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# Modelling of anti-inflammatory treatment in the Alzheimer disease: optimal regimen and outcome

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## Abstract

The application of non-steroidal anti-inflammatory drugs (NSAIDs) for Alzheimer's disease is considered to be a promising therapeutic approach. Epidemiological studies suggest potential benefits of NSAIDs; however, these findings are not consistently supported by clinical trials. This long-standing discrepancy has persisted for decades and remains a significant barrier to developing effective treatment strategies. To assess the efficacy of NSAIDs in Alzheimer's disease, we have developed a mathematical model based on a system of ordinary differential equations. The model captures the dynamics of key players in disease progression, including  $A\beta$ -monomers, oligomers, pro-inflammatory mediators (M1 microglial cells and pro-inflammatory cytokines), and anti-inflammatory mediators (M2 microglial cells and anti-inflammatory cytokines). The effects of NSAIDs are modeled through a reduction in the production rate of inflammatory cytokines (IC). While a single NSAID administration temporarily reduces IC levels, their concentration eventually returns to baseline due to drug elimination. The return time depends on the drug dose, resulting in a patient-specific return time function. By analyzing this function, we propose an optimal treatment regimen and identify conditions under which NSAID treatment is most effective in reducing IC levels. Our results suggest that NSAID efficacy in Alzheimer's disease is influenced by the stage of the disease (with earlier intervention being more effective), patient-specific parameters, and the treatment regimen. The approach developed here can also be generalized to evaluate the efficacy of anti-inflammatory treatments for other diseases.

**Keywords:** Alzheimer's diseases, inflammation, anti-inflammatory treatment, NSAID

## 1 Introduction

### 1.1 Biological background

According to the latest statistical reports, around 57.4 million of people are living with Alzheimer's diseases (AD) globally and this number is expected to increase to 152.8 million in 2050 [1]. AD is a progressive

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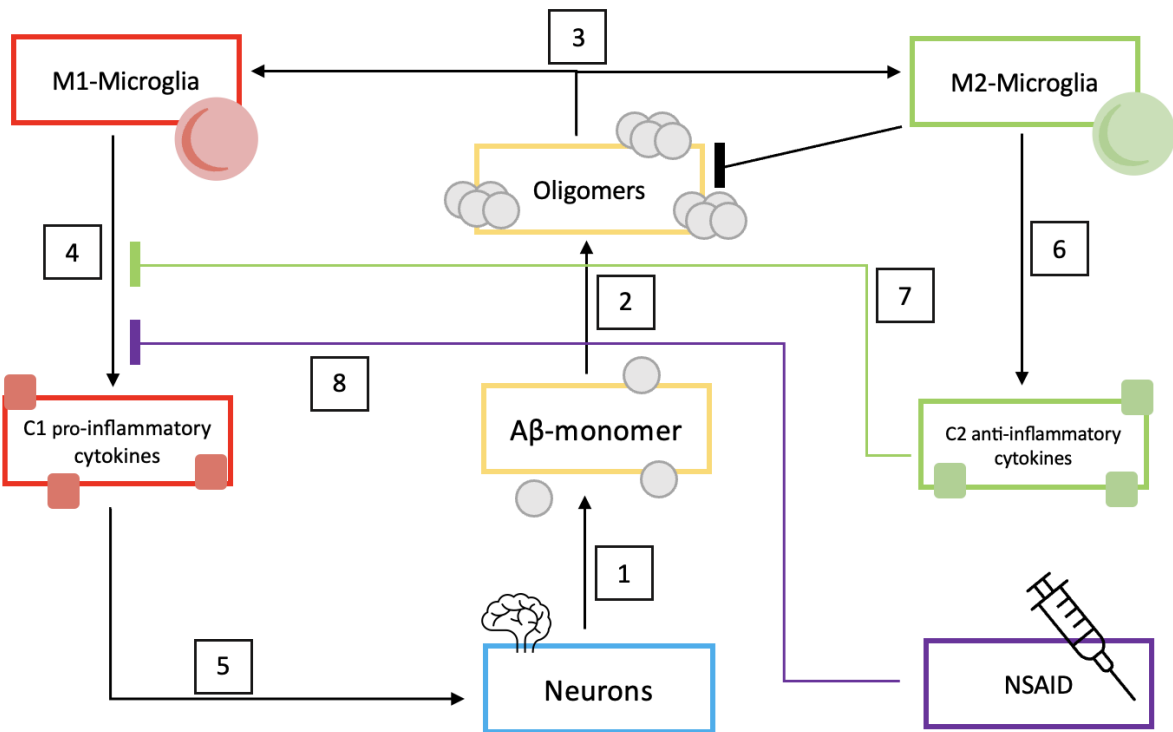
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neurodegenerative disease that affects cognitive abilities. It is linked to the misfolding, aggregation and accumulation of various proteins within the nervous system [2, 3]. These proteins form stable oligomers, one of them is  $A\beta$ , which are considered to be the cause of progressive and irreversible damage to neurons [4, 5]. Neurons produce  $A\beta$ -monomers that undergo polymerization to become proto-oligomers. Proto-oligomers polymerize and depolymerize until reaching a critical size, they become stable under the form of  $A\beta$ -oligomers. Under such form, oligomers cannot undergo polymerization nor depolymerization [6, 7, 8] and are considered cytotoxic [9]. The latter mechanism involving the misfolding of  $A\beta$ -oligomers is referred to as the amyloid cascade hypothesis [10], and it plays a major role in the progression of Alzheimer’s disease (AD) [2, 8]. The presence of cytotoxic  $A\beta$ -oligomers in the brain leads to the set-up of an immune response by the activation of microglial cells, as shown in Figure 1. Microglia are immune cells of the central nervous system that regulate brain development and injury repair. Microglia activation is an important stage of inflammation leading to the production of pro-inflammatory cytokines (such as  $TNF-\alpha$ ,  $IL-1$ ) [11]. The release of pro-inflammatory cytokines up-regulates the production of  $A\beta$ -monomers [12].

During neuroinflammation, the interplay between pro-inflammatory and anti-inflammatory pathways coordinates the dynamics of immune responses in the brain (Figure 1). We distinguish two phenotypes of activated microglial cells, namely M1 and M2 phenotypes. M1 activated microglia are considered pro-inflammatory because they promote the development of inflammation by producing pro-inflammatory cytokines, causing the death of neurons [13]. They also interact with astrocytes leading them to produce neurotoxic factors and to decrease phagocytic activity [14]. In contrast, M2 microglia produce anti-inflammatory cytokines such as  $IL-10$  and transforming growth factor ( $TGF-\beta$ ) [15]. They promote phagocytosis of cell debris and misfolded proteins, inhibit the production of pro-inflammatory agents, and support neuron survival [16]. Some studies have shown the primary role of neuroinflammation in the process of Alzheimer’s disease revealing the alteration in the levels of cytokines in AD patients [17, 18]. For example, increased  $TNF-\alpha$  is a key element in inflammatory cascade and increases the  $A\beta$ -monomer production [19]. Moreover, it has been shown that short-term anti- $TNF-\alpha$  treatment improves cognition in AD patients [20]. The role of the anti-inflammatory cytokine  $IL-4$  is important in neutralizing the neuroinflammatory process in AD brains. Some in vivo experiments show that  $IL-4$  reduces the accumulation of non-plaque forms of  $A\beta$ -proteins [21]. However, AD patients show a decrease in the concentration of  $IL-4$  leading to an imbalance between pro- and anti-inflammatory cytokines which accelerate the AD process [18].

Inflammation plays a major role in the progression of the diseases and several therapeutic strategies are implemented to attenuate the negative effect of AD. For example, non-steroidal anti-inflammatory drugs (NSAIDs) are medicines that are widely used as a treatment for fever, pain and inflammation. Several epidemiological studies show that NSAIDs can be considered as neuroprotective since they target microglia, major contributors to neurodegeneration [22, 23, 24]. For example, diclofenac-based drugs might be associated with slower cognitive decline [25]. Furthermore, some studies have suggested that, if started early enough, a daily regimen of the non-prescription NSAID ibuprofen can prevent the onset of Alzheimer’s disease [26]. Although this type of drugs crosses the blood brain barrier (BBB) efficiently, the dose reaching the brain is different due to many neuropathological conditions [27]. The effect of such drugs on microglial functions consists in the inhibition of COX activity (cyclooxygenase enzymes involved in inflammation) [23], in down-regulation of the expression of genes responsible for activating inflammatory pathways ( $NF-\kappa B$ ) [28] and activating  $PPAR-\gamma$  (nuclear receptor) [29]. Several studies show that  $PPAR-\gamma$  control brain inflammation and is highlighted as a promising therapeutic use in human brain diseases.

Though epidemiological studies support the evidence that the use of NSAID reduces the risk of AD [25, 27, 30], clinical studies have not confirmed that NSAID has a positive effect on the Alzheimer patients. Some possible explanations for such discrepancy is that NSAID can only be effective in early stages of



**Figure 1:** Scheme depicting the biological phenomena of  $A\beta$ -monomers and inflammation including neurons,  $A\beta$ -monomers, oligomers, M1-M2 microglial cells, C1-C2 inflammatory cytokines and non-steroidal anti-inflammatory drugs (NSAID). Neurons produce  $A\beta$ -monomers (1) that polymerize into stable oligomers (2). Stable oligomers activate microglial cells (3) that causes the set-up of an inflammatory response by producing inflammatory cytokines. M1 type microglia produce C1 pro-inflammatory cytokines (4) that in return stimulate neurons (5) to produce additional  $A\beta$ -monomers. In contrast, M2 type microglia produce C2 anti-inflammatory cytokines (6) and eliminates oligomers. Anti-inflammatory cytokines (7) and NSAID (8) inhibit the production of pro-inflammatory cytokines.

78 the disease and is non-beneficial for later stages [22, 25, 30] or that the concentration of NSAID reaching  
 79 the brain is not sufficient because of the blood-brain barrier. Furthermore, such type of drugs require a  
 80 prolonged period of administration in order to provide a protective effect [31].

81 In this work we use mathematical modelling in order to study whether NSAID treatment can be  
 82 beneficial for virtual patients and to determine the optimal treatment regimen.

