

Parameters	Description
$t \geq 0$	the observation time
$N \in \mathbb{N}^*$	the maximum size of Aβ proto-oligomers
$N_{ol} = N + 1$	the size of the Aβ oligomers
$\mu_i(t), i = 2, \ldots, N$	the nucleation rate of proto-oligomers of size i at time t
$r_i \geq 0, i = 1, \ldots, N$ with $r_1 = 0$	the polymerization rate of proto-oligomers of size i
$b > 0$	the (constant) depolymerization rate of proto-oligomers
$u_1(t)$	the concentration of monomers Aβ at time t
$u_i(t), i = 2, \ldots, N$	the concentration of proto-oligomers Aβ of size i at time t
$u_{ol}(t) = u_{N+1}(t)$	the concentration of oligomers at time t
$u_d(t)$	the concentration of desired oligomers at time t

TABLE 1. *List of parameters used in the model .*

The model considered is as follows: find $u_1, \ldots, u_{N+1} :]0,T] \longrightarrow \mathbb{R}$ of class C^1 solution of the system of equations defined for all $t \in]0,T]$ by

$$\begin{cases} \dfrac{du_1(t)}{dt} = -u_1(t)\displaystyle\sum_{i=1}^{N} r_i u_i(t) + b\left(2u_2(t) + \sum_{i=3}^{N} u_i(t)\right) - u_1(t)\sum_{i=2}^{N} i\mu_i(t), \\ \dfrac{du_i(t)}{dt} = r_{i-1}u_1(t)u_{i-1}(t) - \Big(b + r_i u_1(t)\Big)u_i(t) + bu_{i+1}(t) + u_1(t)\mu_i(t), \\ \qquad i = 2, \ldots, N-1, \\ \dfrac{du_N(t)}{dt} = r_{N-1}u_1(t)u_{N-1}(t) - \Big(b + r_N u_1(t)\Big)u_N(t) + u_1(t)\mu_N(t), \\ \dfrac{du_{N+1}(t)}{dt} = r_N u_1(t)u_N(t), \\ u(0) = u^0, \end{cases} \tag{2.2}$$

where $u^0 = \left(u_1^0, \ldots, u_{N+1}^0\right)^T \in \mathbb{R}_+^{N+1}$ is the initial position of the Equation 2.2.

Let $u(t) = \left(u_1(t), \ldots, u_{N+1}(t)\right)^T \in \mathbb{R}^{N+1}$ denote the solution of the Equation 2.2 where b and $r_i, i = 1, \ldots, N$ are problem data.

The fourth equation represents the dynamics of oligomers Aβ of size $N+1$, and the last equations of the system 2.2 represent the initial condition.

With this model, we seek to quantify (estimate) the nucleation rate at which monomers fuse and form a proto-oligomer core. This quantification is crucial in modeling Alzheimer's disease according to the amyloid cascade hypothesis, because without the nucleation process, the polymerization and depolymerization mechanisms never start.

We introduce the function S dependent on u and μ called the cost function, which will be of the form

$$S\big(u,\mu\big) = \int_0^T \left(\Big(u_{N+1}(t) - u_d(t)e_{N+1}\Big)^2 + \frac{\varepsilon}{2}\big\|\mu(t)\big\|^2\right)dt, \tag{2.3}$$

where $u_{N+1}(t)$ represents the concentration of oligomers and $u_d(t)$ represents the desired concentration of oligomers (desired state).

Remark 2.1. *In system 2.2, we have the classic model of interaction between Aβ monomers and Aβ proto-oligomers and Aβ oligomers .*

3. Linear-quadratic (LQ) system

In this section, we assume that the concentration of monomers $u_1(t) = m(t)$ is known on $]0,T]$.

