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2026-10-29

Deposited version:

Accepted Version

Peer-review status of attached file:

Peer-reviewed

Citation for published item:

Boudjellal, L. & Silva, C. J. (2025). Analysis of the impact of time delay incorporation in mathematical models of cellular population dynamics. In Hemen Dutta (Ed.), *Mathematical modeling in bioscience: Theory and applications* (pp. 1?17). Elsevier. <https://doi.org/10.1016/B978-0-44-315445-4.00007-X>

Further information on publisher's website:

[10.1016/B978-0-44-315445-4.00007-X](https://doi.org/10.1016/B978-0-44-315445-4.00007-X)

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Chapter 1

Analysis of the Impact of Time Delay Incorporation in Mathematical Models of Cellular Population Dynamics

ABSTRACT

In this work, we investigate the effects of introducing a time delay in a mathematical model of cellular population dynamics with relevance in the development of chronic autoimmune diseases. Then, we determine the equilibrium states of the delayed system and investigate their asymptotic stability. We construct a Lyapunov function and use LaSalle's invariance principle to study the global stability of a biologically meaningful disease-free equilibrium. Some numerical simulations are performed in which we can observe the long-time behaviour of the solution and its approach to a stable equilibrium state. The simulations also show how the delay affect the behaviour of the solution and its asymptotic trend.

KEYWORDS

Mathematical biology, Kinetic models, Autoimmune diseases, Time delay, Dynamical systems

1.1 INTRODUCTION

There are many types of autoimmune diseases. In general terms, autoimmune diseases can be described as heterogeneous conditions characterized by the disruption of tolerogenic mechanisms and subsequent activation of self-reactive immune cells¹. In other words, autoimmune diseases occur when the immune system attacks and destroys its own healthy cells, tissues and organs, as a consequence of an interruption of their mechanisms. Due to its complexity, autoimmune diseases are a very interesting topic for mathematicians, and mathematical models have been successfully used to study this complex dynamics.

Over the years, many mathematicians have focused their work on this topic and several mathematical approaches have been used to investigate the dynamical behaviour of the different cellular populations in the context of autoimmune diseases. See, for instance, kinetic theory of active particles^{2,3,4}, optimal control theory⁵, dynamical system theory⁶, among others. Mathematical models of

autoimmune diseases can have a significant role in understanding the underlying mechanisms, predicting disease progression, and also evaluating potential treatment strategies.

In this work, we study the effect of considering a discrete time delay in the dynamical biological model proposed in⁷. The model in⁷ aims to study the cellular interactions and the global population behaviour in autoimmune diseases. It is based on a kinetic theory description of the cellular dynamics and possesses a macroscopic counterpart derived on the hydrodynamical limit of the kinetic system that is able to describe the global behaviour of the cellular populations. The macroscopic analogue is a system of ordinary differential equations (ODEs) that constitutes an autonomous dynamical system. Three cellular populations are involved, namely the population of self-antigen presenting cells (SAPCs), the population of self-reactive T cells (SRTC), and the population of immunosuppressive cells (ISCs). The immunosuppressive cells, such as Treg and Natural Killer cells, are essential components of immune homeostasis, since they provide a therapeutic opportunity for active immune regulation that can have a long time effect in controlling the development of autoimmunity.

We are interested in the role of ISCs in controlling autoimmunity and we consider a time delay describing the cumulative duration of the processes of viral attachment and interaction between the ISCs and SAPCs. This time delay is associated with different aspects that result from both internal effects, as the ability of spread of immune response, and external effects, as the age and gender. This represents the innovative aspect of our model.

For the delayed model proposed here, we study the local asymptotic stability of its equilibrium states. Then, we study the global stability of a biologically meaningful disease-free equilibrium. The extension of the global stability analysis to the other equilibrium points of the time delayed model is not a trivial task and is a challenge for a future work.

After this Introduction, our work is organized as follows. In Section 1.2, we recall the non-delayed model from⁷ and present the time delayed model, explaining their main assumptions and computing the equilibrium points. In Section 1.3, we study the local asymptotical stability of the equilibrium states. In Section 1.4, we prove the global stability of the disease-free equilibrium. In Section 1.5, we determine numerically the solution of both the non-delayed model and the delayed model and compare their behavior in order to appraise the effect of the time delay on the solution. The simulations illustrate the stability results proved in the previous sections. Finally, in Section 1.6, we summarize our results and present new perspectives in connection with our work.