## 83 1.2 Mathematical modeling of Alzheimer disease in the literature

84 During the last decades, several studies were devoted to the onset of AD [32] and the role of prions  
 85 interacting with  $A\beta$  [33]. In [32], the authors propose a system of transport and diffusion equation to  
 86 study the set-up and the progression of the disease with a focus on the diffusion and removal of  $A\beta$ . They  
 87 study the spread of neuronal damage at different stages of the disease evolution and particularly the  
 88 cerebral damage at the early stages.

89 Mathematical models study the interactions between key components in the brain, including oligomers  
 90 [34] and  $A\beta$ -plaques [35], emphasizing their roles in disease progression. For example, authors in [34]

91 suggest a model to study the spatial propagation of amyloid-beta ( $A\beta$ ) oligomers in the early stages of  
92 AD. Numerical simulations are used to study the balance between oligomers diffusion and replication, and  
93 show that fragmentation rate of oligomers considerably affects their neurotoxic effects on the progression  
94 of the disease. Authors in [35] propose a model based on macroscopic integro-differential equations to  
95 study the interplay between amyloid-beta and tau proteins in the development of AD. Through transport  
96 and diffusion equations, they highlight that  $A\beta$  and tau interactions significantly impact the disease  
97 distribution in the brain at early and advanced stages of the disease. Moreover, they showed that the  
98 removal of toxic  $A\beta$  from the cerebrum promotes tissue regeneration.

99 Inflammation processes plays a crucial role in the progression of AD. Hence, some studies are devoted  
100 to investigate the role of inflammatory processes, namely the activation of microglial cells [36], the role of  
101 pro-inflammatory cytokines [37] and the anti-inflammatory effect [38, 39]. In [36] the authors present a  
102 system of ordinary differential equations modeling the interaction between seven key-players of the disease  
103 such as neurons,  $A\beta$  and microglial cells. They highlight that inflammatory activation of resting microglial  
104 cells is a crucial step for progressive neuron death and should be further studied. The work [37] suggests  
105 a spatially homogeneous system of equations to study the interactions between monomers, oligomers,  
106 microglial cells and pro-inflammatory cytokines. It is shown that inflammation can trigger the disease  
107 through a hysteresis effect, where disease development or remission depend on the degradation rate of  
108 oligomers. Furthermore, they discuss some perspectives of anti-inflammatory treatments of AD. Similarly,  
109 authors in [39] suggest that some anti-inflammatory drug therapy could slow the development of the  
110 disease. They develop a system of partial differential equations describing the interactions between neurons,  
111 microglia, tumor necrosis factor alpha  $TNF-\alpha$  and anti-inflammatory cytokines. Through numerical  
112 simulations, they assess the efficacy of  $TNF-\alpha$  inhibitor and anti-amyloid  $\beta$  as a possible therapy.

113 In this work, we propose a mathematical model describing  $A\beta$  production, inflammation and effect of  
114 NSAID (Section 1.3). The proposed model describes the pro- and anti-inflammatory aspects in the case of  
115 Alzheimer disease. We begin with the analysis of the existence of solutions, existence of stationary points  
116 and their stability (Section 2). Then, we focus on the role of NSAID in the inflammation progression for a  
117 simplified model (Section 3) and subsequently for the complete model (Section 4). The main objective of  
118 this work is to elucidate why a NSAID treatment may not be efficient in some cases and to propose an  
119 optimal treatment regimen.

### 120 1.3 Mathematical model

121 In this section, we present a mathematical model describing  $A\beta$  production and inflammation, as shown  
122 in Figure 1. The model consists of an ordinary differential system of equations for the concentrations  
123  $A\beta$ -monomers,  $A\beta$ -proto-oligomers of size  $i$ ,  $A\beta$ -oligomers, M1 pro-inflammatory microglial cells, pro-  
124 inflammatory cytokines, M2 anti-inflammatory microglial cells and anti-inflammatory cytokines.

125 **Proto-oligomers and oligomers production.** Abnormal amyloid- $\beta$  is produced by activated neurons,  
126 and form proto-oligomers and oligomers. The concentration of neurons  $N$  is considered to be constant.  
127 Their death can be neglected in the beginning of AD. In the later stages, when they start to die,  
128 their concentration can be considered as quasi-stationary since it is a slow process in the time scale of  
129 inflammation processes. We denote the amyloid- $\beta$  concentration by  $A$  and the concentration of proto-  
130 oligomers of length  $i$  by  $u_i$ . We do not take into account the process of depolymerization of proto-oligomers.  
131 We fix  $n \in \mathbb{N}$ , the maximal size of proto-oligomers by polymerization, meaning they can no longer undergo  
132 either polymerization or depolymerization [6, 7, 8]. Then, their concentrations are described by the system  
133 of equations

$$\frac{dA}{dt} = k_1 C_1 N - 2k_2 A^2 - \sigma_1 A - \sum_{i=2}^n r_i A u_i, \quad (1.1)$$

$$\frac{du_2}{dt} = k_2 A^2 - r_2 A u_2 - \sigma_2 u_2 (1 + bM_2), \quad (1.2)$$

$$\frac{du_3}{dt} = r_2 A u_2 - r_3 A u_3 - \sigma_2 u_3 (1 + bM_2), \quad (1.3)$$

$$\frac{du_i}{dt} = r_{i-1} A u_{i-1} - r_i A u_i - \sigma_2 u_i (1 + bM_2), \quad i \in \{2, \dots, n-1\} \quad (1.4)$$

$$\frac{du_n}{dt} = r_{n-1} A u_{n-1} - \sigma_2 u_n (1 + bM_2), \quad (1.5)$$

134 The first term in the right-hand side of equation (1.1) describes production of abnormal amyloid- $\beta$   
 135 under the influence of inflammatory cytokines  $C_1$ . For simplicity, production of normal amyloid without  
 136 inflammation is not taken into consideration. The second term in equation (1.1) characterizes aggregation  
 137 of two molecules leading to production of  $u_2$  proto-oligomers, and the third term represent the natural  
 138 degradation rate of amyloid- $\beta$ . The last term in equation (1.1) represents the polymerization of one  
 139 monomer with a proto-oligomer of size  $i$  to form an oligomer of size  $i + 1$ . We denote by  $r_i$ ,  $i \in \{2, \dots, n\}$ ,  
 140 the polymerization rate. Equation (1.2) describes the evolution in time of the concentration of  $u_2$  proto-  
 141 oligomers. The first term in the right-hand side of this equation represents the production of  $u_2$  from  $A$   
 142 and the second term corresponds to the polymerization of an proto-oligomer of size 2. The last term in  
 143 equation (1.2) characterizes the degradation and elimination of  $u_2$  by activated microglia cells  $M_2$ . Similar  
 144 terms are present in the next equations. For simplicity of presentation, we assume that  $n$  can take any  
 145 large value.

146 For simplification, we consider that the length of proto-oligomers,  $n$ , is sufficiently large so that we  
 147 can set  $u$  to be the sum of all size of proto-oligomers  $i$  for  $i \in \{2, \dots, n\}$ . We set  $u = \sum_{i=2}^n u_i$ , and take a  
 148 sum of equations (1.2)-(1.5), we obtain

$$\frac{du}{dt} = k_2 A^2 - \sigma_2 u (1 + bM_2). \quad (1.6)$$

For simplicity, we denote by  $u$  the concentration of oligomers. In fact, we consider a bi-monomeric  
 nucleation as used in [37]. We assume that two monomers can merge to form a free oligomer ( $A + A \rightarrow u$ )  
 and the intermediate proto-oligomer phase is neglected. Therefore, equations (1.1) and (1.6) become:

$$\frac{dA}{dt} = k_1 C_1 N - 2k_2 A^2 - \sigma_1 A, \quad (1.7)$$

$$\frac{du}{dt} = k_2 A^2 - \sigma_2 u (1 + bM_2). \quad (1.8)$$

149 **Microglia activation.** Microglia phenotype  $M_1$  are activated by oligomers  $u$ :

$$\frac{d\tilde{M}_1}{dt} = -k_3 u \tilde{M}_1, \quad (1.9)$$

$$\frac{dM_1}{dt} = k_3 u \tilde{M}_1 - \sigma_3 M_1. \quad (1.10)$$

150 Here  $\tilde{M}_1$  is the concentration of inactive microglia and  $M_1$  the concentration of activated microglia.  
 151 The last term of equation (1.10) corresponds to the rate of death or exhaustion. We assume that  $\sigma_3$   
 152 is sufficiently small, then we can use approximate equality  $\tilde{M}_1 + M_1 = M_1^0$ , where  $M_1^0$  is the initial  
 153 microglia concentration. Under such assumptions, we exclude  $\tilde{M}_1$  and consider the following equation for  
 154  $M_1$  microglia:

$$\frac{dM_1}{dt} = k_3 u(M_1^0 - M_1) - \sigma_3 M_1. \quad (1.11)$$

155 A similar equation is considered for the concentration  $M_2$  of alternatively activated microglia:

$$\frac{dM_2}{dt} = k_6 u(M_2^0 - M_2) - \sigma_5 M_2. \quad (1.12)$$

156 **Cytokine production.** Classically activated microglia produce pro-inflammatory cytokines  $C_1$  [13]:

$$\frac{dC_1}{dt} = \frac{k_4 M_1}{1 + k_5 C_2} - \sigma_4 C_1. \quad (1.13)$$

157 Their production rate is down-regulated by anti-inflammatory cytokines  $C_2$  produced by alternatively  
 158 activated microglia  $M_2$ :

$$\frac{dC_2}{dt} = k_7 M_2 - \sigma_6 C_2. \quad (1.14)$$

159 The last terms in these equations represent the degradation rate of the corresponding cytokines.

160 **Anti-inflammatory treatment.** Non-steroidal anti-inflammatory drugs (NSAIDs) act on COX1,  
 161 COX2 and other molecules participating in production of inflammatory cytokines. We consider here  
 162 a simplified pharmacokinetics of the NSAID treatment either with a constant drug concentration or  
 163 exponentially decreasing in time due to its elimination from the body. We take into account in equation  
 164 (1.13) that NSAIDs with concentration  $D$  down-regulate  $C_1$  production rate, where  $a$  denotes the rate of  
 165 down-regulation:

$$\frac{dC_1}{dt} = \frac{k_4 M_1}{(1 + k_5 C_2)(1 + aD)} - \sigma_4 C_1. \quad (1.15)$$

166 **Resulting model.** We obtain the following model:

$$\frac{dA}{dt} = k_1 C_1 N - 2k_2 A^2 - \sigma_1 A, \quad (1.16)$$

$$\frac{du}{dt} = k_2 A^2 - \sigma_2 u(1 + bM_2), \quad (1.17)$$

$$\frac{dM_1}{dt} = k_3 u(M_1^0 - M_1) - \sigma_3 M_1, \quad (1.18)$$

$$\frac{dC_1}{dt} = \frac{k_4 M_1}{(1 + k_5 C_2)(1 + aD)} - \sigma_4 C_1, \quad (1.19)$$

$$\frac{dM_2}{dt} = k_6 u(M_2^0 - M_2) - \sigma_5 M_2, \quad (1.20)$$

$$\frac{dC_2}{dt} = k_7 M_2 - \sigma_6 C_2. \quad (1.21)$$

In general, the drug concentration is a function of time,  $D = D(t)$ . We describe the evolution in time for  $D$  by the equation

$$\frac{dD}{dt} = -kD. \quad (1.22)$$

167 Equation (1.22) states that the concentration of NSAID decreases with time due to its elimination from  
 168 the body, and its solution is  $D(t) = D_0 e^{-kt}$ , where  $D_0$  is the initial drug concentration.