For a function $\mu(t) : [0,T] \longrightarrow \Gamma \subset \mathbb{R}^{N-1}$, $\Gamma = \Big(\Big[0,+\infty\Big[\Big)^{N-1}$ given with $\mu(t) = \Big(\mu_2(t),\ldots,\mu_N(t)\Big)^T$, we obtain the following system: find $u(t) : [0,T] \longrightarrow \mathbb{R}^N$ with $u(t) = \Big(u_2(t),\ldots,u_{N+1}(t)\Big)^T$ satisfying $\forall t \in [0,T]$, $T > 0$:

$$\begin{cases} \dfrac{du_2(t)}{dt} = r_1 m^2(t) - \Big(b + r_2 m(t)\Big)u_2(t) + bu_3(t) + m(t)\mu_2(t), \\ \dfrac{du_i(t)}{dt} = r_{i-1}m(t)u_{i-1}(t) - \Big(b + r_i m(t)\Big)u_i(t) + bu_{i+1}(t) + m(t)\mu_i(t), \\ \qquad i = 3,\ldots,N-1, \\ \dfrac{du_N(t)}{dt} = r_{N-1}m(t)u_{N-1}(t) - \Big(b + r_N m(t)\Big)u_N(t) + m(t)\mu_N(t), \\ \dfrac{du_{N+1}(t)}{dt} = r_N m(t)u_N(t), \\ u(0) = u^0, \end{cases} \tag{3.1}$$

where $u^0 = \Big(u_2^0,\ldots,u_{N+1}^0\Big)^T \in \mathbb{R}_+^N$ is the initial position of the system 3.1.

The system 3.1 is a Cauchy problem that can be written as:

$$\begin{cases} \dfrac{du(t)}{dt} &= F\Big(t,u(t),\mu(t)\Big), \quad t \in]0,T] \\ u(0) &= u^0, \end{cases} \tag{3.2}$$

where $F : [0,T] \times \mathbb{R}^N \times \Gamma \longrightarrow \mathbb{R}^N$ is given by $F(t,\tilde{u},\tilde{\mu}) = \Big(F_2,\ldots,F_{N+1}\Big)^T$ with

$$\begin{cases} F_2(t,\tilde{u},\tilde{\mu}) = r_1 m^2(t) - \Big(b + r_2 m(t)\Big)\tilde{u}_2 + b\tilde{u}_3 + m(t)\tilde{\mu}_2, \\ F_j(t,\tilde{u},\tilde{\mu}) = r_{j-1}m(t)\tilde{u}_{j-1} - \Big(b + r_j m(t)\Big)\tilde{u}_j + b\tilde{u}_{j+1} + m(t)\tilde{\mu}_j, \\ \qquad j = 3,\ldots,N-1, \\ F_N(t,\tilde{u},\tilde{\mu}) = r_{N-1}m(t)\tilde{u}_{N-1} - \Big(b + r_N m(t)\Big)\tilde{u}_N + m(t)\tilde{\mu}_N, \\ F_{N+1}(t,\tilde{u},\tilde{\mu}) = r_N m(t)\tilde{u}_N. \end{cases}$$

The system 3.2 is a controlled system where $u(t)$ is the state of the system and $\mu(t)$ is the control.

We define two matrix-valued functions

$$A : [0,T] \longrightarrow \mathcal{M}_N(\mathbb{R}) \text{ with } A(t) = \Big(A_{ij}(t)\Big)_{ij=2\cdots N+1} \text{ and}$$

$$B : [0,T] \longrightarrow \mathcal{M}_{N,N-1}(\mathbb{R}) \text{ with } B(t) = \Big(B_{ij}(t)\Big)_{i=2\cdots N+1, j=2\cdots N}$$

and a vector-valued function

$$g : [0,T] \longrightarrow \mathcal{M}_N(\mathbb{R}) \text{ with } g(t) = \Big(g_2(t),\cdots,g_{N+1}(t)\Big)^T.$$

