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MATHEMATICAL ANALYSIS FOR A TIME-DELAYED ALZHEIMER DISEASE MODEL

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ABSTRACT. In this paper, we investigate a time-delayed model describing the evolution of Alzheimer disease (AD). A necessary and sufficient conditions for the existence of steady states are given. After that, we analyze the asymptotic behavior of the model, and study the local asymptotic stability of each equilibrium.

1. INTRODUCTION

Alzheimer disease (AD) is a neurodegenerative incurable disease of cerebral tissue that causes progressive and irreversible loss of mental functions such as memory. it's the most frequent cause of dementia in humans. (AD) was first described by German physiologist Alois Alzheimer in 1906.

Alzheimer disease (AD) is characterized by the presence of amyloide plaques. Amyloide plaques, or senile plaques are small dense depots of a protein beta-amyloide ($A\beta$) which is chemically adhesive and agglomerates progressively to form plaques.

Beta-amyloide comes from a bigger protein (called APP) present in the membrane surrounding healthy nervous cells.

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There are a multitude of articles that deals specifically with the modeling of the evolution of Alzheimer disease (AD), we can see [4] and some works of the L. Pujo-Menjouet group ([2], [6] and [7]).

Although factors that causes (AD) are still being investigated, recent studies such as [1] and [5] suggest that $A\beta$ oligomers (which are small aggregates of $A\beta$ monomers) after binding with healthy prions (PrPc) misfold these latter into a pathogenic form (PrPsc) that could be responsible for Alzheimer disease (AD).

In 2014, [6] proposed an in vivo model that takes into account for the first time prions in modeling the evolution of Alzheimer disease (AD). Their model consists of 4 species:

(1) $A\beta$ oligomers concentration,
(2) Prions PrPc concentration,
(3) Concentration of complexes obtained by the biding of an oligomer and a prion,
(4) The fourth equation describes the density of the insoluble plaque $A\beta$.

2. Description of the model

The model consisting of a system of three delayed differential equations is schematized in Figure 1. The first equation describes the temporal evolution of concentration of oligomers $A\beta$ denoted by the variable U.

In the second equation, concentration of healthy prions is denoted by P.

Finally, in the third equation the variable P_c represents the concentration of pathogenic prions.

We assume that there are fixed sources of oligomers and healthy prions denoted respectively S_u and S_p.

Both oligomers, healthy and pathogenic prions are eliminated with a constant rates called respectively d_u, d_p and d_{pc}.

Any prion can interact with $m \in \mathbb{N}^*$ oligomers to form a complex with a constant rate δ_1.

Only after a certain time τ, the complex can split into the original m oligomers and a pathogenic prion with a constant rate δ_2.

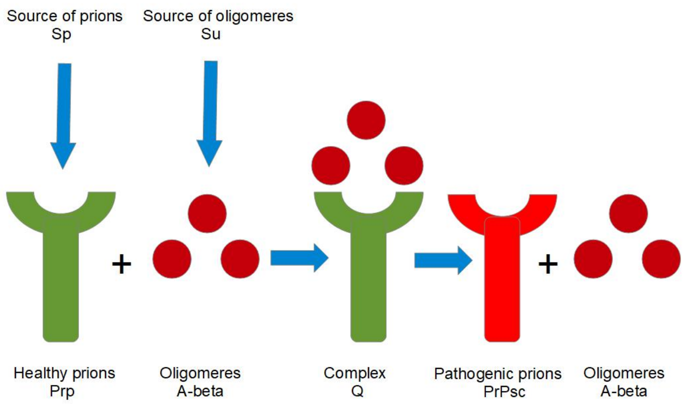


FIGURE 1. Schematic representation of the model described by the system (2.1)

Under those assumptions, for $t \geq 0$, we obtain the following system:

$$\left\{\begin{array}{lcl} \dot{U}(t) & = & S_u - d_u U(t) - \delta_1 m P(t) U^m(t) + m\delta_2 P(t-\tau) U^m(t-\tau) \\ \dot{P}(t) & = & S_p - d_p P(t) - \delta_1 P(t) U^m(t) \\ \dot{P}_c(t) & = & -d_{pc} P_c(t) + \delta_2 P(t-\tau) U^m(t-\tau). \end{array}\right. \tag{2.1}$$

For $t \in [-\tau, 0)$, the model is described with the same equations without delay, as prions and oligomers are not yet let out from the complex in the first τ units of time.

Table 1 summarize variables and parameters used in the system (2.1)

3. MAIN RESULTS

3.1. **Existence and non negativity of solutions.** The following results are useful to prove global existence and non negativity of solutions, which can be found in the literature (see [8]).

Consider the system of DDE:

$$\dot{x} = f(t, x(t), x(t-\tau)), \tag{3.1}$$

with a single delay $\tau > 0$.

TABLE 1. Parameter description of the model

Parameter and variable	Definition	Unit
U	Concentration of oligomers $A\beta$	-
P	Concentration of healthy prions	-
P_c	Concentration of pathogenic prions	-
S_u	Source of oligomers $A\beta$	Days $^{-1}$
S_p	Source of healthy prions	Days $^{-1}$
d_u	Elimination rate of oligomers $A\beta$	Days $^{-1}$
d_p	Elimination rate of healthy prions	Days $^{-1}$
d_{pc}	Elimination rate of pathogenic prions	Days $^{-1}$
δ_1	Binding rate between oligomers and healthy prions	Days $^{-1}$
δ_2	Unbinding rate between oligomers and pathogenic prions	Days $^{-1}$
t	Time	Days
m	Number of oligomers in the complex	$\mathbb{N}^*$

Let $s \in \mathbb{R}$ and $\phi : [s-r, s] \to \mathbb{R}^n$ be continuous.

We seek a solution $x(t)$ of (3.1) that satisfies:

$$x(t) = \phi(t), \ s - \tau \leq t \leq s \tag{3.2}$$

Theorem 3.1. *Let $f(t, x, y)$ and $f_x(t, x, y)$ be continuous on $\mathbb{R}^n$, $s \in \mathbb{R}$ and $\phi : [s-r, s] \to \mathbb{R}^n$ be continuous. Then there exists $\sigma > s$ and a unique solution of the initial value problem (3.1)-(3.2) on $[s-r, \sigma]$.*

Let $x \in \mathbb{R}^n$, we write $x \geq 0$ when $x_i \geq 0, \quad 1 \leq i \leq n$.

The same notation is used for $x \leq 0$.

Let $\mathbb{R}^n_+$ be the set of vectors $x \in \mathbb{R}^n$ such that $x \geq 0$.

Theorem 3.2. *Suppose that $f : \mathbb{R} \times \mathbb{R}^n_+ \times \mathbb{R}^n_+ \to \mathbb{R}^n$ satisfies the hypotheses of theorem 3.1 and*

$$\forall i, t \forall x, y \in \mathbb{R}^n_+ : x_i = 0 \Rightarrow f_i(t, x, y) \geq 0. \tag{3.3}$$

If the initial condition $\phi \geq 0$, then the corresponding solution $x(t)$ of equation (3.1) satisfies $x(t) \geq 0$ for all $t \geq s$ where it is defined.