1.2 THE MATHEMATICAL MODEL FOR AUTOIMMUNITY WITH TIME DELAY

In this section we describe the mathematical model considered in our study. Such model is derived from a previous model without time delay, which has been proposed in⁷. Hereby, we present first the original model and then we introduce our delayed model.

1.2.1 The non-delayed model

The macroscopic model proposed in⁷ considers three cellular populations, namely the population p_1 of self-antigen presenting cells (SAPCs), the population p_2 of self-reactive T cells (SRTCs), and the population p_3 of immunosuppressive cells (ISCs) mainly constituted by Treg cells and Natural Killer cells. We represent by $n_i(t)$, with $i = 1, 2, 3$, the expected number of cells of each population p_i at time $t \geq 0$. In the model of paper⁷, the density $n_i(t)$ is defined by

$$n_i(t) = \int_0^1 f_i(t, u) du, \quad i = 1, 2, 3,$$

with $f_i(t, u)$ being the distribution function associated to the population p_i , which denotes the number of cells of the population p_i with biological activity $u \in [0, 1]$, at time $t \geq 0$. The biological activity u describes the functional state expressed by each cellular population and is explained in⁷. Functions $f_i(t, u)$ are the unknowns of the kinetic model considered in⁷ and their behaviour is specified by a system of nonlinear partial differential equations (PDEs), involving integral terms of quadratic type that describe binary interactions among cells. See paper⁷ and the references cited therein for a detailed account of the kinetic models for biological processes.

The effective interactions among the populations p_i occur between a pair of cells, and are instantaneous and homogeneous in space. At the macroscopic scale, the admissible interactions are of proliferative or destructive type and are the following: proliferative interactions between SAPCs and SRTCs which increase both populations, and between SAPCs and ISCs which increase the population of ISCs; destructive interactions between SAPCs and ISCs which decrease the population of SAPCs, and between SRTCs and ISCs which decrease the population of SRTCs. Both the proliferative and the destructive rates are assumed to be constant, and are here denoted by α, γ, δ and by β, ρ , respectively. Moreover, the model considers a source term representing a constant input of SAPCs, due to the effect of certain environmental factors and unhealthy dietary habits. Such recruitment term is denoted here by Λ . Finally, the model considers the natural death rates of all populations, here denoted by $\mu_i, i = 1, 2, 3$. Omitting here other details, for sake of brevity, we introduce the ODE system of paper⁷

in the form

$$\begin{cases} \dot{n}_1(t) = \Lambda + \alpha n_1(t)n_2(t) - \beta n_1(t)n_3(t) - \mu_1 n_1(t) \\ \dot{n}_2(t) = \gamma n_2(t)n_1(t) - \rho n_2(t)n_3(t) - \mu_2 n_2(t) \\ \dot{n}_3(t) = \delta n_3(t)n_1(t) - \mu_3 n_3(t), \end{cases} \quad (1.1)$$

where all parameters are strictly positive. Model (1.1) is studied in detail in paper⁷, for what concerns the equilibrium states, asymptotical stability and bifurcations. An interesting result of paper⁷ is the capability of the model in capturing the recurrent dynamics describing the relapse-remission pattern typical of many autoimmune diseases, in terms of long-term periodic oscillations.

1.2.2 The model with time delay

The mathematical model with time delay considered in the present work constitutes a simple variant of model (1.1), in the sense that we introduce a delay only in one destructive interaction. Specifically, we assume that there exists a latent period for the effectiveness of the destructive interactions among SAPCs and ISCs. Such period is represented by a time-delay $\tau > 0$ that is introduced in the term describing the above referred interactions. Accordingly, the new model becomes

$$\begin{cases} \dot{n}_1(t) = \Lambda + \alpha n_1(t)n_2(t) - \beta n_1(t - \tau)n_3(t - \tau) - \mu_1 n_1(t) \\ \dot{n}_2(t) = \gamma n_2(t)n_1(t) - \rho n_2(t)n_3(t) - \mu_2 n_2(t) \\ \dot{n}_3(t) = \delta n_3(t - \tau)n_1(t - \tau) - \mu_3 n_3(t), \end{cases} \quad (1.2)$$

where $\tau \geq 0$. In the particular case in which $\tau=0$, system (1.2) reduces to system (1.1). Again, all parameters that figure in system (1.2) are strictly positive, that is $\Lambda, \alpha, \beta, \gamma, \rho, \delta, \mu_1, \mu_2, \mu_3 > 0$.