We observe that F can be written in the form

$$F(t,\tilde{u},\tilde{\mu}) = A(t)\tilde{u} + B(t)\tilde{\mu} + g(t), \ \forall (t,\tilde{u},\tilde{\mu}) \in [0,T] \times \mathbb{R}^N \times \Gamma,$$

where the matrix $A(t)$ is given by

$$\begin{pmatrix} a_0 & b & 0 & 0 & \dots & 0 & 0 & 0 & 0 \\ r_2 m(t) & b_0 & b & 0 & \dots & 0 & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & & & & & \\ 0 & 0 & 0 & 0 & \dots & r_{N-2} m(t) & c_0 & b & 0 \\ 0 & 0 & 0 & 0 & \dots & 0 & r_{N-1} m(t) & d_0 & 0 \\ 0 & 0 & 0 & 0 & \dots & 0 & 0 & r_N m(t) & 0 \end{pmatrix}. \tag{3.3}$$

where $a_0 = -b - r_2 m(t)$, $b_0 = -b - r_3 m(t)$, $c_0 = -b - r_{N-1} m(t)$, and $d_0 = -b - r_N m(t)$.

$$B(t) = \begin{pmatrix} m(t) & 0 & 0 & 0 & \dots & 0 & 0 & 0 & 0 \\ 0 & m(t) & 0 & 0 & \dots & 0 & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & & & & & \\ 0 & 0 & 0 & 0 & \dots & m(t) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \dots & 0 & 0 & m(t) & 0 \\ 0 & 0 & 0 & 0 & \dots & 0 & 0 & 0 & 0 \end{pmatrix} = \begin{pmatrix} m(t) I_{N-1} & 0 \\ 0 & 0 \end{pmatrix} \tag{3.4}$$

and

$$g(t) = \Big(r_1 m^2(t), \dots, 0\Big)^T = r_1 m^2(t) e_1,\ e_1 = \Big(1, 0, \dots, 0\Big)^T \tag{3.5}$$

The controlled system 3.2 can then be written as

$$\begin{cases} \dfrac{du(t)}{dt} &= A(t)u(t) + B(t)\mu(t) + g(t),\ t \in]0, T] \\ u(0) &= u^0. \end{cases}$$

We introduce the function S dependent on u and μ called the cost function, which will be of the form

$$S\Big(u, \mu\Big) = \int_0^T \left(\Big(u_{N+1}(t) - u_d(t) e_{N+1}\Big)^2 + \frac{\varepsilon}{2} \big\|\mu(t)\big\|^2 \right) dt, \tag{3.6}$$

where $u_{N+1}(t)$ represents the concentration of oligomers and $u_d(t)$ represents the desired concentration of oligomers (desired state). Furthermore, suppose that $u_d(t)$ is a bounded function in L^∞.

We ask

$$J = J(\mu) = S\Big(u(\mu), \mu\Big) = \int_0^T L\Big(t, u(t), \mu(t)\Big) dt,$$

with $L : [0,T] \times \mathbb{R}^N \times \Gamma \longrightarrow \mathbb{R}$ given by

$$L\Big(t, \tilde{u}, \tilde{\mu}\Big) = \Big(\tilde{u}_{N+1} - u_d(t)e_{N+1}\Big)^2 + \tfrac{\varepsilon}{2}\|\tilde{u}\|^2.$$

We observe that $L\Big(t, \tilde{u}, \tilde{\mu}\Big)$ is a quadratic function that can be rewritten as

$$L\Big(t, \tilde{u}, \tilde{\mu}\Big) = \Big(\tilde{u} - u_d(t)e_{N+1}\Big)^T Q\Big(\tilde{u} - u_d(t)e_{N+1}\Big),$$

where the matrix Q is symmetric, defined, non-negative, and is given by:

$$Q = \begin{pmatrix} 0 & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \\ 0 & 0 & \cdots & 1 \end{pmatrix} \in \mathcal{M}_N(\mathbb{R}). \tag{3.7}$$

Having a linear system 3.1 associated with a quadratic cost 3.6, the associated optimal control problem is said to be linear-quadratic (LQ).