## 169 2 Analysis of the system

### 170 2.1 Existence and properties of solution

171 In this section, we study the existence, uniqueness, positivity and boundedness of the solution of system  
 172 of equations (1.16)-(1.21).

173 **Proposition 2.1.** *For any non-negative initial condition  $(A(0), u(0), M_1(0), M_2(0), C_1(0), C_2(0))$ , the  
 174 system (1.16)-(1.21) has a unique global solution which is bounded.*

175 *Proof.* Existence and uniqueness of a local solution directly follows from the Cauchy–Lipschitz theorem  
 176 for ordinary differential equations.

177 The solution is bounded because from the fifth equation of system (1.16)-(1.21), we conclude that  
 178 if  $M_2(t)$  is large enough then  $\frac{dM_2}{dt} < 0$  and, therefore,  $M_2$  remains bounded. By reapplying the same  
 179 argument, we subsequently conclude the same result for the rest of the variables of the system. Since the  
 180 solutions of system (1.16)-(1.21) are bounded, they are defined for all  $t > 0$ .  $\square$

181 **Proposition 2.2.** *From Proposition 2.1 in [40], for any positive initial condition, the solution of the  
 182 system (1.16)-(1.21) is positive.*

*Proof.* Consider the vector field  $F = (f_1, \dots, f_6)$  for  $x = (x_1, \dots, x_6) \in \mathbb{R}^6$  given by

$$\begin{cases} f_1(x) = k_1 x_4 N - 2k_2 x_1^2 - \sigma_1 x_1, \\ f_2(x) = k_2 x_1^2 - \sigma_2 x_2 (1 + b x_5), \\ f_3(x) = k_3 x_2 (M_1^0 - x_3) - \sigma_3 x_3, \\ f_4(x) = \frac{k_4 x_3}{(1 + k_5 x_6)(1 + a D)} - \sigma_4 x_4, \\ f_5(x) = k_6 x_2 (M_2^0 - x_5) - \sigma_5 x_5, \\ f_6(x) = k_7 x_5 - \sigma_6 x_6, \end{cases}$$

and observe that  $F$  satisfies the quasi-positivity property, that is, for all indices  $i \in \{1, \dots, 6\}$  we have

$$\text{for all } (x_j)_{j \neq i} \in (\mathbb{R}^+)^5, f_i(x_1, \dots, x_{i-1}, 0, x_{i+1}, \dots, x_6) \geq 0.$$

183 Hence, from Proposition 2.1 in [40], we conclude that the solution remains positive because of this  
 184 property.  $\square$

## 2.2 Equilibrium points of the complete model

In order to study the steady states, we let  $D(t) = 0$  and find the stationary points of the following system:

$$k_1 C_1 N - 2k_2 A^2 - \sigma_1 A = 0, \quad (2.1)$$

$$k_2 A^2 - \sigma_2 u(1 + bM_2) = 0, \quad (2.2)$$

$$k_3 u(M_1^0 - M_1) - \sigma_3 M_1 = 0, \quad (2.3)$$

$$k_6 u(M_2^0 - M_2) - \sigma_5 M_2 = 0, \quad (2.4)$$

$$\frac{k_4 M_1}{(1 + k_5 C_2)} - \sigma_4 C_1 = 0, \quad (2.5)$$

$$k_7 M_2 - \sigma_6 C_2 = 0. \quad (2.6)$$

From equation (2.1), we get

$$A = A(C_1) = \frac{(-\sigma_1 + \sqrt{\sigma_1^2 + 8k_1 k_2 C_1 N})}{4k_2}.$$

From equations (2.2) and (2.4), we write two formulas for  $u$ , namely

$$\begin{cases} u := g_1(C_1, M_2) = \frac{1}{\sigma_2} \frac{k_2 A^2}{bM_2 + 1}, \\ u := g_2(M_2) = \frac{\sigma_5 M_2}{k_6(M_2^0 - M_2)}. \end{cases} \quad (2.7)$$

Equating both equations of system (2.7), we express  $M_2$  in terms of  $C_1$ :

$$M_2 = \frac{-(\sigma_5 \sigma_2 + k_2 k_6 A^2) + \sqrt{(\sigma_5 \sigma_2 + k_2 k_6 A^2)^2 + 4\sigma_5 \sigma_2 b (k_2 k_6 A^2 M_2^{02})}}{2\sigma_5 \sigma_2 b}.$$

Similarly, we express  $u$ ,  $C_2$  and  $M_1$  in terms of  $C_1$  from equations (2.2), (2.6) and (2.3), respectively:

$$u = \frac{k_2 A^2}{\sigma_1(1 + bM_2)} = \frac{2k_2 \sigma_5 A^2}{\sigma_2 \sigma_5 - k_2 k_6 A^2 + \sqrt{(\sigma_5 \sigma_2 + k_2 k_6 A^2)^2 + 4\sigma_5 \sigma_2 b (k_2 k_6 A^2 M_2^{02})}},$$

$$C_2 = \frac{k_7}{\sigma_6} M_2,$$

$$M_1 = \frac{k_3 u M_1^0}{k_3 u + \sigma_3} = \frac{2\sigma_5 k_2 k_3 A^2 M_1^0}{\sigma_3 \left( \sigma_2 \sigma_5 - k_6 k_2 A^2 + \sqrt{(\sigma_5 \sigma_2 + k_2 k_6 A^2)^2 + 4\sigma_5 \sigma_2 b (k_2 k_6 A^2 M_2^{02})} \right) + 2k_3 k_2 \sigma_5 A^2}.$$

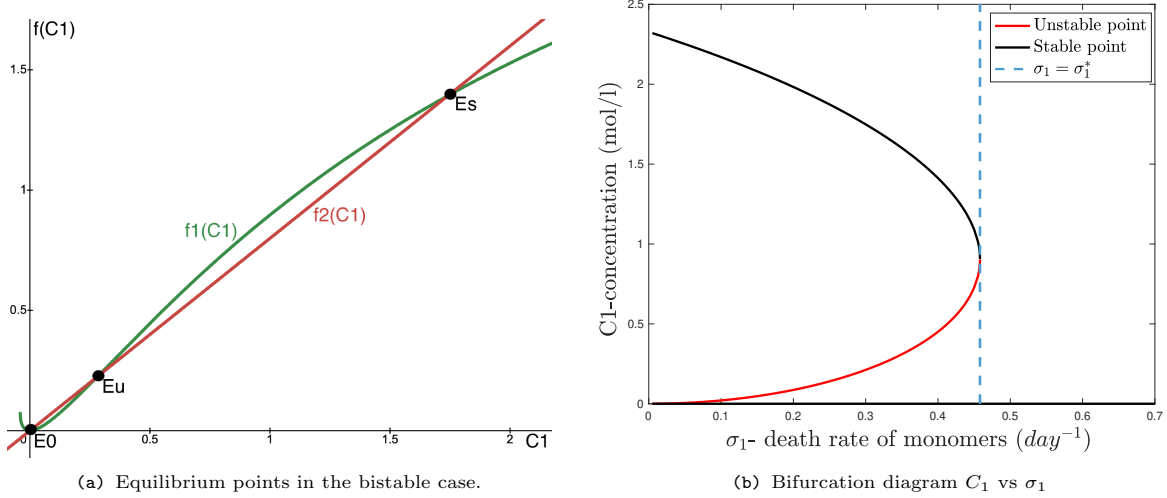
Replacing those expression in equation (2.5), we get the following expression in terms of  $C_1$ :

$$\frac{k_4 M_1(C_1)}{1 + k_5 C_2(C_1)} = \sigma_4 C_1.$$

We obtain that the trivial equilibrium point  $E_0 = (0, 0, 0, 0, 0, 0)$  exists for all values of parameters. The computation of the solution with respect to  $C_1$  are too tedious. Hence, we suggest a geometrical perspective in order to find the number of non-negative steady states. We define the functions

$$f_1(C_1) = \frac{k_4 M_1(C_1)}{1 + k_5 C_2(C_1)}, \quad f_2(C_1) = \sigma_4 C_1.$$

The curves  $f_1$  and  $f_2$  have up to three intersection where  $C_1 \geq 0$  (see Figure 2a).



**Figure 2:** Existence and stability of equilibrium points. Figure 2a represents the bistable case where three equilibrium points exist  $E_0$ ,  $E_u$  and  $E_s$ , with  $\sigma_4 = 1.2$ . Figure 2b represents a bifurcation diagram of the equilibrium points for the concentration of pro-inflammatory cytokines  $C_1$  in terms of the degradation rate  $\sigma_1$  of monomers ( $A\beta$ ). The disease-free equilibrium exists for all values of  $\sigma_1 > 0$  and it is stable. For  $\sigma_1 < \sigma_1^*$ , we have two other equilibrium points  $E_u$  unstable (red line) and  $E_s$  stable (black line). Values of parameters are taken from Table 2.

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We conclude that system (2.1)-(2.6) may end up with a total of three positive equilibrium points, namely  $E_0$ ,  $E_u$  and  $E_s$ . The case with only one equilibrium point  $E_0$  corresponds to the non-inflammatory case. The bistable case is depicted in Figure 2(a) and is represented by the existence of three equilibrium points  $E_0$ ,  $E_u$  and  $E_s$ . Another classification of the equilibrium points, based on the parameter  $\sigma_1$ , is presented in Section 2.3.