Proposition 3.1. *System (2.1) has a unique solution on $[0, +\infty)$. Furthermore, if initial conditions are non negative, solution remains non negative.*

Proof. To prove existence and uniqueness of solution, we follow the reasoning developed in [7].

The method consists of proving existence and uniqueness of solutions with a method of steps.

We start by proving existence, uniqueness and non negativity on $[-\tau, 0)$, then on $[0, \tau)$, before we generalize those results on intervals $[n\tau, (n+1)\tau)$ for all $n \in \mathbb{N}$.

For $t \in [-\tau, 0)$, the system is given by

$$\begin{cases} \dot{\varphi}_u(t) &= S_u - d_u\varphi_u(t) - \delta_1 m \varphi_p(t)\varphi_u^m(t) \\ \dot{\varphi}_p(t) &= S_p - d_p\varphi_p(t) - \delta_1 \varphi_p(t)\varphi_u^m(t) \\ \dot{\varphi}_{pc}(t) &= -d_{pc}\varphi_{pc}(t). \end{cases} \tag{3.4}$$

Let $X(t) = (\varphi_u(t), \varphi_p(t), \varphi_{pc}(t))^T$.

Consider the following Cauchy problem

$$\begin{cases} \dot{X}(t) &= F(X(t)), \qquad t \in [-\tau, 0) \\ X(0) &= (U_0, P_0, P_0^c). \end{cases} \tag{3.5}$$

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

$$F(t, X) = \begin{pmatrix} S_u - d_u X_1 - \delta_1 m X_2 X_1^m \\ S_p - d_p X_2 - \delta_1 X_2 X_1^m \\ -d_{pc} X_3 \end{pmatrix} = \begin{pmatrix} F_1(t, X) \\ F_2(t, X) \\ F_3(t, X) \end{pmatrix}.$$

Since $F \in C^1(\mathbb{R}^3)$, then theorem of Cauchy-Lipschitz gives local existence and uniqueness for the solution of (3.5).

We can prove that solutions are bounded and non negative, then we have the global existence of positive solutions on $[-\tau, 0)$.

Define $X(0) = \lim_{t \to 0^-} X(t)$.

We shall study the system (2.1) on $[0, \tau]$.

Consider the following Cauchy problem

$$\begin{cases} \dot{Y}(t) &= G(Y(t), Y(t-\tau)), \qquad t \in [0, \tau) \\ Y(t) &= \tilde{X}(t), \qquad t \in [-\tau, 0], \end{cases} \tag{3.6}$$

where $Y(t) = (U(t), P(t), P_c(t))^T$, $\tilde{X}(t) = (\varphi_u(t), \varphi_p(t), \varphi_{pc}(t))^T$ and

$$G(Y,Z)=\begin{pmatrix} S_u-d_uY_1-\delta_1 mY_2Y_1^m+m\delta_2Z_2Z_1^m\\ S_p-d_pY_2-\delta_1Y_2Y_1^m\\ -d_{pc}Y_3+\delta_2Z_2Z_1^m\end{pmatrix}.$$

System (3.6) could be rewritten as

$$\text{(3.7)}\qquad \begin{cases} \dot{Y}(t) &= G(Y(t),\tilde{X}(t-\tau))=\tilde{G}(Y(t)), \qquad t\in[0,\tau)\\ Y(t) &= \tilde{X}(t), \qquad t\in[-\tau,0],\end{cases}$$

Since $\tilde{G}$ is C^1, Theorem of Cauchy-Lipschitz guarantees existence and uniqueness of the solution on $[0,\tau]$.

Polynomial function $\tilde{G}$ is bounded on $[0,\tau]$, then Theorem (3.2) conditions are satisfied, which implies that solutions are global on $[0,\tau]$.

Following the same reasoning on $[n\tau,(n+1)\tau), n\in\mathbb{N}^*$, we prove global existence, uniqueness and non-negativity of solutions of system (2.1) on $[-\tau,+\infty)$. □

In this section, we investigate existence and local stability of steady states of the system (2.1).

3.2. **Existence of steady states.** As the following result suggests, the number of steady states depends on the parameter δ_2.

When the unbinding rate is below a certain threshold δ^*, system (2.1) has a unique equilibrium, but when δ_2 exceeds that value δ^*, one can can have one two or three equilibria. Let

$$\begin{cases} G(U) &= \left(\frac{mS_p(\delta_2-\delta_1)}{(d_uU-S_u)}-\delta_1\right)U^m,\\ P_i^* &= \dfrac{S_p}{d_p+\delta_1U_i^{*m}},\\ P_{ci}^* &= \dfrac{\delta_2U_i^{*m}}{d_{pc}}\Big(\dfrac{S_p}{d_p+\delta_1U_i^{*m}}\Big),\\ U_0 &= \dfrac{S_u}{d_u},\\ U_1 &= U_0+\frac{(m-1)(\delta_2-\delta_1)S_p-\sqrt{\Delta_1}}{2\delta_1d_u},\\ U_2 &= U_0+\frac{(m-1)(\delta_2-\delta_1)S_p+\sqrt{\Delta_1}}{2\delta_1d_u},\\ U_3 &= U_0+\dfrac{mS_p(\delta_2-\delta_1)}{d_u\delta_1},\\ \Delta_1 &= (\delta_2-\delta_1)S_p\left[(m-1)^2S_p(\delta_2-\delta_1)-4S_u\delta_1\right].\end{cases}$$

Theorem 3.3. *Let* $\delta^* = \left(\frac{4S_u}{(m-1)^2S_p} + 1\right)\delta_1$, *then system (2.1) has the following assumption*

(1) *If* $\delta_2 \leq \delta_1$ *then system (2.1) has one nontrivial equilibrium* E_1 *with* $0 < U_1^* \leq U_0$.
(2) *If* $\delta_1 < \delta_2 < \delta^*$ *then system (2.1) has one nontrivial equilibrium* E_1 *with* $U_0 < U_1^* < U_3$.
(3) *If* $\delta_2 = \delta^*$ *and* $d_p < G(U_1)$ *then system (2.1) has one nontrivial equilibrium* E_1 *with* $U_1 < U_1^* < U_3$.
(4) *If* $\delta_2 = \delta^*$ *and* $d_p = G(U_1)$ *then system (2.1) has one nontrivial equilibrium* E_1 *with* $U_1^* = U_1$.
(5) *If* $\delta_2 = \delta^*$ *and* $d_p > G(U_1)$ *then system (2.1) has one nontrivial equilibrium* E_1 *with* $U_0 < U_1^* < U_1$.
(6) *If* $\delta_2 > \delta^*$ *and* $d_p < G(U_1)$ *then system (2.1) has one nontrivial equilibrium* E_3 *with* $U_2 < U_3^* < U_3$.
(7) *If* $\delta_2 > \delta^*$ *and* $d_p = G(U_1)$ *then system (2.1) has two nontrivial equilibria* E_1 *with* $U_1^* = U_1$ *and* E_3 *with* $U_2 < U_3^* < U_3$.
(8) *If* $\delta_2 > \delta^*$ *and* $G(U_1) < d_p < G(U_2)$ *then system (2.1) has three nontrivial equilibria* E_1 *with* $U_0 < U_1^* < U_1$, E_2 *with* $U_1 < U_2^* < U_2$ *and* E_3 *with* $U_2 < U_3^* < U_3$.
(9) *If* $\delta_2 > \delta^*$ *and* $d_p = G(U_2)$ *then system (2.1) has two nontrivial equilibria* E_3 *with* $U_3^* = U_2$ *and* E_1 *with* $U_0 < U_1^* < U_1$.
(10) *If* $\delta_2 > \delta^*$ *and* $d_p > G(U_2)$ *then system (2.1) has one nontrivial equilibrium* E_1 *with* $U_0 < U_1^* < U_1$.