This LQ problem consists of finding, among all pairs of functions (u, μ) satisfying the system 3.2, those that minimize the function S given by 3.6. We can then write the problem in the form

$$\min_{\mu(t) \in \Gamma} \left\{ \int_0^T L\Big(t, u(t), \mu(t)\Big)dt \right\}.$$

We can view this as a minimization problem with constraints:

$$\min_{\mu(t) \in \Gamma} J(\mu). \tag{3.8}$$

3.1. **Existence and uniqueness of the solution to the optimal control problem.** The existence and uniqueness of the solution to our optimal control problem is obtained by direct application of Theorem 4.1.1 ([22], page 54), a simplified version of which is given below.

Theorem 3.1. *(Simplified version of theorem 4.1.1 [22]).*

Let us consider a shape control system

$$\begin{cases} \frac{du(t)}{dt} &= \tilde{A}(t)u(t) + \tilde{B}(t)\mu(t) + \tilde{g}(t), \\ u(0) &= u^0, \end{cases} \tag{3.8}$$

with a quadratic cost of the form

$$J(\mu) = \int_0^T \left[\Big(u(t) - \tilde{u}_d(t)\Big)^T \tilde{Q}\Big(u(t) - \tilde{u}_d(t)\Big) + \mu(t)^T R\mu(t) \right] dt,$$

where $u(t)$ is a solution to Equation 3.8 with $\tilde{A}(t) : [0,T] \longrightarrow \mathcal{M}_N(\mathbb{R})$, $\tilde{B}(t) : [0,T] \longrightarrow \mathcal{M}_{N,N-1}(\mathbb{R})$ of measurable and bounded functions, $\tilde{Q} \in \mathcal{M}_N(\mathbb{R})$ a positive symmetric matrix, $R \in \mathcal{M}_{N-1}(\mathbb{R})$ a positive definite symmetric matrix, and $\tilde{u}_d(t)$ a function in $L^2\Big([0,T],\ \mathbb{R}^N\Big)$.

Let $\Gamma \subset \mathbb{R}^{N-1}$ be convex and closed, and define U_{adm} as the set

$$U_{adm} = \Big\{ \mu \in L^2\Big([0,T],\ \mathbb{R}^{N-1}\Big), \mu \in \Gamma \quad p.p \quad t \in [0,T] \Big\}.$$

Then the optimal control problem, finding $\mu(t) \in U_{adm}$ that minimizes $J(\mu)$, has a unique solution.

The proof of the theorem is given in [22] and is essentially based on a coercivity assumption on μ.

Thanks to Theorem 3.1, we state the following theorem associated with our optimal control problem (3.1).

Theorem 3.2. *The optimal control problem 3.8 has a unique solution $\mu^* \in U_{adm}$.*

Proof of Theorem 3.2. Our control problem is a special case of the problem described in Theorem 3.1 with $\tilde{A} = A$ given in 3.3, $\tilde{B} = B$ is given in 3.4, $\tilde{g} = g$ is given in 3.5, $\tilde{Q} = Q$ is given in 3.7, $\Gamma = \Big(\Big[0, +\infty\Big[\Big)^{N-1}$, $R = \varepsilon I_d$ and $\tilde{u}_d(t) = u_d(t)e_{N+1}$. It is very easy to see that the assumptions of Theorem 3.1 are satisfied, so by applying this theorem we obtain the result of Theorem 6.1.

Indeed, we have

$$\mu(t)^T R\mu(t) = \Big(\mu_2(t), \dots, \mu_N(t)\Big) \begin{pmatrix} \varepsilon & 0 & \cdots & 0 \\ 0 & \varepsilon & \cdots & 0 \\ \vdots & \vdots & \vdots & \\ 0 & 0 & \cdots & \varepsilon \end{pmatrix} \begin{pmatrix} \mu_2(t) \\ \mu_3(t) \\ \vdots \\ \mu_N(t) \end{pmatrix} = \varepsilon \|\mu(t)\|^2 \text{ and } \mu(t)^T \mu(t) =$$

$$\Big(\mu_2, \dots, \mu_N\Big) \begin{pmatrix} \mu_2(t) \\ \mu_3(t) \\ \vdots \\ \mu_N(t) \end{pmatrix} = \|\mu(t)\|^2.$$

We set $c = \frac{\varepsilon}{2} > 0$ such that for all $t \in [0,T]$ and for all vectors $\mu \in \Gamma$ we have $\mu^T R\mu > c\mu^T\mu$.