The initial conditions for model (1.2) describe the past history of each population density in the time interval $[-\tau, 0]$, and are given by

$$n_1(\theta) = \Phi_1(\theta) > 0, \quad n_2(\theta) = \Phi_2(\theta) > 0, \quad n_3(\theta) = \Phi_3(\theta) > 0, \quad \text{for } \theta \in [-\tau, 0], \quad (1.3)$$

where Φ_1, Φ_2, Φ_3 are continuous functions from the interval $[-\tau, 0]$ into $\mathbb{R}_+$.

1.2.3 Equilibrium states of the model with delay

In order to investigate the effects of the time delay introduced in our model, we first determine the equilibrium states of the model. Models (1.1) and (1.2) have the same equilibria, as expected. We restrict our analysis to the set of biologically significant solutions to the Cauchy problem (1.2-1.3), namely

$$\mathcal{D} = \left\{ (n_1(t), n_2(t), n_3(t)) \in \mathbb{R}^3 : n_1(t) \geq 0, n_2(t) \geq 0, n_3(t) \geq 0 \right\}. \quad (1.4)$$

Our result is the following.

Theorem 1.2.1. [Equilibrium states] *The model (1.2) has four equilibrium states in $\mathcal{D}$, which are given by*

- a) $E_0 = \left(\frac{\Lambda}{\mu_1}, 0, 0 \right)$, representing an equilibrium state without both SRTC and ISC cells;
- b) $E_1 = \left(\frac{\mu_3}{\delta}, 0, \frac{\Lambda\delta - \mu_1\mu_3}{\beta\mu_3} \right)$, representing an equilibrium state without SRTC cells, that exists if $\Lambda\delta \geq \mu_1\mu_3$;
- c) $E_2 = \left(\frac{\mu_3}{\delta}, \frac{-\Lambda\delta^2\rho + \gamma\beta\mu_3^2 - \delta\beta\mu_2\mu_3 + \delta\rho\mu_1\mu_3}{\alpha\delta\rho\mu_3}, \frac{\gamma\mu_3 - \delta\mu_2}{\delta\rho} \right)$ representing an equilibrium state of co-existence of all population's cells, that exists if $\gamma\mu_3 \geq \delta\mu_2$ and $\Lambda \leq \frac{\mu_1\mu_3}{\delta} + \frac{\mu_3\gamma - \mu_2\delta}{\delta\rho} \frac{\mu_3\beta}{\delta}$;
- d) $E_3 = \left(\frac{\mu_2}{\gamma}, \frac{\mu_1\mu_2 - \Lambda\gamma}{\alpha\mu_2}, 0 \right)$, representing an equilibrium state without ISC cells, that exists if $\mu_1\mu_2 \geq \Lambda\gamma$.

We note that equilibrium E_2 , with strict inequalities in its existence conditions, is the unique with meaningful significance in the context of our study, since the other equilibria predict the extinction of some populations. Anyway, all other equilibria have their mathematical importance and are relevant for our study.

The following sections in this work will focus on stability and asymptotic behaviour of the equilibria of the model (1.2). In Section 1.3, we study the local asymptotic stability of the equilibria, and Section 1.4 is devoted to the global stability. Finally, in Section 1.5 we study, numerically, the time behaviour of the solution to our system (1.2) and investigate the asymptotic behaviour of the equilibria.

1.3 LOCAL ASYMPTOTICAL STABILITY OF THE EQUILIBRIUM STATES

The stability analysis developed here for system (1.2) is based on a general result for non-linear delay equations, see⁸ and⁹. For sake of completeness, we introduce this result below.

Let us consider the following system of n delay differential equations,

$$\dot{x} = f(x, x_\tau), \quad (1.5)$$

where f is a continuously differentiable function as many times as we need, $\tau > 0$ represents the time delay, and $x, x_\tau \in \mathbb{R}^n$. Let us assume that the system (1.5) can be written in the form

$$\dot{x} = f_1(x) + f_2(x_\tau), \quad (1.6)$$

with f_1, f_2 being continuously differentiable functions as many times as we need. Then, we have the following result, based on the linearization of system (1.6), as usual, see^{8, 9} and¹⁰.