Results are summarized in Table 2.

Proof. Let $E_i = (U_i^*, P_i^*, P_{ci}^*)$ be a steady state of system (2.1). Then, it satisfies

$$
\left\{\begin{array}{lcl} F(U^*) & = & 0, \\ P^* & = & \dfrac{S_p}{d_p + \delta_1 U^{*m}}, \\ P_c^* & = & \dfrac{\delta_2 U^{*m}}{d_{pc}}\Big(\dfrac{S_p}{d_p + \delta_1 U^{*m}}\Big), \end{array}\right. \tag{3.8}
$$

where $F(U) = \delta_1(d_u U - S_u)U^m - mS_p(\delta_2 - \delta_1)U^m + d_p(d_u U - S_u)$.

TABLE 2. Existence of equilibria depending on the parameter δ_2

<table>
<tr><th>δ_2</th><th>number of equilibria</th></tr>
<tr><td>$0 < \delta_2 \leq \delta_1$</td><td>one nontrivial equilibrium E_1</td></tr>
<tr><td>$\delta_1 < \delta_2 < \delta^*$</td><td>one nontrivial equilibrium E_1</td></tr>
<tr><td>$\delta_2 = \delta^*$</td><td>one nontrivial equilibrium E_1</td></tr>
<tr><td rowspan="5">$\delta_2 > \delta^*$</td><td>one nontrivial equilibrium E_3
if $d_p < G(U_1)$</td></tr>
<tr><td>two nontrivial equilibria E_1 and E_3
if $d_p = G(U_1)$</td></tr>
<tr><td>three nontrivial equilibria
E_1, E_2 and E_3
if $G(U_1) < d_p < G(U_2)$</td></tr>
<tr><td>two nontrivial equilibria E_1 and E_3
if $d_p = G(U_2)$</td></tr>
<tr><td>one nontrivial equilibrium E_1
if $d_p > G(U_2)$</td></tr>
</table>

We analyze the following cases

- If $\delta_2 = \delta_1$, then system (2.1) has a unique equilibria $E_1 = (U_1^*, P_1^*, P_{c1}^*)$ with $U_1^* = \dfrac{S_u}{d_u}$.
- If $\delta_2 \neq \delta_1$, then $F(U^*) = 0$ is equivalent to $G(U^*) = d_p$ with $G(U) = \left(\frac{mS_p(\delta_2-\delta_1)}{(d_uU-S_u)} - \delta_1\right) U^m$.

  From the study of function G on $[0, +\infty)$, we find that $G(U) = 0$ is equivalent to $U = 0$ or $U = U_3$.

  Moreover, we have

$$G'(U) = \frac{mU^{m-1}}{(d_uU - S_u)^2} T(U),$$

  where

$$T(U) = -\delta_1 d_u^2 U^2 + d_u[2S_u\delta_1 + (m-1)S_p(\delta_2 - \delta_1)]U - S_u[S_u\delta_1 + mS_p(\delta_2 - \delta_1)].$$

  To find the sign of G' we compute Δ the discriminant of second degree polynomial T.

  We have $\Delta = d_u^2 \Delta_1$ with

$$\Delta_1 = (\delta_2 - \delta_1)S_p \left[(m-1)^2 S_p(\delta_2 - \delta_1) - 4S_u\delta_1\right].$$

(1) If $\delta_2 < \delta_1$, then $\Delta_1 > 0$ and T has two different real roots U_1 and U_2.
We notice that $0 < U_0 < U_2$ and $G(U_2) < 0$.
- If $S_u\delta_1 + mS_p(\delta_2 - \delta_1) \leq 0$, then $U_3 \leq U_1 \leq 0 < U_0 < U_2$ and system (2.1) has one nontrivial equilibrium E_1 with $0 < U_1^* < U_0$.
- If $S_u\delta_1 + mS_p(\delta_2 - \delta_1) > 0$, then $0 < U_1 < U_3 < U_0 < U_2$ and system (2.1) has one nontrivial equilibrium E_1 with $U_3 < U_1^* < U_0$.

(2) If $\delta_1 < \delta_2 < \delta^*$, then $\Delta_1 < 0$, $0 < U_0 < U_3$ and system (2.1) has one nontrivial equilibrium E_1 with $U_0 < U_1^* < U_3$.

(3) If $\delta_2 = \delta^*$, then $0 < U_0 < U_1 = U_2 < U_3$, $\Delta_1 = 0$ and system (2.1) has one nontrivial equilibrium E_1 with $U_0 < U_1^* < U_3$.

(4) If $\delta_2 > \delta^*$, then $0 < U_0 < U_1 < U_2 < U_3$, $\Delta_1 > 0$ and system (2.1) has one, two or three nontrivial equilibria, in fact
   (a) If $d_p < G(U_1)$, then system (2.1) has one nontrivial equilibrium E_3 with $U_2 < U_3^* < U_3$.
   (b) If $d_p = G(U_1)$, then system (2.1) has two nontrivial equilibria E_1 with $U_1^* = U_1$ and E_3 with $U_2 < U_3^* < U_3$.
   (c) If $G(U_1) < d_p < G(U_2)$, then system (2.1) has three nontrivial equilibria E_1 with $U_0 < U_1^* < U_1$, E_2 with $U_1 < U_2^* < U_2$ and E_3 with $U_2 < U_3^* < U_3$.
   (d) If $d_p = G(U_2)$, then system (2.1) has two nontrivial equilibria E_3 with $U_3^* = U_2$ and E_1 with $U_0 < U_1^* < U_1$.
   (e) If $d_p > G(U_2)$, then system (2.1) has one nontrivial equilibrium E_1 with $U_0 < U_1^* < U_1$.