3.2. **Optimality conditions and Pontryagin's maximum principle (PMP).** We define the Hamiltonian H associated with our optimal control problem $H : [0,T] \times \mathbb{R}^N \times \mathbb{R}^N \times \Gamma \longrightarrow \mathbb{R}^N$ such that:

$$H(t, \tilde{u}, \tilde{p}, \tilde{\mu}) = L(t, \tilde{u}, \tilde{\mu}) + \tilde{p} \cdot F(t, \tilde{u}, \tilde{\mu}),$$

where $\tilde{p}$ is the vector adjoint to the state vector $\tilde{u}$ of the same dimension N.

Definition 3.1. *(Normal cone, ([13], [11]))*

Let $Q \subseteq \mathbb{R}^n$ be a convex, closed set. Let $x_0 \in \partial Q$. We call the following set the normal cone to Q at x_0 and denote it by $N_Q(x_0)$:

$$N_Q(x_0) = \Big\{ y \in \mathbb{R}^n, \langle y, x - x_0 \rangle \leq 0,\ \forall x \in Q \Big\}.$$

Pontrygin's necessary conditions are ([22], [14]):

$$\begin{cases} \dfrac{du(t)}{dt} &= F\Big(t,u(t),\mu(t)\Big), \\ u(0) &= u^0, \\ \dfrac{dp_i(t)}{dt} &= -\frac{\partial H}{\partial u_i}\Big(t,u(t),p(t),\mu(t)\Big), \\ & \quad i=2,\dots,N+1 \\ p(T) &= 0, \\ -\dfrac{\partial H}{\partial \mu}\Big(t,u(t),p(t),\mu(t)\Big) &\in \mathcal{N}_{\left([0,+\infty[\right)^{N-1}}(\mu(t)), \end{cases} \tag{3.9}$$

where $\mathcal{N}_{\left([0,+\infty[\right)^{N-1}}(\mu(t))$ is the normal cone at μ, it is in the Euclidean space $\mathbb{R}^{N-1}$.

This translates into the fact that $-\dfrac{\partial H}{\partial \mu_i}\Big(t,u(t),p(t),\mu(t)\Big)$ is in the normal cone to $[0,+\infty[$ at $\mu_i, i=2,\dots,N$ and it is in the space $\mathbb{R}$. Therefore,

$$-\frac{\partial H}{\partial \mu_i}\Big(t,u(t),p(t),\mu(t)\Big)\begin{cases} = & 0 \; if \; \mu_i(t)>0, \\ & \\ \leq & 0 \; if \; \mu_i(t)=0. \end{cases} \tag{3.10}$$

We have $H(t,\tilde{u},\tilde{p},\tilde{\mu}) =$

$$\begin{cases} \Big(\tilde{u}_{N+1}-u_d(t)\Big)^2+\frac{\varepsilon}{2}\|\tilde{\mu}\|^2+\tilde{p}\cdot\Big(A(t)\tilde{u}+B(t)\tilde{\mu}+g(t)\Big) \\ \\ \Big(\tilde{u}_{N+1}-u_d(t)\Big)^2+\dfrac{\varepsilon}{2}\|\tilde{\mu}\|^2+\langle\tilde{p},A(t)\tilde{u}+B(t)\tilde{\mu}+g(t)\rangle \\ \\ \Big(\tilde{u}_{N+1}-u_d(t)\Big)^2+\dfrac{\varepsilon}{2}\|\tilde{\mu}\|^2+\langle\tilde{p},A(t)\tilde{u}\rangle+\langle\tilde{p},B(t)\tilde{\mu}\rangle+\langle\tilde{p},g(t)\rangle \\ \\ \Big(\tilde{u}_{N+1}-u_d(t)\Big)^2+\dfrac{\varepsilon}{2}\|\tilde{\mu}\|^2+\langle A^T(t)\tilde{p},\tilde{u}\rangle+\langle B^T(t)\tilde{p},\tilde{\mu}\rangle+\langle\tilde{p},g(t)\rangle. \end{cases} \tag{3.11}$$