Theorem 1.3.1. [Stability of the delayed system] Assume that $\bar{x}$ is an equilibrium solution of system (1.6), and denote by A_1 and A_2 the Jacobian matrices of f_1 and f_2 , respectively, with respect to x and x_τ , that is $A_1 = D_x f_1(x)$ and $A_2 = D_{x_\tau} f_2(x_\tau)$. For $k \in \mathbb{N}$, $k \leq n$, suppose that the characteristic equation of system (1.6),

$$\det(\lambda I_n - A_1 - e^{-\lambda\tau} A_2) = 0,$$

evaluated at the equilibrium state $\bar{x}$, has k different solutions $\lambda_1, \dots, \lambda_k$. Therefore:

- i) the equilibrium solution $\bar{x}$ is locally asymptotically stable if $\operatorname{Re}(\lambda_i) < 0$, for all $i = 1, \dots, k$;
- ii) the equilibrium solution $\bar{x}$ is unstable if $\operatorname{Re}(\lambda_i) > 0$ for some $i = 1, \dots, k$.

Having Theorem 1.3.1 in mind, we start by re-writing our system (1.2) in a more compact form, similar to that of the general system (1.6). Let us introduce $n_i^\tau(t) = n_i(t - \tau)$, for $i = 1, 2, 3$, and

$$N(t) = \begin{pmatrix} n_1(t) \\ n_2(t) \\ n_3(t) \end{pmatrix}, \quad N^\tau(t) = \begin{pmatrix} n_1^\tau(t) \\ n_2^\tau(t) \\ n_3^\tau(t) \end{pmatrix}.$$

System (1.2) can be written as

$$\dot{N}(t) = F_1(N(t)) + F_2(N^\tau(t)), \quad (1.7)$$

where

$$F_1(N(t)) = \begin{pmatrix} \Lambda + \alpha n_1(t)n_2(t) - \mu_1 n_1(t) \\ \gamma n_2(t)n_1(t) - \rho n_2(t)n_3(t) - \mu_2 n_2(t) \\ -\mu_3 n_3(t) \end{pmatrix} \quad (1.8)$$

and

$$F_2(N^\tau(t)) = \begin{pmatrix} -\beta n_1^\tau(t)n_3^\tau(t) \\ 0 \\ \delta n_3^\tau(t)n_1^\tau(t) \end{pmatrix}. \quad (1.9)$$

Then, we define the Jacobian matrices of functions F_1 and F_2 with respect to t and τ , given by

$$A_1 = J_{F_1}(N(t)) = \begin{pmatrix} \alpha n_2(t) - \mu_1 & \alpha n_1(t) & 0 \\ \gamma n_2(t) & \gamma n_1(t) - \rho n_3(t) - \mu_2 & -\rho n_2(t) \\ 0 & 0 & -\mu_3 \end{pmatrix}$$

and

$$A_2 = J_{F_2^\tau}(N^\tau(t)) = \begin{pmatrix} -\beta n_3^\tau(t) & 0 & -\beta n_1^\tau(t) \\ 0 & 0 & 0 \\ \delta n_3^\tau(t) & 0 & \delta n_1^\tau(t) \end{pmatrix}.$$

The characteristic equation of model (1.2) is then given by

$$\det(\lambda I_3 - A_1 - e^{-\lambda\tau} A_2) = 0. \quad (1.10)$$

1.3.1 Local stability of E_0

Consider the equilibrium state E_0 determined in Theorem 1.2.1, which is specified by

$$n_1(t) = \frac{\Lambda}{\mu_1}, \quad n_2(t) = n_3(t) = 0.$$

The characteristic equation of system (1.2), referred to the equilibrium state E_0 , is given by

$$\frac{1}{\mu_1^2} [(\lambda + \mu_1)(-\Lambda\gamma + \lambda\mu_1 + \mu_1\mu_2)(-\Lambda\delta e^{-\lambda\tau} + \lambda\mu_1 + \mu_1\mu_3)] = 0, \quad (1.11)$$

which possesses the two real roots given by

$$\lambda_1 = -\mu_1, \quad \lambda_2 = \frac{\Lambda\gamma - \mu_1\mu_2}{\mu_1} \quad (1.12)$$

and a third real root, λ_3 , such that

$$-\Lambda\delta e^{-\lambda_3\tau} + \lambda_3\mu_1 + \mu_1\mu_3 = 0. \quad (1.13)$$

Using theorem 1.3.1, we state the following result.