□

3.3. **Stability of steady states.** In this section, we investigate local stability of equilibrium points of system (2.1). The linearized system around equilibria is given by

$$\begin{bmatrix}\dot{U}(t)\\ \dot{P}(t)\end{bmatrix} = A\begin{bmatrix}U(t)\\ P(t)\end{bmatrix} + B\begin{bmatrix}U(t-r)\\ P(t-r)\end{bmatrix} \tag{3.9}$$

where A and B are

$$A = \begin{bmatrix}-d_u - \delta_1 m^2 P^* U^{*m-1} & -\delta_1 m U^{*m}\\ -\delta_1 m P^* U^{*m-1} & -d_p - \delta_1 U^{*m}\end{bmatrix}, \qquad B = \begin{bmatrix}m^2\delta_2 P^* U^{*m-1} & \delta_2 m U^{*m}\\ 0 & 0\end{bmatrix}.$$

The characteristic equation of the system (2.1) for the nontrivial equilibrium point $E_i = (U_i^*, P_i^*, P_{ci}^*)$ is

$$P(\lambda) = \lambda^2 + a_i\lambda + c_i - (b_i\lambda + d_i)e^{-\lambda\tau} = 0, \tag{3.10}$$

where

$$\begin{aligned} a_i &= d_u + d_p + \delta_1 m^2 P_i^* U_i^{*m-1} + \delta_1 U_i^{*m}, \\ c_i &= d_p d_u + \delta_1 m^2 d_p P_i^* U_i^{*m-1} + \delta_1 d_u U_i^{*m}, \\ b_i &= \delta_2 m^2 P_i^* U_i^{*m-1} \text{ and} \\ d_i &= \delta_2 m^2 d_p P_i^* U_i^{*m-1}. \end{aligned}$$

Let

$$\begin{aligned} C_1 &= \frac{2\delta_1 S_u + (m-1)(\delta_2 - \delta_1)S_p - \sqrt{\Delta_1}}{2\delta_1}, \\ C_2 &= \delta_1 C_2^m \left(\tfrac{(m+1)S_p(\delta_2-\delta_1)+\sqrt{\Delta_1}}{(m-1)(\delta_2-\delta_1)S_p-\sqrt{\Delta_1}}\right), \\ C_3 &= \sqrt[m+1]{\tfrac{C_2}{\delta_1 C_1^m}}[C_2 + \delta_1 C_1^m], \\ C_4 &= \frac{2\delta_1 S_u + (m-1)(\delta_2 - \delta_1)S_p + \sqrt{\Delta_1}}{2\delta_1}, \\ C_5 &= \delta_1 C_4^m \left(\tfrac{(m+1)S_p(\delta_2-\delta_1)-\sqrt{\Delta_1}}{(m-1)(\delta_2-\delta_1)S_p+\sqrt{\Delta_1}}\right) \text{ and} \\ C_6 &= \sqrt[m+1]{\tfrac{C_5}{\delta_1 C_4^m}}[C_5 + \delta_1 C_4^m]. \end{aligned}$$

Without delay, we have the following result.

Theorem 3.4. *Suppose $\tau = 0$, then we have*

(1) *If $0 < \delta_2 \le \delta_1$, then the unique equilibrium E_1 is asymptotically locally stable.*
(2) *If $\delta_1 < \delta_2 < \delta^*$, then the unique equilibrium E_1 is asymptotically locally stable for $d_p \ge d_u$.*
(3) *If $\delta_2 = \delta^*$ and $d_u \le d_p < G(U_1)$, then the unique equilibrium E_1 is asymptotically locally stable.*
(4) *If $\delta_2 = \delta^*$ and $d_p = G(U_1)$, then the unique equilibrium E_1 is unstable for $d_u > C_3$.*
(5) *If $\delta_2 = \delta^*$ and $d_p > Max(d_u, G(U_1))$, then the unique equilibrium E_1 is asymptotically locally stable.*
(6) *If $\delta_2 > \delta^*$ and $d_u \le d_p < G(U_1)$, then the unique equilibrium E_3 is asymptotically locally stable.*

(7) *If $\delta_2 > \delta^*$ and $d_p = G(U_1)$, then the equilibrium E_1 is unstable for $d_u > C_3$.*

(8) *If $\delta_2 > \delta^*$ and $d_u \le d_p = G(U_1)$, then the equilibrium E_3 is asymptotically locally stable.*

(9) *If $\delta_2 > \delta^*$ and $Max(d_u, G(U_1)) < d_p < G(U_2)$, then the equilibrium E_1 is asymptotically locally stable.*

(10) *If $\delta_2 > \delta^*$ and $G(U_1) < d_p < G(U_2)$, then the equilibrium E_2 is unstable.*

(11) *If $\delta_2 > \delta^*$ and $Max(d_u, G(U_1)) < d_p < G(U_2)$, then the equilibrium E_3 is asymptotically locally stable.*

(12) *If $\delta_2 > \delta^*$ and $d_u \le d_p = G(U_2)$, then the equilibrium E_1 is asymptotically locally stable.*

(13) *If $\delta_2 > \delta^*$ and $d_p = G(U_2)$, then the equilibrium E_3 is unstable for $d_u > C_6$.*

(14) *If $\delta_2 > \delta^*$ and $d_p > Max(d_u, G(U_2))$, then the unique equilibrium E_1 is asymptotically locally stable.*

Proof. When $\tau = 0$, the characteristic equation (3.10) becomes

$$\lambda^2 + (a_i - b_i)\lambda + c_i - d_i = 0. \tag{3.11}$$

We have

$$\begin{aligned}(c_i - d_i)U_i^* &= d_p d_u U_i^* + \delta_1 d_u U_i^{*m+1} - (\delta_2 - \delta_1)m^2 d_p P_i^* U_i^{*m} \\ &= \left\{(m+1)\delta_1 d_u U_i^{*m} - m\left[mS_p(\delta_2 - \delta_1) + S_u\delta_1\right]U_i^{*m-1} + d_p d_u\right\}U_i^* \\ &= U_i^* F'(U_i^*).\end{aligned}$$

In another hand, for $i \ne 2$ we have

$$\begin{aligned}(a_i - b_i)d_p U_i^* &= d_p(d_u + d_p)U_i^* + \delta_1 d_p U_i^{*m+1} - m^2 d_p(\delta_2 - \delta_1)P_i^* U_i^{*m} \\ &= \left\{(m+1)\delta_1 d_u U_i^{*m} - m\left[mS_p(\delta_2 - \delta_1) + S_u\delta_1\right]U_i^{*m-1}\right. \\ &\quad \left. + d_p d_u + \delta_1(d_p - d_u)U_i^{*m} + d_p^2\right\}U_i^* \\ &= \left\{F'(U_i^*) + \delta_1(d_p - d_u)U_i^{*m} + d_p^2\right\}U_i^*.\end{aligned}$$

Moreover, $F'(U^*) = -(d_u U^* - S_u)G'(U^*)$.

(1) If $\delta_2 \le \delta_1$, then $a_i - b_i > 0$ and $c_i - d_i > 0$. Therefore, the unique equilibrium E_1 is locally asymptotically stable for $\tau = 0$.

(2) If $\delta_1 < \delta_2 < \delta^*$ and $d_p \ge d_u$, then $a_i - b_i > 0$ and $c_i - d_i > 0$. Therefore, the unique equilibrium E_1 is locally asymptotically stable for $\tau = 0$.

(3) If $\delta_2 = \delta^*$ and $d_u \leq d_p < G(U_1)$, then $a_i - b_i > 0$ and $c_i - d_i > 0$. Therefore, the unique equilibrium E_1 is locally asymptotically stable for $\tau = 0$.

(4) If $\delta_2 = \delta^*$ and $d_p = G(U_1)$, then $c_i - d_i = 0$ and

$$(a_i - b_i)d_p = \frac{1}{d_u^{m-1}} \left(\frac{C_2[C_2 + \delta_1 C_1^m]}{d_u^{m+1}} - \delta_1 C_1^m \right).$$

Moreover, we have

(a) If $d_u < C_3$, then $a_i - b_i > 0$ and we have an undetermined case.

(b) If $d_u = C_3$, then $a_i - b_i = 0$ and we have an undetermined case.