By differentiating Equation 3.11 with respect to $\tilde{\mu}_i, i=2,\dots,N$, we obtain

$$\frac{\partial H}{\partial \tilde{\mu}_i}(t,\tilde{u},\tilde{p},\tilde{\mu}) \;=\; \varepsilon\tilde{\mu}_i+m(t)\tilde{p}_i.$$

According to 3.10, we have:

$$\mu_i(t)=\begin{cases} -\dfrac{1}{\varepsilon}m(t)p_i(t) \; si \; p_i(t)<0, \\ 0 \; si \; p_i(t)\geq 0. \end{cases}$$

We set for all $i=2,\dots,N+1$

$$p_i^- = -\min\{p_i,0\}=\begin{cases} 0 \; if \; p_i\geq 0, \\ -p_i \; if \; p_i<0, \end{cases}$$

so that $\forall i = 2,\dots,N,\ \mu_i(t) = \frac{1}{\varepsilon} m(t) p_i^-(t)$.Noting that $p^-(t) = \begin{pmatrix} p_2^-(t) \\ \vdots \\ p_{N+1}^-(t) \end{pmatrix}$ then the vector can be written as follows

$$\mu(t) = \frac{1}{\varepsilon} B^T(t) p^-(t). \tag{3.12}$$

By deriving Equation 3.11 with respect to $\tilde{u}_i, i = 2,\dots,N+1$, we obtain

$$\nabla_{\tilde{u}} H(t,\tilde{u},\tilde{p},\tilde{\mu}) = 2\Big(\tilde{u}_{N+1} - u_d(t)\Big)e_{N+1} + A^T(t)\tilde{p}.$$

So the third equation of the system 3.9 gives us

$$p'(t) = -A^T(t)p(t) - 2\Big(u_{N+1}(t) - u_d(t)\Big)e_{N+1}.$$

Finally, we obtain the following optimal system:

$$\begin{cases} \dfrac{du(t)}{dt} &= A(t)u(t) + \dfrac{1}{\varepsilon} m^2(t) \begin{pmatrix} I_{N-1} & 0 \\ 0 & 0 \end{pmatrix} p^-(t) + r_1 m^2(t) e_1, \\ u(0) &= u^0, \\ \dfrac{dp(t)}{dt} &= -A^T(t)p(t) - 2\Big(u_{N+1}(t) - u_d(t)\Big)e_{N+1}, \\ p(T) &= 0. \end{cases} \tag{3.13}$$

where the expression of $\mu_i(t), i = 2,\dots,N$ is given by

$$\mu_i(t) = \frac{1}{\varepsilon}\ m(t)\ p_i^-(t),\ i = 2,\dots,N.$$

4. Conclusion

In this article, we have developed the optimal control theory approach in the linear case for estimating the nucleation rate appearing in the modeling of Alzheimer's disease according to the amyloid cascade hypothesis. This nucleation rate, which is biologically unmeasurable, explains the genesis of Aβ oligomer formation, which is considered to be the main cause of extracellular neuronal death. The results obtained clearly allow this nucleation rate to be estimated, and the prospects would be, first, to study the nonlinear case (existence, uniqueness, and optimality condition) and, second, to propose an algorithm that would allow this parameter to be estimated numerically.