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### 2.3 Stability of equilibrium points

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**Proposition 2.3.** For the system (1.16)-(1.21), the disease-free equilibrium  $E_0 = (0, 0, 0, 0, 0, 0)$  is stable for every choice of positive parameters.

*Proof.* The Jacobian matrix around the vector  $(0, 0, 0, 0, 0, 0)$  is given by

$$J = \begin{pmatrix} -\sigma_1 & 0 & 0 & 0 & k_1 N & 0 \\ 0 & -\sigma_2 & 0 & 0 & 0 & 0 \\ 0 & k_3 M_1^0 & -\sigma_3 & 0 & 0 & 0 \\ 0 & k_6 M_2^0 & 0 & -\sigma_5 & 0 & 0 \\ 0 & 0 & k_4 & 0 & -\sigma_4 & 0 \\ 0 & 0 & 0 & k_7 & 0 & -\sigma_6 \end{pmatrix}.$$

195 The eigenvalues of this matrix are  $\{-\sigma_1, -\sigma_2, -\sigma_3, -\sigma_4, -\sigma_5, -\sigma_6\}$ . Since they are all negative, then the  
 196 disease-free equilibrium is locally asymptotically stable.  $\square$

197 We determine the stability of the equilibrium points  $E_u$  and  $E_s$  using numerical simulations, as shown  
 198 in Figure 2(b). We perform a bifurcation analysis with respect to the variation of the parameter  $\sigma_1$ , where  
 199 we consider the  $C_1$ -coordinate of the equilibrium points. Numerical simulations show that there are two  
 200 different cases depending on the parameter  $\sigma_1$ :

- 201 • If  $\sigma_1 > \sigma_1^*$ , there is a single point  $E_0$ , AD does not develop and we denote this case by disease-free  
 202 case.
- 203 • If  $\sigma_1 < \sigma_1^*$ , there are three points  $(E_0, E_u, E_s)$ , AD develops if the initial perturbation (inflammation)  
 204 is sufficiently large. We denote this case by bistable case.

## 205 2.4 Biological interpretation

206 In this section, we provide a biological interpretation of the equilibrium points.

- 207 •  $E_0$  corresponds to the non-inflammatory state where all concentrations are zeros. In other words,  
 208 there are no oligomers, immune cells or inflammatory cytokines. Thus, there is no interaction  
 209 between inflammatory agents; hence, no inflammation reaction can happen in this case. This point  
 210 exists for all values of parameters and is stable.
- 211 •  $E_u$  is an intermediate equilibrium point, it is unstable whenever it exists. Indeed, it represents a  
 212 threshold to overcome in order to move from the non-inflammatory state  $E_0$  to the inflammatory  
 213 state  $E_s$ .
- 214 •  $E_s$  represents an inflammatory state. All inflammatory agents and key-players of AD have positive  
 215 concentrations. This point characterizes the set-up of AD along with an inflammatory reaction.  
 216 Therefore,  $E_s$  characterizes the disease state and is stable whenever it exists.

217 We study then the development of the disease in the bistable case (existence of three equilibrium  
 218 points). We are interested in showing how NSAID affects the dynamics of the solution and whether it  
 219 can limit or reverse the development of the disease at an early stage. Since the study of the system of  
 220 equations (1.1)-(1.9) is analytically challenging, we begin with a simplified model in order to illustrate the  
 221 method of analysis and the main results. Then we apply this method to the complete model.

### 3 Simplified model

In this section, we derive a simplified model in order to study the dynamics of the solution. We assume that the concentration of  $A\beta$ -monomers  $A$  is sufficiently small and neglect then the term  $A^2$  with respect to  $A$  in equation (2.1). Then  $A = a_1 C_1$ , where  $a_1 = k_1 N / \sigma_1$ . From equation (2.4) we conclude that for when concentrations of M2 type microglia  $M_2$  is small, it is considered proportional to  $u$  (concentration of oligomers):  $M_2 = a_4 u$ , where  $a_4 = k_6 M_2^0 / \sigma_5$ . Hence, equation (2.2) is rewritten as:

$$k_2 A^2 - \sigma_2 b a_4 u^2 - \sigma_2 u = 0, \quad (3.1)$$

Neglecting the term  $u^2$  compared to the term  $u$  in equation (3.1), we get  $u = a_2 A^2$ , where  $a_2 = k_2 / \sigma_2$ . Next, from equation (2.3) we write:  $M_1 = a_3$ , where  $a_3 = k_3 M_1^0 / \sigma_3$ , and from equation (2.6),  $C_2 = a_5 M_2$ , where  $a_5 = k_7 / \sigma_6$ . Substituting these expressions into equation (2.5), we obtain the following equation with respect to  $C_1$ :

$$\frac{C_1^2}{(1 + \alpha C_1^2)} = \gamma C_1, \quad (3.2)$$

where

$$\alpha = a_1^2 a_2 a_4 a_5 k_5, \quad \gamma = \frac{\sigma_4}{a_1^2 a_2 a_3 k_4}.$$

Equation (3.2) has solution  $C_1 = 0$  and, depending on parameters, up to two positive solutions denoted by  $C_1^{(1)}$  and  $C_1^{(2)}$ ,  $C_1^{(1)} < C_1^{(2)}$ .

- If  $\Delta = 1 - 4\alpha\gamma^2 < 0$ , there exists only one stationary solution  $C_1 = 0$ .
- If  $\Delta = 1 - 4\alpha\gamma^2 > 0$ , there exist three stationary solutions  $C_1 = 0$ ,  $C_1^{(1)} = \frac{1 - \sqrt{\Delta}}{2\alpha\gamma}$  and  $C_1^{(2)} = \frac{1 + \sqrt{\Delta}}{2\alpha\gamma}$ .

Thus, under the simplifying assumptions formulated above (small concentrations), system (1.16)-(1.21) has a zero stationary point  $P_0$  and up to two positive stationary points  $P_1$  and  $P_2$ . In terms of stability analysis,  $P_0$  and  $P_2$  are stable whereas  $P_1$  is unstable.

#### 3.1 Formulation of the model problem

Let us consider the time-dependent simplified equation obtained from system (1.16)-(1.21) similar to (3.2) under the quasi-stationary approximation for all variables except for  $C_1$ :

$$\frac{dC_1}{dt} = \frac{C_1^2}{(1 + \alpha C_1^2)(1 + aD(t))} - \gamma C_1. \quad (3.3)$$

Here we take into account down-regulation of the rate of inflammatory cytokine production by NSAID with time-dependent concentration  $D(t)$  described by the equation  $D(t) = D_0 e^{-kt}$ , where  $D_0$  is the initial drug concentration. For  $D = 0$ , stationary solutions of equation (3.3) are provided by equation (3.2).

By linearizing equation (3.3) about the intermediate stationary point, we obtain a linear equation with time-dependent coefficients. This time dependence changes the position of the intermediate point in such a way that its value increases for larger  $D$ . We preserve this property in the model problem

$$\frac{du}{dt} = a(u - u_1(t)) - bu, \quad (3.4)$$

243 where  $u_1(t) = (1 + D(t))u_0$ ,  $u(0) = u_*$ . This linear equation has a similar behavior in the vicinity of the  
 244 intermediate zero of the right-hand side as equation (3.3). We consider this simplified model to determine  
 245 the properties of the analytical solution.

246 In order to solve equation (3.4), we write it in the form

$$\frac{du}{dt} = (a - b)u - au_0 - au_0D_0e^{-kt}, \quad (3.5)$$

247 and set  $\alpha = a - b$ ,  $\beta = au_0D_0$ ,  $v = u - au_0/(a - b)$ . We assume here that  $a \neq b$ . Then

$$\frac{dv}{dt} = \alpha v - \beta e^{-kt}, \quad v(0) = u_* - au_0/(a - b). \quad (3.6)$$

248 We find

$$v(t) = c_1 e^{\alpha t} + \frac{\beta}{\alpha + k} e^{-kt},$$

249 where  $c_1$  is determined from the initial condition:

$$c_1 = u_* - \frac{au_0}{a - b} - \frac{\beta}{\alpha + k}.$$

250 Hence

$$u(t) = v(t) + \frac{au_0}{a - b} = \left( u_* - \frac{au_0}{a - b} - \frac{\beta}{\alpha + k} \right) e^{\alpha t} + \frac{\beta}{\alpha + k} e^{-kt} + \frac{au_0}{a - b},$$

251 or

$$u(t) = (u_* - p - q) e^{\alpha t} + q e^{-kt} + p,$$

252 where

$$p = \frac{au_0}{a - b}, \quad q = \frac{\beta}{\alpha + k} = \frac{au_0D_0}{a - b + k}.$$

253 **Properties of solutions.** Behavior of solution depends on the values of parameters. There are the  
 254 following cases:

- 255 • If  $u_* < \frac{au_0}{a - b}$ , inflammation decays even without treatment.
- 256 • If  $\frac{au_0}{a - b} < u_* < \frac{au_0}{a - b} + \frac{\beta}{\alpha + k}$ , inflammation decays after the first drug administration.
- If

$$u_* > \frac{au_0}{a - b} + \frac{\beta}{\alpha + k}, \quad (3.7)$$

257 and  $\alpha \left( u_* - \frac{au_0}{a - b} - \frac{\beta}{\alpha + k} \right) > \frac{\beta k}{\alpha + k}$ , inflammation grows after the single drug administration.

258 Therefore, it also grows for any further administrations with the same  $D_0$  since the initial condition  
 259 is larger than the first time.