(c) If $d_u > C_3$, then $a_i - b_i < 0$ and the equilibrium E_1 is unstable for $\tau = 0$.

(5) If $\delta_2 = \delta^*$ and $d_p > Max(d_u, G(U_1))$, then $a_i - b_i > 0$ and $c_i - d_i > 0$. Therefore, the unique equilibrium E_1 is locally asymptotically stable for $\tau = 0$.

(6) If $\delta_2 > \delta^*$ and and $d_u \leq d_p < G(U_1)$, then $a_i - b_i > 0$ and $c_i - d_i > 0$. Therefore, the unique equilibrium E_3 is locally asymptotically stable for $\tau = 0$.

(7) If $\delta_2 > \delta^*$, $d_p = G(U_1)$, then $U_1^* = U_1$, $c_i - d_i = 0$ and

$$(a_i - b_i)d_p = \frac{1}{d_u^{m-1}} \left(\frac{C_2[C_2 + \delta_1 C_1^m]}{d_u^{m+1}} - \delta_1 C_1^m \right).$$

Moreover, we have

(a) If $d_u < C_3$, then $a_i - b_i > 0$ and we have an undetermined case.

(b) If $d_u = C_3$, then $a_i - b_i = 0$ and we have an undetermined case.

(c) If $d_u > C_3$, then $a_i - b_i < 0$ and the equilibrium E_1 is unstable for $\tau = 0$.

(8) If $\delta_2 = \delta^*$ and $d_p > Max(d_u, G(U_1))$, then $a_i - b_i > 0$ and $c_i - d_i > 0$. Therefore, the unique equilibrium E_1 is locally asymptotically stable for $\tau = 0$.

(9) If $\delta_2 > \delta^*$ and $d_u \leq d_p < G(U_1)$, then $a_i - b_i > 0$ and $c_i - d_i > 0$. Therefore, the unique equilibrium E_3 is locally asymptotically stable for $\tau = 0$.

(10) If $\delta_2 > \delta^*$ and $du \leq d_p = G(U_1)$, then $a_i - b_i > 0$ and $c_i - d_i > 0$. Therefore, the equilibrium E_3 is locally asymptotically stable for $\tau = 0$.

(11) If $\delta_2 > \delta^*$ and $Max(d_u, G(U_1)) < d_p < G(U_2)$, then $a_i - b_i > 0$ and $c_i - d_i > 0$. Therefore, the equilibrium E_1 is locally asymptotically stable for $\tau = 0$.

(12) If $\delta_2 > \delta^*$ and $G(U_1) < d_p < G(U_2)$, then $c_i - d_i < 0$. Therefore, the equilibrium E_2 is unstable for $\tau = 0$.

(13) If $\delta_2 > \delta^*$ and $Max(d_u, G(U_1)) < d_p < G(U_2)$, then $a_i - b_i > 0$ and $c_i - d_i > 0$. Therefore, the equilibrium E_3 is locally asymptotically stable for $\tau = 0$.

(14) If $\delta_2 > \delta^*$ and $d_u \leq d_p = G(U_2)$, then $a_i - b_i > 0$ and $c_i - d_i > 0$. Therefore, the equilibrium E_1 is locally asymptotically stable for $\tau = 0$.

(15) If $\delta_2 > \delta^*$ and $d_p = G(U_2)$, then $U_3^* = U_2$, $c_i - d_i = 0$ and

$$(a_i - b_i)d_p = \frac{1}{d_u^{m-1}} \left(\frac{C_5[C_5 + \delta_1 C_4^m]}{d_u^{m+1}} - \delta_1 C_4^m \right).$$

Moreover, we have

(a) If $d_u < C_6$, then $a_i - b_i > 0$ and we have an undetermined case.

(b) If $d_u = C_6$, then $a_i - b_i = 0$ and we have an undetermined case.

(c) If $d_u > C_6$, then $a_i - b_i < 0$ and the equilibrium E_3 is unstable for $\tau = 0$.

(16) If $\delta_2 > \delta^*$ and $d_p > Max(d_u, G(U_2))$, then $a_i - b_i > 0$ and $c_i - d_i > 0$. Therefore, the equilibrium E_1 is locally asymptotically stable for $\tau = 0$.

□

When $\tau > 0$, we have the following results.

Theorem 3.5.

(1) *If $0 < \delta_2 < \delta_1$, then the unique equilibrium E_1 is locally asymptotically stable for all $\tau > 0$.*

(2) *If $\delta_2 = \delta^*$, $d_u \geq C_3$ and $d_p = G(U_1)$, the unique equilibrium E_1 is unstable for all $\tau > 0$.*

(3) *If $\delta_2 > \delta^*$, $d_u \geq C_3$ and $d_p = G(U_1)$, then the equilibrium E_1 is unstable for all $\tau > 0$.*

(4) *If $\delta_2 > \delta^*$ and $G(U_1) < d_p < G(U_2)$, then the equilibrium E_2 is unstable for all $\tau > 0$.*

(5) *If $\delta_2 > \delta^*$, $d_u \geq C_6$ and $d_p = G(U_2)$, then the equilibrium E_3 is unstable for all $\tau > 0$.*

Proof.

(1) If $0 < \delta_2 < \delta_1$, then the characteristic equation is given by

$$P(\lambda) = \lambda^2 + a_i\lambda + c_i - (b_i\lambda + d_i)e^{-\lambda\tau} = 0.$$

We look for purely imaginary roots $\lambda = iw$ with $w > 0$.

We must resolve equation (6.4) (see appendix 1).

In order to find w we need to resolve quadratic equation (6.5) (see appendix 1).

We have $c_i^2 - d_i^2 > 0$ and

$$\begin{aligned} a_i^2 - b_i^2 - 2c_i =& d_u^2 + 2d_u\delta_1 m^2 P^* U^{*m-1} + (\delta_1^2 - \delta_2^2)(m^2 P^* U^{*m-1})^2 \\ &+ 2\delta_1 U^{*m}(\delta_1 m^2 P^* U^{*m-1}) + d_p^2 + 2d_p\delta_1 U^{*m} + (\delta_1 U^{*m})^2 > 0. \end{aligned}$$

Then, equation (6.5) has only roots of negative real parts, which implies that equation (6.4) has no real roots.

Therefore, the unique equilibrium E_1 is locally asymptotically stable for all $\tau > 0$.

(2) If $\delta_2 = \delta^*$ and $d_p = G(U_1)$, then to find purely imaginary roots, we must resolve equation (6.4).

In order to find w we need to resolve quadratic equation (6.5).

We have $c_i^2 - d_i^2 = 0$ and $a_i^2 - b_i^2 - 2c_i < 0$ for $d_u \geq C_3$.

Then, equation (6.5) has two roots

$$w_-^2 = 0 \text{ and } w_+^2 = -(a_i^2 - b_i^2 - 2c_i) > 0.$$

Sign of the derivative is given by (6.10) (see appendix 2).

In this case, we obtain $sign\ Re\Big[\frac{d\lambda}{d\tau}\Big]^{-1}_{\lambda=iw} = sign[-(a_i^2 - b_i^2 - 2c_i)] > 0.$

Therefore, the equilibrium E_1 is unstable for all $\tau > 0$.