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

$$\rho(t) = \sum_{i=1}^{N} iu_i(t) = u_1(t) + \sum_{i=2}^{N} iu_i(t), \quad t \geq 0. \tag{3.14}$$

Deriving 3.14 with respect to t we write

$$\rho'(t) = u_1'(t) + \sum_{i=2}^{N-1} iu_i'(t) + Nu_N'(t). \tag{3.15}$$

From the differential equations governing the considered system, the relation is 3.15 as follow

$$\begin{aligned}\rho'(t) = -u_1(t)\sum_{i=1}^{N} r_i u_i(t) + b\Big(2u_2(t) + \sum_{i=3}^{N} u_i(t)\Big) - u_1(t)\sum_{i=2}^{N} i\mu_i + \\ u_1(t)\sum_{i=2}^{N-1} i\Big(r_{i-1}u_{i-1}(t) - r_i u_i(t)\Big) + b\sum_{i=2}^{N-1} i\Big(u_{i+1}(t) - u_i(t)\Big) + \\ u_1(t)\sum_{i=2}^{N-1} i\mu_i + Nr_{N-1}u_1(t)u_{N-1}(t) - Nbu_N(t) - Nr_N u_1(t)u_N(t) + Nu_1(t)\mu_N.\end{aligned}$$

Rearranging the terms leads to

$$\rho'(t) = -u_1\sum_{i=1}^{N} r_i u_i + b\Big(2u_2 + \sum_{i=3}^{N} u_i\Big) + u_1 A + bB - Nbu_N, \tag{3.16}$$

where

$$A = \sum_{i=2}^{N} i\Big(r_{i-1}u_{i-1} - r_i u_i\Big) \qquad \text{and} \qquad B = \sum_{i=2}^{N-1} i\Big(u_{i+1} - u_i\Big).$$

Computing A and B we obtain in one hand

$$\begin{aligned}A &= \sum_{i=2}^{N} i\Big(r_{i-1}u_{i-1} - r_i u_i\Big) = \sum_{i=2}^{N} ir_{i-1}u_{i-1} - \sum_{i=2}^{N} ir_i u_i \\ &= \sum_{i=1}^{N-1}\big(i+1\big)r_i u_i - \sum_{i=2}^{N} ir_i u_i = \sum_{i=1}^{N-1} ir_i u_i + \sum_{i=1}^{N-1} r_i u_i - \sum_{i=2}^{N} ir_i u_i \\ &= r_1 u_1 + \sum_{i=2}^{N-1} ir_i u_i + \sum_{i=1}^{N-1} r_i u_i - \sum_{i=2}^{N-1} ir_i u_i - Nr_N u_N \\ A &= \sum_{i=2}^{N-1} r_i u_i - Nr_N u_N\end{aligned}$$

and in other hand

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

Injecting the computed values of A and B in 3.16 get

$$\begin{aligned}
\rho'(t) &= -u_1\sum_{i=1}^{N} r_iu_i + b\Big(2u_2 + \sum_{i=3}^{N} u_i\Big) + u_1\Big(\sum_{i=2}^{N-1} r_iu_i - Nr_Nu_N\Big) + \\
&\quad b\Big((N-1)u_N - 2u_2 - \sum_{i=3}^{N-1} u_i\Big) - Nbu_N \\
&= -u_1\sum_{i=1}^{N} r_iu_i + b\sum_{i=3}^{N} u_i + u_1\sum_{i=2}^{N-1} r_iu_i - Nr_Nu_1u_N - b\sum_{i=3}^{N} u_i, \\
&= -u_1\sum_{i=1}^{N} r_iu_i + u_1\sum_{i=2}^{N-1} r_iu_i - Nr_Nu_1u_N, \\
&= -u_1r_1u_1 - u_1\sum_{i=2}^{N-1} r_iu_i - r_Nu_1u_N + u_1\sum_{i=2}^{N-1} r_iu_i - Nr_Nu_1u_N, \\
&= -u_1r_1u_1 - r_Nu_1u_N - Nr_Nu_1u_N, \\
\rho'(t) &= -\Big(r_1u_1 + r_Nu_N + Nr_Nu_N\Big)u_1.
\end{aligned}$$

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

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