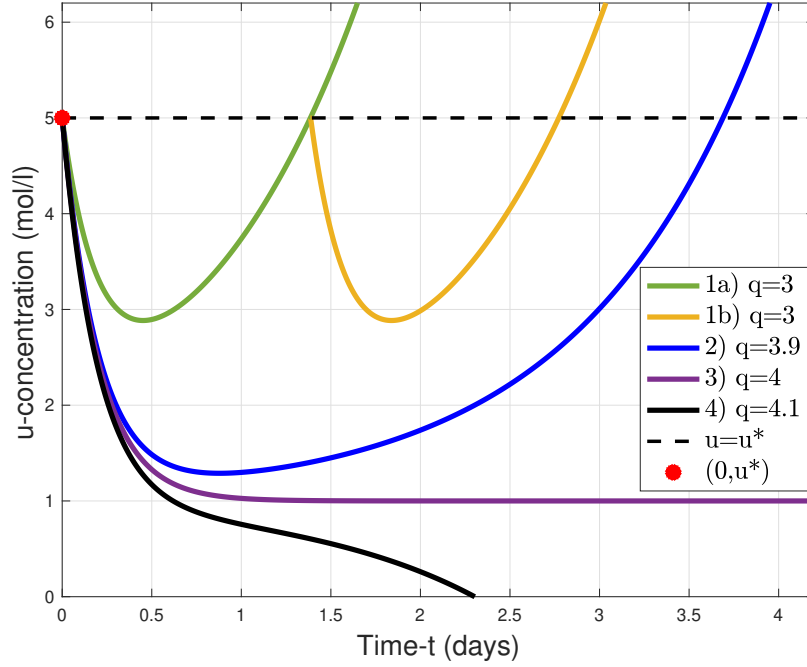


Figure 3: Solutions of equation (3.4) with initial condition  $u(0) = u_*$  and single drug administration. The values of parameters:  $u_* = 5, p = 1, \alpha = 1, k = 5, q = 3$  (curve **1a**),  $q = 3.9$  (curve **2**),  $q = 4$  (curve **3**),  $q = 4.1$  (curve **4**). The curve (curve **1b**) corresponds to the solution with the same values of parameters as (curve **1a**) but shifted in time.

- If (3.7) is satisfied and  $\alpha \left( u_* - \frac{au_0}{a-b} - \frac{\beta}{\alpha+k} \right) < \frac{\beta k}{\alpha+k}$ , then  $u(t)$  first decreases, then grows.

Figure 3 shows the behavior of solution depending on the value of parameter  $q$  (proportional to  $D_0$ ) for all other parameters fixed. If  $D_0$  is sufficiently small, then solution is exponentially growing (not shown). For larger values, the solution first decays, then grows. Finally, if  $D_0$  is large enough, the solution decreases. It becomes negative because we replaced the nonlinear problem by its linear approximation. This approximation is appropriate for the values of solution close to the unstable stationary point. Let us note that for a unique value of  $q$ , solution converges to this unstable stationary solution (curve 3). Thus, even a single administration of drug can inverse dynamics of inflammation.

For some intermediate values of  $D_0$ , solution decreases after drug administration and begins to grow after some time. In this case, consecutive drug administrations should be applied. We discuss the optimal administration regimen below.

### 3.2 Optimal drug regimen

We suppose that there are two limitations on drug administration [41, 42]: (a) single drug dose should not exceed some maximal value  $D_m$ , (b) total drug dose during some time period  $T$  should not exceed the maximal value  $D_T$ .

275 Different treatment regimens can be used. For example, we apply the maximal single dose  $D_m$  every  
 276 time interval  $\tau$ , or half of this dose  $D_m/2$  twice more often. Which of them is theoretically better from the  
 277 point of view of minimization of solution? We answer this question in the following setting. Consider some  
 278 given initial condition  $u(0) = u_*$ . Our aim is to keep the value of solution below this value  $u_*$ , that is,  
 279 prevent inflammation growth. Hence, at the first step of the analysis, we determine the optimal strategy  
 280 to keep  $u(t) \leq u_*$  depending on the value of single dose administration without taking into account the  
 281 total amount  $D_T$ .

282 Consider a single drug administration (Figure 3, curves 1a and 2) and denote by  $\tau$  the value of time  
 283 for which  $u(\tau) = u_*$ . We call this value  $\tau$  the return time. We aim to maximize the return time with  
 284 the same (or smaller) drug dose. Let us begin with the following example: for  $q = 3$ , we have  $\tau \approx 1.4$ ,  
 285 and for  $q = 3.9$ ,  $\tau \approx 3.7$ . Hence, increasing drug dose in  $3.9/3 = 1.3$  folds, we increase the time period in  
 286  $3.7/1.4 \approx 2.6$  folds. Therefore, time increase is larger than the dose increase, and it is more efficient to use  
 287 the maximum tolerated single dose  $D_m$ .

288 Figure 3 shows the solution for the second drug administration for  $q = 3$  at the moment of time  
 289 when the solution returns to the value  $u_*$  at time  $t = 1.4$ . We see that in this example two consecutive  
 290 applications of drug dose with  $q = 3$  is less efficient than a single drug administration with  $q = 3.9$ , in the  
 291 sense that return time is larger. As before, we conclude that the optimal strategy is to use the maximal  
 292 tolerated single dose  $D_m$ .

293 From the equality  $u(\tau) = u_*$  we obtain

$$q = (u_* - p) \frac{1 - e^{-\alpha\tau}}{1 - e^{-(\alpha+k)\tau}} \equiv F(\tau).$$

294 If  $\tau$  is increased  $s$  times, we can verify that the corresponding increase of  $q$  is less than  $s$  times, that is,

$$F(s\tau) < sF(\tau), \quad s > 1. \tag{3.8}$$

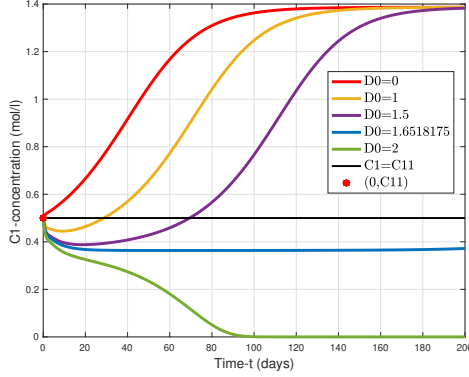
295 This means that the increase of a single dose leads to a larger increase of the time interval when the  
 296 solution returns to the initial value. Therefore, the maximum tolerated single dose provides optimal  
 297 treatment from the point of view of maximization of return time. Inequality (3.8) is verified numerically  
 298 in a large parameter range.

## 299 4 Anti-inflammatory drugs treatment in the complete model

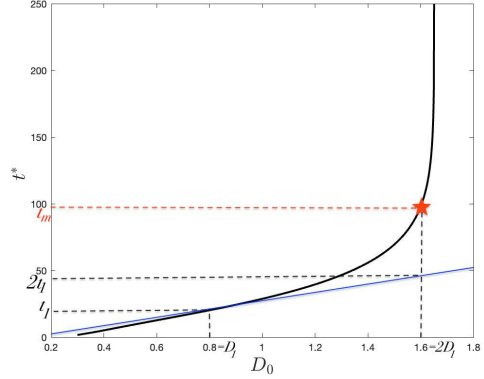
300 In this section, we study numerically the complete system of equations (1.16)-(1.21) and we seek to  
 301 determine optimal regimen using the method presented in Section 3. In numerical simulations, we find  
 302 the return time as a function of drug dose. Analysis of this function allows us to figure out the regimen  
 303 maximizing the return time. Values of parameters are taken from Table 2 (Appendix).

### 304 4.1 Beginning of inflammation

305 We consider the initial condition near the unstable equilibrium point  $E_u$ , as presented in Table 1. This  
 306 case characterizes the beginning of inflammation. We retrieve similar solution behavior as presented in  
 307 Section 3.2. However, the solution converges to equilibrium points  $E_0$  and  $E_s$  for larger times, instead  
 308 of divergence to  $\pm\infty$ . The numerical time step is considered  $\Delta t = 10^{-4}$  and final time of simulations is  
 309  $T = 200$ .



(4a) Solutions of equation (1.16)-(1.21) with initial condition  $C_1(0) = C_0 = 0.5$  (black curve) and single drug administration. The values of the parameter  $D_0$ :  $D_0 = 0$  (red curve),  $D_0 = 1$  (yellow curve),  $D_0 = 1.5$  (magenta curve),  $D_0 = 1.6518175$  (blue curve),  $D_0 = 2$  (green curve).



(4b) The return time function  $F$  determines the dependence of the return time  $t^*$  on the parameter  $D_0$ . Denote by  $t_1$  and  $t_m$  the return time for the single dose  $D_0 = D_1$  and  $D_0 = 2D_1$ , respectively. Applying two consecutive times the initial dose  $D_0 = D_1$ , leads to a return time  $2t_1 < t_m$ .

310 Figure 4a shows the behavior of solution depending on the value of  $D_0$  for all other parameters fixed.  
 311 If  $D_0$  is sufficiently small, then solution is exponentially growing (red curve). For intermediate values, the  
 312 solution first decays, then grows (yellow and magenta curves). Finally, if  $D_0$  is large enough, the solution  
 313 decreases (green curve). It decays to the  $C_1 = 0$  stationary solution. Let us note that for a unique value  
 314 of  $D_0$ , solution converges to this unstable stationary solution (blue curve). The value of such threshold  
 315 value is obtained via the bracketing method. Thus, even a single administration of drug can inverse  
 316 dynamics of inflammation. We retrieve a similar solution properties for the remaining concentrations,  
 317 namely  $U, A, M_1, M_2$  and  $C_2$ .

318 **Return time.** We fix the initial condition  $C_1(0) = 0.5$ , as an example, and for the value of  $D_0 < 1.66$ ,  
 319 the solution first decays due to the effect of the initial dose as shown in Figure 4a (magenta and yellow  
 320 curves), then grows and reaches after some time the value of the initial concentration  $C_1(0)$ . We denote  
 321 by  $t^*$  this specific time. We study, through numerical simulations, the dependence of the return time  $t^*$   
 322 on the value of  $D_0$ .

Figure 4b shows that the dependence between the time needed to reach the initial value condition  
 $C_0 = 0.5$  and the value of  $D_0$  is not linear. For values of  $D_0 > 1.66$ , the solution decays to the zero  
 equilibrium point, hence there is no return time to the initial condition. We have shown for the simplified  
 model that for large enough values of  $D_0$ , even a single administration of drug can inverse dynamics of  
 inflammation. A similar case is seen in this case for value of  $D_0 > 1.66$ . However, for doses  $D_0 < 1.66$ ,  
 inflammation decays then grows until reaching the initial condition at time  $t^* > 0$  (this case is seen in  
 Figure 4a for  $D_0 = 1$ ). We notice in Figure 4b that for any value of  $D$ , the return time function  $F(D)$   
 satisfies the following condition:

$$F'(D) \geq \frac{F(D)}{D}. \quad (4.1)$$

323 Condition (4.1) means that any straight line from the origin intersect the curve  $F(D)$  only in one point.  
 324 We show in Section 4.3 that the optimal dose in this case is the maximum tolerated dose.