(3) If $\delta_2 > \delta^*$, $d_p = G(U_1)$. Then, to find purely imaginary roots, we must resolve equation (6.4).

In order to find w we need to resolve quadratic equation (6.5).

We have $c_i^2 - d_i^2 = 0$ and $a_i^2 - b_i^2 - 2c_i < 0$ for $d_u \geq C_3$.

Then, equation (6.5) has two roots

$$w_-^2 = 0 \text{ and } w_+^2 = -(a_i^2 - b_i^2 - 2c_i) > 0$$

In this case, we obtain $sign\ Re\Big[\frac{d\lambda}{d\tau}\Big]^{-1}_{\lambda=iw} = sign[-(a_i^2 - b_i^2 - 2c_i)] > 0.$

Therefore, the equilibrium E_1 is unstable for all $\tau > 0$

(4) If $\delta_2 > \delta^*$ and $G(U_1) < d_p < G(U_2)$, then to find purely imaginary roots, we must resolve equation (6.4).

In order to find w we need to resolve quadratic equation (6.5).

We have $c_i^2 - d_i^2 < 0$ and $\Delta = (a_i^2 - b_i^2 - 2c_i)^2 - 4c_i^2 - d_i^2 > 0$.

Then, equation (6.5) has one positive root $w_+^2 = \dfrac{-(a_i^2 - b_i^2 - 2c_i) + \sqrt{\Delta}}{2}$.

Therefore, equation (6.4) has one positive root $w_+ = \sqrt{\dfrac{-(a_i^2 - b_i^2 - 2c_i) + \sqrt{\Delta}}{2}}$.

In this case, we obtain $sign\ Re\Big[\dfrac{d\lambda}{d\tau}\Big]^{-1}_{\lambda=iw} = sign[\sqrt{\Delta}] > 0$.

Therefore, the equilibrium E_2 is unstable for all $\tau > 0$

(5) If $\delta_2 > \delta^*$ and $d_p = G(U_2)$, then to find purely imaginary roots, we must resolve equation (6.4).

In order to find w we need to resolve quadratic equation (6.5).

We have $c_i^2 - d_i^2 = 0$ and and $a_i^2 - b_i^2 - 2c_i < 0$ for $d_u \geq C_6$.

Then, equation (6.5) has two roots

$$w_-^2 = 0 \text{ and } w_+^2 = -(a_i^2 - b_i^2 - 2c_i) > 0.$$

In this case, we obtain $sign\ Re\Big[\dfrac{d\lambda}{d\tau}\Big]^{-1}_{\lambda=iw} = sign[-(a_i^2 - b_i^2 - 2c_i)] > 0$.

Therefore, the equilibrium E_3 is unstable for all $\tau > 0$.

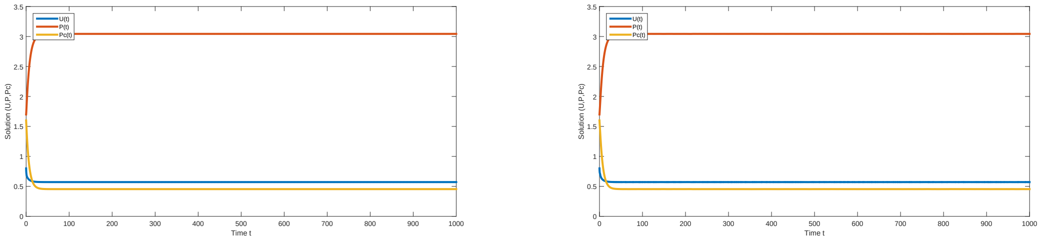
□

4. Numerical simulation

In this section, we give some numerical simulations for our model in order to illustrate our theoretical results (see subsection 4.1) and to see what happens in the non studied cases (see subsection 4.2). We discuss the simulation results of the system (2.1) according to the values of δ_2 and τ.

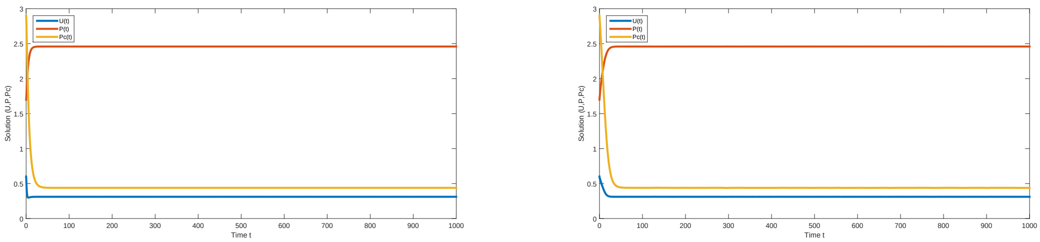
4.1. **Case** $\delta_2 \leq \delta^*$**.** Choosing $m = 3$, $d_u = 0.16$, $d_p = 0.13$, $d_q = 0.11$, $d_{pc} = 0.15$, $S_u = 0.5$ and $S_p = 0.6$, then the system will have a unique equilibrium E_1 which is locally asymptotically stable when $\tau = 0$ (see Figure 2).

4.2. **Case** $\delta_2 > \delta^*$ **and** $G(U_1) < d_p < G(U_2)$**.** Choosing $m = 3$,$\delta_1 = 0.36$, $d_{pc} = 0.15$, $S_u = 0.5$ and $S_p = 0.6$, then the system will have three equilibria: E_1, E_2 and E_3 (see Figures 3 and 5).



(A) Case $\tau = 0$ (B) Case $\tau = 1.4$

FIGURE 2. In this case, $\delta_2 = 0.12 < \delta_1 = 0.36$, the unique equilibrium E_1 is locally asymptotically stable for initial condition $(0.8, 1.7, 1.6)$.



(A) Case $\tau = 0$ (B) Case $\tau = 1.4$

FIGURE 3. In this case, $\delta_2 = 0.89 > \delta^* = 0.66$, $d_u = 1.98$ and $d_p = 0.23$, the equilibrium E_2 is unstable and it seems that E_1 is stable for initial condition $(0.6, 1.7, 2.9)$.

5. CONCLUSION

In this work, we have developed a new mathematical model for Alzheimer disease, this model consists of a system of three delayed differential equations, it describes the dynamics of oligomers and prions. We have studied the existence of equilibria and their stability according to parameters of our model. In theorem (3.5), we have found conditions of stability and instability of equilibria for some values of parameters δ_1, δ_2, d_u and d_p. The remaining cases may need other methods to be analyzed. We have performed simulations for one instance where we can see oscillatory solutions, it will be interesting to investigate this case to find possible periodic solutions.

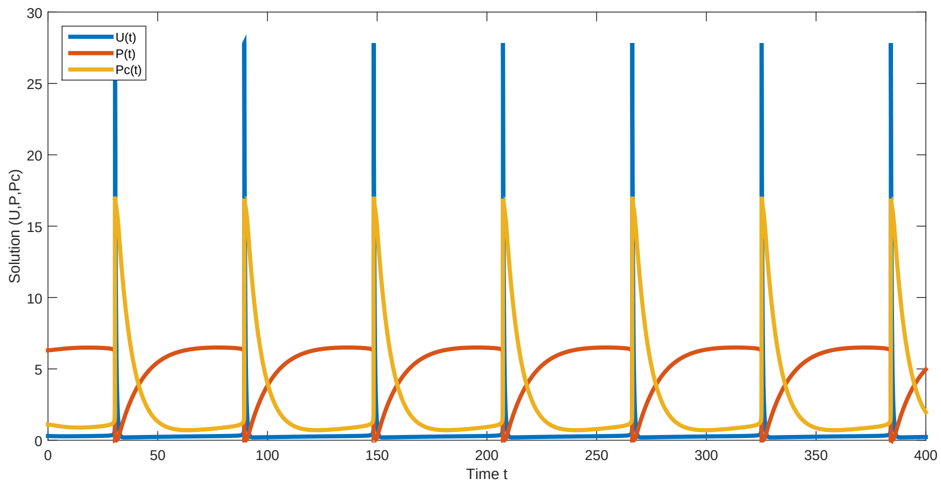


FIGURE 4. In this case, $\delta_2 = 0.89 > \delta^* = 0.66$, $d_p = 0.08$ and $d_u = 2.58$ with initial condition $(0.3, 6.3, 1.1)$, we observe the existence of oscillatory solutions for $\tau = 0$.

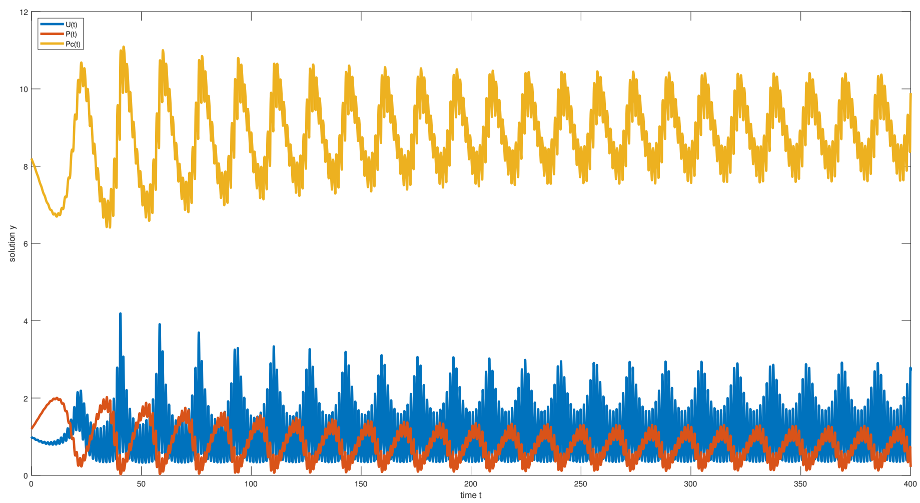


FIGURE 5. In this case, $\delta_2 = 0.89 > \delta^* = 0.66$, $d_p = 0.08$ and $d_u = 2.58$ with initial condition $(1, 1.2, 8.2)$, we observe the existence of oscillatory solutions for $\tau = 1.4$.

6. Appendix

6.1. Analysis of characteristic equation. The following results are taken from [3].

The characteristic polynomial is given by

$$P(\lambda) = \lambda^2 + a_i\lambda + c_i - (b_i\lambda + d_i)e^{-\lambda\tau} = 0 \tag{6.1}$$

with

$$\begin{aligned} a_i &= d_u + \delta_1 m^2 P^* U^{*m-1} + d_p + \delta_1 U^{*m}, \\ c_i &= d_p\Big(d_u + \delta_1 m^2 P^* U^{*m-1}\Big) + d_u\delta_1 U^{*m}, \\ b_i &= m^2\delta_2 P^* U^{*m-1}, \\ d_i &= d_p m^2 \delta_2 P^* U^{*m-1}. \end{aligned}$$

For $\tau = 0$, the characteristic equation (6.1) becomes

$$\lambda^2 + (a_i - b_i)\lambda + c_i - d_i = 0. \tag{6.2}$$

<u>Case 1</u>: If $c_i - d_i < 0$, then equation (6.2) has one real positive root, therefore the equilibrium is unstable.

<u>Case 2</u>: If $c_i - d_i = 0$, we must look at $a_i - b_i$.

- If $a_i - b_i < 0$, then the equilibrium is unstable.
- If $a_i - b_i = 0$, then we have an undetermined case.
- If $a_i - b_i > 0$, then we have an undetermined case.

<u>Case 3</u>: If $c_i - d_i > 0$, we must look at $a_i - b_i$.

- If $a_i - b_i < 0$, the equilibrium is unstable.
- If $a_i - b_i = 0$, then we have an undetermined case.
- If $a_i - b_i > 0$, the equilibrium is stable.

Now for $\tau > 0$, we let $\lambda = iw$ with $w > 0$. Then, equation (6.1) is equivalent to

$$\left\{ \begin{array}{lcl} -w^2 + c_i & = & d_i\cos(w\tau) + b_i w\sin(w\tau), \\ a_i w & = & b_i w\cos(w\tau) - d_i\sin(w\tau). \end{array} \right. \tag{6.3}$$

That is,

$$w^4 + (a_i^2 - 2c_i - b_i^2)w^2 + c_i^2 - d_i^2 = 0. \tag{6.4}$$

In order to find w we need to resolve quadratic equation

$$X^2 + (a_i^2 - b_i^2 - 2c_i)X + (c_i^2 - d_i^2) = 0 \tag{6.5}$$

with $X = w^2$.

Case 1. If $c_i - d_i < 0$, then $c_i^2 - d_i^2 < 0$ and equation (6.5) has one real positive root $w_+^2 = \dfrac{-(a_i^2 - 2c_i - b_i^2) + \sqrt{\Delta}}{2}$ with $\Delta = (a_i^2 - 2c_i - b_i^2)^2 - 4(c_i^2 - d_i^2) > 0$.

From 6.10, we know that

$$\text{sign } Re\Big[\frac{d\lambda}{d\tau}\Big]^{-1}_{\lambda=iw} = 1.$$

Therefore the equilibrium remains unstable for $\tau > 0$. Case 2. If $c_i - d_i = 0$, then $c_i^2 - d_i^2 = 0$. In this case, we have

- If $a_i - b_i \leq 0$, then $a_i^2 - b_i^2 - 2c_i < 0$ and equation (6.5) has one real positive root $w_+^2 = -(a_i^2 - b_i^2 - 2c_i)$.

  From 6.10, we know that

  $$\text{sign } Re\Big[\frac{d\lambda}{d\tau}\Big]^{-1}_{\lambda=iw} = 1.$$

  Therefore the equilibrium remains unstable for $\tau > 0$.
- If $a_i - b_i > 0$, we must look at $a_i^2 - b_i^2 - 2c_i$.
  (1) When $a_i^2 - b_i^2 - 2c_i < 0$, equation (6.5) has one real positive root $w_+^2 = -(a_i^2 - b_i^2 - 2c_i)$.

  From 6.10, we know that

  $$\text{sign } Re\Big[\frac{d\lambda}{d\tau}\Big]^{-1}_{\lambda=iw} = 1.$$

  Therefore the equilibrium becomes unstable for $\tau > 0$.

  (2) When $a_i^2 - b_i^2 - 2c_i \geq 0$, no conclusion can be made.