## 4.2 Advanced inflammation

Advanced inflammation is considered here as solution essentially larger than the intermediate stationary point. It eventually approaches the stable equilibrium point  $E_s$ . Suppose that the initial condition is close to this point, as presented in Table 1. This starting point corresponds to an advanced inflammatory stage. We retrieve a similar solution behavior as presented in Section 4.1.

The solution depends on the value of  $D_0$  for all other parameters fixed. If  $D_0$  is sufficiently small, then solution is exponentially growing. For intermediate values, the solution first decays, then grows. Finally, if  $D_0$  is large enough, the solution decreases. It decays to the  $C_1 = 0$  stationary solution. Let us note that for a unique value of  $D_0$ , solution converges to this unstable stationary solution. Figure 5a shows the return time function. We note that this function has a concave shape for small  $D_0$  and convex shape for large  $D_0$ . Condition (4.1) is not satisfied in this case.

## 4.3 Optimal drug regimens

In this section, we study the optimal dose by comparing between the two scenarios of initial conditions. A treatment by NSAID should have appropriate dosage and duration [41, 42]. Therefore, we suppose two limitations on drug administration:

- A. A single drug dose should not exceed some maximal value denoted by  $D_m$ ,
- B. The total drug dose during some time period  $T$  should not exceed the maximal value  $D_T$ .

We aim to maximize the return time of the solution to the initial concentration. Let the return time for some dose  $D_1$  be  $t_1$ . Then applying consecutively the same dose we obtain the total return time  $2t_1$ . However, applying single dose  $2D_1$ , we obtain return time  $t_m > 2t_1$  (Figure 4b). For illustration, we let  $D_m = 1$ ,  $T = 100$  days and  $D_T = 4$ . Then a single dose  $D_0 = D_m = 1$ , does not inverse the dynamics of the solution (Figure 4a) leading to the problem of maximizing the return time  $t^*$ . We consider two different initial doses  $D_0 = D_m = 1$  and  $D_1 = D_m/2 = 0.5$  with their respective return time  $t_m = 28$  days and  $t_1 = 9$  days. If we apply two consecutive time the same dose  $D_1$ , the maximal return time is  $2t_1 = 18$  days which is less compared to  $t_m = 28$  days. Hence, in order to maximize the return time  $t^*$ , we should use the maximal tolerated dose  $D_m$ .

For the advanced stage, we denote by  $D_m$  the maximum tolerated dose and by  $D_1$  the dose chosen as pictured in Figure 5a and it satisfies the following condition:

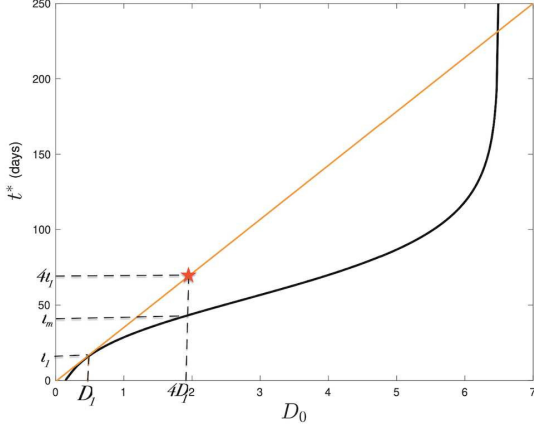
$$F'(D) = \frac{F(D)}{D}. \quad (4.2)$$

We note here that applying consecutive time ( $k$  times) the dose  $D_1$  has a return time larger than for the maximal tolerated dose,  $kt_1 > t_m$ , as shown for in Figure 5a.

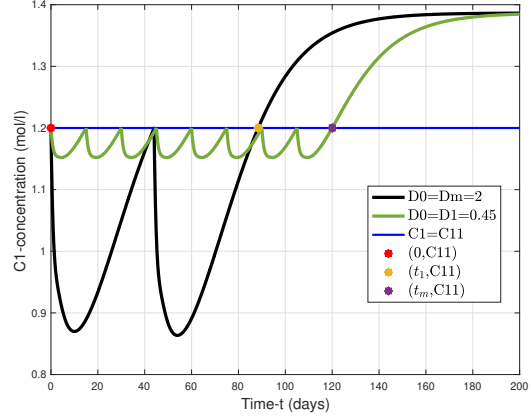
For illustration, we consider two different values of the administrated drug concentration, the maximum tolerated dose  $D_m = 2$  and the value  $D_1 = 0.45$ . For the initial dose  $D_m = 2$ , the return time is  $t^* = 43$  days, whereas for  $D_1 = 0.45$ , the return time is  $t_1^* = 15$  days.

Under the constraint imposed by condition B, suppose that the total drug dose for a period of 100 days is  $D_T = 4$ . Hence, for  $D_m = 2$ , we apply this dose a second time after 43 days, leading to the maximal return time to be 86 days. In opposition, we apply the same dose  $D_1 = 0.45$  in total for eight times with 15 days between two doses and the maximal return time is 120 days. Both cases of consecutive doses are pictured in Figure 5b. We notice that, the optimal dose in this case is not the maximal dose as in case 1, but the dose  $D_1$ . The dose  $D_1$  is the value chosen to satisfy condition (4.2). We deduce that for

362 an advanced stage of the disease, the optimal dose is not the maximum tolerated dose as for the previous  
 363 case.



(5a) The function  $F(D)$  showing the cross time  $t^*$  dependence on the parameter  $D_0$  (black curve). The tangent line to the curve  $F(D)$  at the point  $(D_1, F(D_1))$  (orange curve). Denote by  $t_1$  and  $t_m$  the return time for the single dose  $D_0 = D_1$  and  $D_0 = 4D_1$ , respectively. Applying four consecutive times the initial dose  $D_0 = D_1$ , leads to a return time  $4t_1 > t_m$ .



(5b) The solution behavior for the application of consecutive doses of two different small doses:  $D_0 = D_1 = 0.45$  (green curve) and  $D_0 = D_m = 2$  (black curve). The maximal return time, under condition A and B, are highlighted in dots (purple and yellow, respectively). Consecutive doses of small doses increases the maximal return time.

**Consecutive doses.** We have shown above how to choose the optimal single dose on the basis of the return time function. This can be the maximum tolerated dose at the initial stage of the disease or a different dose for an advanced stage. At the second stage of this analysis we evaluate the result of treatment taking into account the total admissible dose  $D_T$ . Let  $t^*$  be the return time for the optimal dose  $D^*$ . Applying this dose  $T/t^*$  times, we obtain the total dose  $D^*T/t^*$ . If

$$D^*T/t^* < D_T, \quad (4.3)$$

364 that is, the total applied dose is less than the total admissible dose, then we decrease the time interval between  
 365 drug administrations to some  $t^{**} < t^*$  such that  $D^*T/t^{**} = D_T$ . After the first drug administration,  
 366 the concentration of inflammatory cytokines  $C_1(t^{**})$  is less than the initial concentration  $C_1(0) = C_1(t^*)$ .  
 367 Similarly, after each next drug administration the concentration decreases in comparison with the previous  
 368 administration. Thus, in this treatment protocol inflammation gradually decreases.

369 At the end of treatment, after  $T/t^{**}$  drug administrations, solution of problem (1.16)-(1.21) returns to  
 370 the basin of attraction of the inflammation-free stationary point. In this case, treatment can be stopped,  
 371 and inflammation will gradually disappear. If the solution remains in the basin of attraction of the  
 372 endemic stationary point, then without treatment inflammation will restart. If inequality (4.3) is opposite,  
 373 then the time interval between administrations should be increased to some  $t^\#$  such that  $D^mT/t^\# = D_T$ .  
 374 In this case, after the first drug administration the concentration of inflammatory cytokines will exceed  
 375 the initial concentration,  $C_1(t^\#) > C_1(t^*) = C_1(0)$ . After each next administration, the concentration  
 376 will be larger compared to the previous administration, and the concentration will grow. In this case,  
 377 treatment cannot eliminate inflammation but it slows it down. After the end of treatment, inflammation  
 378 will accelerate.

379 For illustration, we consider the advanced inflammation stage with  $D_m = 1$  and  $T = 100$  days. We  
 380 consider that each administered dose is the maximum tolerated dose ( $D_0 = D_m = 1$ ). Figure 6 shows five  
 381 different cases for the value of  $D_T$ . The case  $D_T = 1$  means that only a maximal dose of  $D_0 = 1$  can be  
 382 administered in 100 days. We note that the solution decays then grows, reaches the initial condition value  
 383 for  $t^* = 28$  days and converges to the stable point  $E_s$ . For  $D_T = 4$ , we apply four times the single dose  
 384  $D_0 = 1$  with a time interval of 28 days between the two doses and the final return time is  $t^* = 112$  days.  
 385 For larger values of  $D_T$ , we increase the frequency of doses so that the time between two administration is  
 386 less than the return time. Figure 6 shows that for  $D_T = 14$ , we apply 14 consecutive doses (each dose  
 387 of  $D_0 = 1$ ) with an interval of 7 days between two consecutive ones. Under such dose administration,  
 388 the solution decays, overcomes the threshold (concentration of the unstable equilibrium point  $E_u$ ) and  
 389 converges to the zero-equilibrium point  $E_0$ . Hence, increasing the frequency of doses can lead to stop the  
 390 development of the disease.

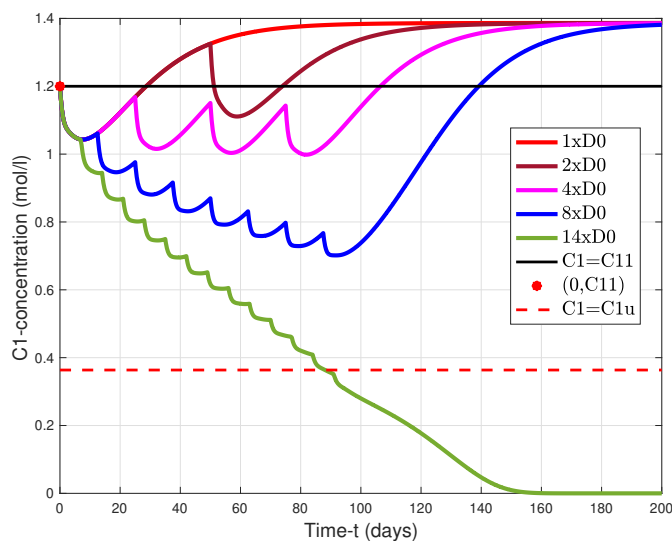
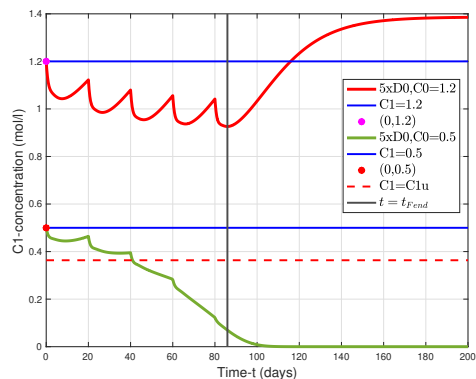


Figure 6: Solutions of equation (1.16)-(1.21) with initial condition  $C_1(0) = C_0 = 1.2$  (black curve) and consecutive drug administration for  $D_T = 1$  (red curve),  $D_T = 2$  (burgundy curve),  $D_T = 4$  (magenta curve),  $D_T = 8$  (blue curve) and  $D_T = 14$  (green curve). The red dash line corresponds to the  $C_1$ -concentration of the unstable point  $E_u$ .