Case 3. If $c_i - d_i > 0$ then $c_i^2 - d_i^2 > 0$. In this case, we have

- If $a_i - b_i < 0$ then $a_i^2 - b_i^2 - 2c_i < 0$. We must look at discriminant Δ with $\Delta = (a_i^2 - 2c_i - b_i^2)^2 - 4(c_i^2 - d_i^2)$.
  (1) When $\Delta < 0$ equation (6.5) has no real roots, therefore the equilibrium remains unstable for $\tau > 0$.

  (2) When $\Delta = 0$ equation (6.5) has a double positive real root

  $$w_+^2 = -\frac{1}{2}(a_i^2 - b_i^2 - 2c_i).$$

  From 6.10, we know that

  $$Re\Big[\frac{d\lambda}{d\tau}\Big]^{-1}_{\lambda=iw} = 0$$

Therefore, no conclusion can be made.

(3) When $\Delta > 0$ equation (6.5) has two real positive roots

$$w_-^2 = \frac{-(a_i^2 - 2c_i - b_i^2) - \sqrt{\Delta}}{2} \text{ and } w_+^2 = \frac{-(a_i^2 - 2c_i - b_i^2) + \sqrt{\Delta}}{2}.$$

From 6.10, we know that

$$\text{sign } Re\Big[\frac{d\lambda}{d\tau}\Big]^{-1}_{\lambda = iw_+} = 1$$

and

$$\text{sign } Re\Big[\frac{d\lambda}{d\tau}\Big]^{-1}_{\lambda = iw_-} = -1.$$

From (6.3) we have

$$\tau = \frac{1}{w}\cos^{-1}\Big[\frac{(a_ib_i - d_i)w^2 + c_id_i}{b_i^2w^2 + d_i^2}\Big] + \frac{2\pi n}{w}.$$

For w_+ (resp. w_-), we obtain

(6.6) $$\tau_n^+ = \frac{1}{w_+}\cos^{-1}\Big[\frac{(a_ib_i - d_i)w_+^2 + c_id_i}{b_i^2w_+^2 + d_i^2}\Big] + \frac{2\pi n}{w_+}$$

(6.7) $$\left(\text{resp.} \quad \tau_n^- = \frac{1}{w_-}\cos^{-1}\Big[\frac{(a_ib_i - d_i)w_-^2 + c_id_i}{b_i^2w_-^2 + d_i^2}\Big] + \frac{2\pi n}{w_-}\right).$$

Since the equilibrium is unstable for $\tau = 0$, then necessarily $\tau_0^- < \tau_n^+$. Since $\tau_{n+1}^+ - \tau_n^+ < \tau_{n+1}^- - \tau_n^-$ there can be only a finite number of switches between instability and stability. More precisely, there exists $p \in \mathbb{N}^*$ such that the equilibrium is stable for $\tau \in \bigcup_{0\le n\le p}]\tau_n^-, \tau_n^+[$ and unstable for $\tau \in]0, \tau_0^-[\cup \left(\bigcup_{0\le n\le p-1}]\tau_n^+, \tau_{n+1}^-[\right) \cup]\tau_p^+, +\infty[$.

- If $a_i - b_i = 0$, then $a_i^2 - b_i^2 - 2c_i < 0$ and $\Delta = 4d_i^2 > 0$.
  Therefore, we have the same result as (3) of Case 3.
- If $a_i - b_i > 0$ we must look at $a_i^2 - b_i^2 - 2c_i$
  (1) When $a_i^2 - b_i^2 - 2c_i \ge 0$, then equation (6.5) has no real roots and equilibrium remains stable.
  (2) When $a_i^2 - b_i^2 - 2c_i < 0$ we must look at discriminant Δ.
    (a) If $\Delta < 0$, then equation (6.5) has no real roots. Therefore the equilibrium remains stable for $\tau > 0$.

(b) if $\Delta = 0$, then equation (6.5) has a double positive real root $w_+^2 = -\frac{1}{2}(a_i^2 - b_i^2 - 2c_i)$.
From 6.10, we know that

$$Re\Big[\frac{d\lambda}{d\tau}\Big]^{-1} = 0.$$

Therefore, no conclusion can be made.

(c) if $\Delta > 0$, then we have the same result as (3) of Case 3.

6.2. **Study of the sign of the derivative.** Let

$$\phi(\lambda, \tau) = \lambda^2 + a_i\lambda + c_i - e^{-\lambda\tau}(b_i\lambda + d_i).$$

Then, we have

$$\begin{aligned}\frac{\partial\phi}{\partial\lambda}(\lambda,\tau) &= 2\lambda + a_i - e^{-\lambda\tau}(b_i - \tau(b_i\lambda + d_i)),\\ \frac{\partial\phi}{\partial\tau}(\lambda,\tau) &= \lambda e^{-\lambda\tau}(b_i\lambda + d_i).\end{aligned}$$

From equation $\phi(\lambda, \tau) = 0$, we obtain

$$\Big[\frac{d\lambda}{d\tau}\Big]^{-1} = -\frac{(2\lambda + a_i)e^{\lambda\tau} - b_i}{\lambda(b_i\lambda + d_i)} - \frac{\tau}{\lambda} \tag{6.8}$$

and

$$e^{\lambda\tau} = \frac{b_i\lambda + d_i}{\lambda^2 + a_i\lambda + c_i}. \tag{6.9}$$

From (6.8) and (6.9), we have

$$\Big[\frac{d\lambda}{d\tau}\Big]^{-1} = -\frac{2\lambda + a_i}{\lambda(\lambda^2 + a_i\lambda + c_i)} + \frac{b_i}{\lambda(b_i\lambda + d_i)} - \frac{\tau}{\lambda}.$$

Then, for $\lambda = iw$ we obtain

$$\begin{aligned}\Big[\frac{d\lambda}{d\tau}\Big]^{-1}_{\lambda=iw} &= \frac{-(a_i + 2iw)\Big[-a_iw^2 - i(-w^3 + c_iw)\Big]}{\Big[-a_iw^2 + i(-w^3 + c_iw)\Big]\Big[-a_iw^2 - i(-w^3 + c_iw)\Big]}\\ &\quad - \frac{b_i(b_iw^2 + id_iw)}{(b_iw^2 - id_iw)(b_iw^2 + id_iw)} - \frac{\tau}{iw}.\end{aligned}$$

That is

$$Re\Big[\frac{d\lambda}{d\tau}\Big]^{-1}_{\lambda=iw}=\frac{a_i^2-2(-w^2+c_i)}{a_i^2w^2+(-w^2+c_i)^2}-\frac{b_i^2}{b_i^2w^2+d_i^2}.$$

From equation (6.4), we have

$$b_i^2w^2+d_i^2=a_i^2w^2+(-w^2+c_i)^2.$$

Therefore

$$Re\Big[\frac{d\lambda}{d\tau}\Big]^{-1}_{\lambda=iw}=\frac{2w^2+(a_i^2-b_i^2-2c_i)}{b_i^2w^2+d_i^2}$$

and

$$\text{sign } Re\Big[\frac{d\lambda}{d\tau}\Big]^{-1}_{\lambda=iw}=sign[2w^2+(a_i^2-b_i^2-2c_i)]. \tag{6.10}$$

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