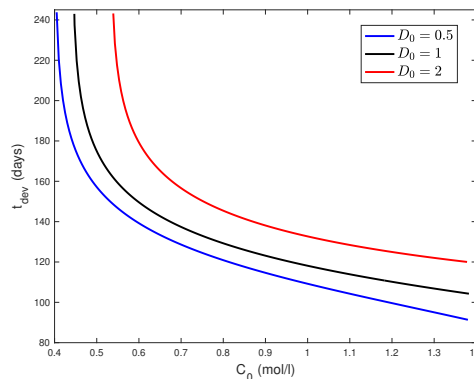
#### 391 4.4 Efficiency of anti-inflammatory drugs treatment

392 We discuss here why the NSAID treatment appears more efficient at early stages of the disease. We  
 393 consider the effect of initial conditions on the disease development after a treatment of consecutive doses.  
 394 Once the treatment is administered, the solution decays until reaching time  $t_{Fend}$ , indicating the end  
 395 of the treatment. After this stage, for  $t > t_{Fend}$ , the solution of problem (1.16)-(1.21) returns to the  
 396 basin of attraction of the inflammation-free stationary point. In this case, treatment can be stopped, and  
 397 inflammation will gradually disappear. If the solution remains in the basin of attraction of the endemic  
 398 stationary point, then without treatment inflammation restarts and grows until reaching the endemic  
 399 stable point  $E_s$ .

400 For illustration, we consider the administration of five consecutive doses of  $D_0 = 1$  with 20 days of gap  
 401 between two successive doses. Figure 7a shows that for small initial conditions, the treatment is sufficient  
 402 to decay the concentration of inflammatory cytokines to zero. In opposition, for large initial conditions,  
 403 the solution grows once the treatment ends and converges to the stable equilibrium point  $E_s$ . Thus, the  
 404 proposed treatment can inverse dynamics of inflammation at the early stage of the disease, but not in an  
 405 advanced inflammatory stage. We note that the solution for the early stage of the disease (green curve)  
 406 reaches the basin of attraction of the inflammation-free stationary point after the administration of the  
 third dose. Hence, the treatment could be stopped without the application of the last two doses.



(7a) Solutions of equation (1.16)-(1.21) with five consecutive doses (20 days between doses of  $D_0 = 1$ ) and initial conditions:  $C_0 = 0.5$  (green curve) and  $C_0 = 1.2$  (red curve). The red dash line corresponds to the  $C_1$ -concentration of the unstable point  $E_u$ . The vertical black line represents the time where the NSAIDs treatment ends.



(7b) The disease development time  $t_{dev}$  dependence on the initial condition  $C_0$  for three different values of a single dose administration:  $D_0 = 0.5$  (blue curve),  $D_0 = 1$  (black curve) and  $D_0 = 2$  (red curve). We consider values of  $C_0$  between the  $C_1$ -concentrations of the unstable point  $E_u$  and the stable point  $E_s$ .

407 We denote by  $t_{dev}$  the time needed for the solution to reach the vicinity of the point  $E_s$ . In other  
 408 words,  $t_{dev}$  represents the time needed for the development of the disease. We study the dependence  
 409 of the disease development time  $t_{dev}$  with respect to the initial condition of inflammatory cytokines  $C_0$ .  
 410 Figure 7b shows that for the same single dose administration  $D_0$ , the disease takes more time to develop  
 411 for larger initial conditions. Such case corresponds to advanced stages of the disease. In contrast, at early  
 412 stages of the disease, a single dose can delay its development for larger period of time. Therefore, NSAIDs  
 413 treatment is more efficient at early stages of the disease. Note that this has been observed in [25] which  
 414 reinforce this theoretical work.  
 415

## 416 5 Discussion

417 The main objective of this work is to model the effect of NSAIDs on the progression of the Alzheimer  
 418 disease. We develop a model describing the interaction of amyloid- $\beta$  production and inflammation, and  
 419 show that the NSAID treatment can delay the inflammation progression or even completely suppress  
 420 it. The result of treatment depends on many factors, such as patient-specific parameters of the model,  
 421 the stage of the disease advancement, the choice of optimal treatment regimen. The primary objective  
 422 of this work is to explore how different parameters influence the qualitative behavior of the system and  
 423 to identify potential mechanisms that need further experimental investigation. Although the modeling

424 approach is simplified, it offers a valuable perspective and can help to formulate hypotheses and guide  
425 future research. These modelling results can give some additional insight on the discrepancy between  
426 epidemiological and clinical studies on the effect of NSAID treatment in the Alzheimer disease [25, 30].

427 **Biological evidences.** This work validates several biological evidences of NSAID efficacy such as  
428 the dose-dependent behavior, the effect of treatment frequency, and the stage-dependent efficacy of  
429 the intervention. The simulations presented in Figures 4a, 6, and 7a capture major role of NSAID on  
430 the development of inflammation in AD. Figure 4a demonstrates the dose-dependent suppression of  
431 pro-inflammatory cytokines, consistent with the inhibitory effects of this type of drugs [43]. Figure 6  
432 highlights the importance of treatment frequency, showing that more frequent dosing drives the system  
433 toward an inflammation-free equilibrium, in line with cumulative pharmacological effects [44]. Figure 7a  
434 pinpoints stage-dependent efficacy, as NSAID treatment effectively reverses inflammation when applied at  
435 early stages but is largely ineffective at advanced stages [26]. Therefore, these results support clinical  
436 observations and highlight the role of both dose and timing in optimizing anti-inflammatory therapies.

437 **Return time and single dose choice.** The choice of the optimal treatment regimen is one of the  
438 main questions in the application of NSAID for all inflammatory diseases. We develop in this work a new  
439 approach to this question and illustrate it on the model of the Alzheimer disease, but it is also applicable  
440 for other diseases.

441 We define the optimal treatment as a regimen which minimizes the concentration of inflammatory  
442 cytokines after some given time interval  $T$  under the constraints that a single drug dose cannot exceed  
443 some maximum tolerated dose (MTD) and the cumulative drug dose during the time interval  $T$  is limited  
444 by the total admissible dose.

445 The approach suggested in this work is different in comparison with conventional optimal control  
446 problem. The determination of optimal treatment regimen developed here is based on the notion of return  
447 time defined as follows. After a single drug administration, the concentration of inflammatory cytokines  
448 can initially decrease, but later it grows again due to drug elimination from the organism. After some  
449 time it returns to its initial level observed before the drug administration. This time interval when the  
450 concentration of inflammatory cytokines returns to the initial level after a single drug administration is  
451 called return time.

452 The value of return time  $t_r$  depends on the parameters of the model, on the initial condition, and on  
453 the drug dose. For fixed values of parameters and initial conditions, return time can be considered as a  
454 function of the drug dose  $D$ , that is,  $t_r = F(D)$ . The properties of this functions determine the optimal  
455 treatment regimen.

456 Suppose, for instance, that the single drug dose is twice larger, that is  $2D$  instead of  $D$ . If the return  
457 time  $F(2D)$  in this case is twice or more larger than  $F(D)$ , then one single dose  $2D$  has advantage in  
458 comparison with two consecutive applications of the dose  $D$ .

459 Hence, we can compare the effect of treatment for different drug doses. There is a simple geometrical  
460 condition which allows us to determine the regimen which maximizes the return time. If any straight line  
461 from the origin, regardless of its slope, intersects the curve  $F(D)$  at a single point (Figure 4b), then a  
462 larger dose has advantage over a smaller dose (with the same total drug quantity) from the point of view  
463 of maximization of the return time. In the analytical form, this condition is given by (4.1). Thus, if this  
464 condition is satisfied, then drug should be administrated by MTD. If condition (4.1) is not satisfied, that  
465 is, if for some slopes the straight line intersects the curve  $F(D)$  at more than one point (Figure 5a), then  
466 the optimal value  $D$  changes. Indeed, the optimal single dose is provided by the value of  $D$  where the

467 straight line is tangent to the curve  $F(D)$  (Figure 5a). Moreover, the optimal dose  $D$  is the first point  
468 where  $F(D)$  satisfies the optimality condition (4.2).

469 **Optimal treatment.** Once we have determined the optimal single dose, which maximizes the return  
470 time, we are able to identify the optimal regimen during a given time interval  $T$ . Let  $t_r$  be the return  
471 time for the optimal single dose. Administration of this dose every  $t_r$  time interval keeps the level of  
472 inflammatory cytokines close to the initial value. It does not grow but does not decrease neither. A more  
473 frequent administration of the same dose decreases the concentration of inflammatory cytokines, while  
474 less frequent administration leads to its growth.

475 The frequency of drug administration is determined by the total admissible dose  $D_T$ . If total dose  
476  $DT/t_r$  with the return time frequency is less than  $D_T$ , then the frequency can be increased, if  $DT/t_r > D_T$ ,  
477 then it should be decreased. The maximal administration frequency is determined from the condition  
478 that the total dose administrated during time interval  $T$  equals the total admissible dose.

479 Thus, the most efficient treatment is provided by the optimal single dose and the maximal frequency  
480 of administration. Depending on patient-specific parameters of the model and on the initial condition  
481 (patients status at the beginning of treatment), the most efficient treatment can have three different  
482 outcomes:

- 483 • Treatment decreases the level of inflammatory cytokines. At the end of treatment, the concentrations  
484 of all involved factors belong to the basin of attraction of the inflammation-free equilibrium. After  
485 the end of treatment, inflammation gradually disappears.
- 486 • Treatment decreases the level of inflammatory cytokines. At the end of treatment, the concentrations  
487 of all involved factors belong to the basin of attraction of the inflammatory equilibrium. After the  
488 end of treatment, inflammation continues to amplify.
- 489 • Treatment can slow down inflammation progression but it cannot stop its growth.

490 **Other formulations of the optimization problem.** Solution of the optimization problem discussed  
491 above allows us to minimize the level of inflammatory cytokines at the end of some given time interval  
492 under the constraints of maximum tolerated dose and total admissible dose. Another possible formulation  
493 of the optimization problem consists in the minimization of total administrated dose for the inflammation  
494 suppression under the constraint of maximum tolerate dose. As previously, we consider the optimal single  
495 dose maximizing the return time. If the frequency of administration exceeds the return time frequency,  
496 then the level of inflammatory cytokines gradually decreases and eventually reaches the basin of attraction  
497 of the inflammation-free equilibrium. The total time of treatment and the administration frequency can  
498 be assessed in numerical modelling with patient-specific parameters and initial conditions.

499 **The role of disease stage.** The stage of the disease progression correlates in the model with the  
500 level of inflammatory cytokines at the moment of the beginning of treatment. Smaller initial condition  
501 corresponds to the early stage of the disease, while larger initial condition to a more advanced stage.  
502 Disease stage determines the optimal single dose and treatment outcome.

503 We show in this work that optimal single dose maximizing the return time is the MTD in the beginning  
504 of the disease progression when the initial condition is close to the unstable equilibrium separating the two  
505 stable ones, inflammation-free stationary point and inflammatory stationary point. In opposition, if the  
506 initial concentration of all agents key-player is larger, the MTD may not the optimal dose, as presented in  
507 Section 4.3.

508 Next, along with disease progression (concentration of inflammatory cytokines at the beginning of  
509 treatment becomes larger), the value of return time decreases. Therefore, more frequent drug administration  
510 is required to restrain inflammation progression. For a given total admissible dose, this means that  
511 treatment is more efficient in the beginning of the disease. Epidemiological studies support that (NSAIDs)  
512 can reduce the disease development if they are started well before clinical signs develop and that a  
513 daily dose can be helpful [45]. On the other hand, clinical studies show that NSAID are non-effective  
514 in advanced stages of the disease [46, 47]. Hence, this work offers a perspective by bridging the gap  
515 between epidemiological and clinical studies. These results support the idea that NSAIDs efficacy in AD  
516 is stage-dependent, with early intervention being more beneficial.

517 **Maximum tolerated dose in pharmacology.** In pharmacology, the maximum tolerated dose (MTD)  
518 refers to the highest dose of a drug or treatment that does not cause unacceptable side effects in patients.  
519 It represents the upper limit of drug administration where the therapeutic benefit can be achieved with  
520 manageable or minimal adverse effects.

521 MTD is established during preclinical studies (animal testing) and Phase 1 clinical trials in humans.  
522 Doses are gradually escalated to identify the highest level that can be tolerated without severe toxicity.  
523 Long-term studies may assess the potential for chronic toxicity at or below the MTD. MTD is essential  
524 for optimizing drug dosing regimens, minimizing risks, and ensuring patient safety during therapeutic  
525 interventions. For example, the standard clinical practice used for cancer patients is the MTD [48, 49]. This  
526 work provides the theoretical conditions under which the maximal dose is the optimal choice (condition  
527 (4.1)). The results obtained coincide with clinical strategies used in the treatment of other diseases, where  
528 the maximal dose is administrated.

529 Using MTD is largely discussed in the pharmacological literature (see the review in [50]) but its  
530 application is empirical and it is often contested. This work provides a theoretical framework for the  
531 assessment of the optimal dose, which can be MTD or different from it.

532 **Limitations and perspectives.** The model developed in this work is necessarily simplified. More  
533 detailed models taking into account pharmacokinetics of NSAIDs can provide efficacy assessment of  
534 specific anti-inflammatory drugs. Further important limitation of such studies is related the estimation of  
535 patient-specific parameters. Due to the lack of available biological data, particularly in the early phases  
536 of AD, it is challenging to approximate the model parameters. Although the choice of parameters is  
537 not patient based, we provided some quantitative conclusions that are independent of specific parameter  
538 values.

539 Medical evidence supports that the use of NSAID can cause additional health complications such as  
540 an increase of the blood pressure [51] or kidney damage [52]. Therefore, instead of maximum tolerated  
541 dose and total admissible dose it may be appropriate to consider dose-dependent side effects.

542 A possible extension of this work is to consider the penetration of drugs in the brain from blood, which  
543 can lead to several optimal control problems in order to optimize both the time and the amount of dose  
544 administered [53]. Another question concerns the effect of diet and food on the development of AD. Several  
545 types of diets have been considered as nonpharmacological risk modifying factors for AD [54]. Hence,  
546 incorporating the role of diet, having anti-inflammatory characteristics, appears as a promising therapeutic  
547 approach for future research. Studies have shown that some drugs known as glucagon-like peptide-1  
548 receptor agonists (GLP-1 RAs) used for type 2 diabetes patients significantly reduce neuroinflammation  
549 and the risk of Alzheimer's disease [55, 56].

## 550 **6 Conclusions**

551 In this work we determine the most efficient protocol of NSAID treatment which allows the minimization  
552 of the concentration of inflammatory cytokines at the end of treatment. It is based on the notion of return  
553 time, optimal single dose, and maximal admissible frequency of drug administration.

554 Though this most efficient protocol is patient-specific, we show that at the early stage of the disease  
555 progression it is provided by the maximum tolerated dose based on easily available data, such as patient  
556 weight, age, and some others.

557 Even the most efficient treatment protocol may not be successful from the point of view of inflammation  
558 suppression. Treatment outcome depends on the disease stage at the beginning of treatment and patient-  
559 specific parameters. These results give some additional insights on the discrepancy between epidemiological  
560 and clinical studies of the NSAID treatment in the Alzheimer disease.

561 Let us also note that the approach developed in this work is potentially applicable for the evaluation  
562 of optimal treatment regimen in other diseases.

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## 567 **Conflicts of interest statement**

568 This work does not have any conflicts of interest.

## 569 **Data Availability**

570 The manuscript has no associated data.

## 571 **Appendix**

572 In this section, we provide values of parameters and initial conditions employed in numerical simulations.  
573 We note that due to the lack of available biological data, particularly in the early phases of AD, it is  
574 challenging to approximate the model parameters. Although the choice of parameters is not patient based,  
575 we provided some quantitative conclusions that are independent of specific parameter values. The units  
576 were taken from previous modeling studies to keep the equations dimensionally consistent [37]. The aim  
577 of the arbitrary choice of parameters is to illustrate the analytical results obtained for both the simplified  
578 and complete versions of the model.

variable	definition	initial condition 1	initial condition 2
$C_1$	concentration of pro-inflammatory cytokines	$0.5 \text{ mol} \times \text{l}^{-1}$	$1.2 \text{ mol} \times \text{l}^{-1}$
$C_2$	concentration of anti-inflammatory cytokines	$0.048397 \text{ mol} \times \text{l}^{-1}$	$0.1326065 \text{ mol} \times \text{l}^{-1}$
$M_1$	concentration of M1 type macrophages	$0.11227 \text{ mol} \times \text{l}^{-1}$	$0.2658713 \text{ mol} \times \text{l}^{-1}$
$M_2$	concentration of M2 type macrophages	$0.0241986 \text{ mol} \times \text{l}^{-1}$	$0.066303 \text{ mol} \times \text{l}^{-1}$
$A$	concentration of $A\beta$ -monomers	$0.3064 \text{ mol} \times \text{l}^{-1}$	$0.5264593 \text{ mol} \times \text{l}^{-1}$
$u$	concentration of oligomers	$0.070263 \text{ mol} \times \text{l}^{-1}$	$0.2011995 \text{ mol} \times \text{l}^{-1}$

**Table 1:** Initial data for the concentration of all variables considered in numerical simulations. Concentration units are taken from [37].

variable	value	units	description
$k_1$	0.5	$1 \times \text{mol}^{-1} \times \text{day}^{-1}$	production rate of monomers by activated neurons
$k_2$	0.75	$1 \times \text{mol}^{-1} \times \text{day}^{-1}$	polymerization rate of monomers attaching to oligomers
$k_3$	0.9	$1 \times \text{mol}^{-1} \times \text{day}^{-1}$	growth coefficient of M1 microglial cells
$k_4$	4	$\text{day}^{-1}$	growth coefficient of C1 cytokines by M1 microglial cells
$k_5$	0.1	$1 \times \text{mol}^{-1}$	inhibition of rate in the production of C1 cytokines by C2 cytokines
$k_6$	0.3	$1 \times \text{mol}^{-1} \times \text{day}^{-1}$	growth coefficient of M2 microglial cells
$k_7$	1	$\text{day}^{-1}$	production rate of C2 cytokines by M2 microglial cells
$k$	0.15	$\text{day}^{-1}$	decay rate of the injection dose
$a$	0.2	$\text{ml} \times \text{mg}^{-1}$	growth coefficient of the dose
$D_0$	variable	$\text{mg} \times \text{ml}^{-1}$	dose injected of NSAID
$M_1^0$	1	$\text{mol} \times \text{l}^{-1}$	initial concentration of M1 microglial cells
$M_2^0$	1	$\text{mol} \times \text{l}^{-1}$	initial concentration of M2 microglial cells
$\sigma_1$	0.35	$\text{day}^{-1}$	degradation rate of monomers
$\sigma_2$	1	$\text{day}^{-1}$	degradation rate of oligomers
$\sigma_3$	0.5	$\text{day}^{-1}$	degradation rate of M1 microglial cells
$\sigma_4$	0.8	$\text{day}^{-1}$	degradation rate of pro-inflammatory cytokines
$\sigma_5$	0.8	$\text{day}^{-1}$	degradation rate of M2 microglial cells
$\sigma_6$	0.5	$\text{day}^{-1}$	degradation rate of anti-inflammatory cytokines
$N$	1	$\text{mol} \times \text{l}^{-1}$	initial concentration of neurons
$b$	0.5	$1 \times \text{mol}^{-1}$	elimination rate of oligomers by M2 microglial cells

**Table 2:** Parameter values for the numerical simulations. The numerical values of the parameters were chosen to reproduce the expected qualitative behavior of the system. Their units were adopted from [37] to ensure dimensional consistency.

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