Theorem 1.3.2. [Local stability of the equilibrium state E_0] *Let $\tau \geq 0$. The equilibrium state E_0 is locally asymptotically stable if*

$$\Lambda\gamma < \mu_1\mu_2 \quad \text{and} \quad \Lambda\delta < \mu_1\mu_3,$$

and it is unstable if

$$\Lambda\gamma > \mu_1\mu_2 \quad \text{or} \quad \Lambda\delta > \mu_1\mu_3.$$

Proof. (a) Let $\tau = 0$. The roots (1.12) and (1.13) of the characteristic equation (1.11) reduce to

$$\lambda_1 = -\mu_1, \quad \lambda_2 = \frac{\Lambda\gamma - \mu_1\mu_2}{\mu_1}, \quad \lambda_3 = \frac{\Lambda\delta - \mu_1\mu_3}{\mu_1}$$

and using theorem 1.3.1, the proof of the local stability of E_0 follows immediately.

(b) Let us consider $\tau > 0$. The first and second roots of the characteristic equation (1.11), namely λ_1 and λ_2 , are not affected by the value of τ . We just

need to study the third root, namely λ_3 . We consider the auxiliary transcendental function defined by

$$g(\lambda) = -\Lambda\delta e^{-\lambda\tau} + \lambda\mu_1 + \mu_1\mu_3, \quad \lambda \in \mathbb{R},$$

such that

$$g'(\lambda) = \tau\Lambda\delta e^{-\lambda\tau} + \mu_1 > 0, \quad \lambda \in \mathbb{R}, \quad \text{and} \quad g'(\lambda) > 0, \quad \lambda \in \mathbb{R}.$$

Therefore, g is a strictly increasing function, such that

$$\begin{cases} g(0) = -\Lambda\delta + \mu_1\mu_3 \\ \lim_{\lambda \rightarrow +\infty} g(\lambda) = +\infty. \end{cases}$$

If $\Lambda\delta > \mu_1\mu_3$, then function g has a positive real root, so that $\lambda_3 > 0$ and E_0 is unstable.

If $\Lambda\delta < \mu_1\mu_3$, then function g has a negative real root, so that $\lambda_3 < 0$. The conclusion about the local stability of E_0 follows immediately. The proof of Theorem 1.3.2 is then completed. $\square$

1.3.2 Local stability of E_1

The second equilibrium point E_1 has a biological meaning if and only if $\Lambda\delta \geq \mu_1\mu_3$. In this case, E_1 is given by

$$n_1(t) = \frac{\mu_3}{\delta}, \quad n_2(t) = 0, \quad n_3(t) = \frac{\Lambda\delta - \mu_1\mu_3}{\beta\mu_3}$$

At the equilibrium point E_1 , the characteristic equation of the model (1.2) is given by

$$(\lambda + K) \left\{ \lambda^2 + \lambda \left[e^{-\lambda\tau} \left(\frac{\Lambda\delta}{\mu_3} - \mu_1 - \mu_3 \right) + \mu_1 + \mu_3 \right] + e^{-\lambda\tau} (\Lambda\delta - 2\mu_1\mu_3) + \mu_1\mu_3 \right\} = 0,$$

where

$$K = \frac{\Lambda\delta^2\rho + \beta\delta\mu_2\mu_3 - \beta\gamma\mu_3^2 - \delta\mu_1\mu_3\rho}{\beta\delta\mu_3}.$$

Theorem 1.3.3. [Local stability of the equilibrium state E_1]

(a) Let $\tau = 0$. The equilibrium state E_1 is locally asymptotically stable if $\Lambda > \frac{\beta\mu_3}{\rho\delta^2} (\gamma\mu_3 - \delta\mu_2) + \frac{\mu_1\mu_3}{\delta}$ and it is unstable if $\Lambda < \frac{\beta\mu_3}{\rho\delta^2} (\gamma\mu_3 - \delta\mu_2) + \frac{\mu_1\mu_3}{\delta}$.

(b) Let $\tau > 0$ and assume that $\Lambda\delta < 2\mu_1\mu_3$. Then, the equilibrium state E_1 is locally asymptotically stable.

Proof. (a) Let $\tau = 0$. Then the characteristic equation (1.10) computed at the equilibrium state E_1 is given by

$$(\lambda + K) \left[\lambda^2 + \lambda \frac{\Lambda\delta}{\mu_3} + \Lambda\delta - \mu_1\mu_3 \right] = 0 \quad (1.14)$$

which has three different roots, namely

- $\lambda_1 = \frac{1}{2\mu_3} \left(-\Lambda\delta + \sqrt{\Lambda^2\delta^2 - 4\mu_3^2(\Lambda\delta - \mu_1\mu_3)} \right),$
- $\lambda_2 = \frac{1}{2\mu_3} \left(-\Lambda\delta - \sqrt{\Lambda^2\delta^2 - 4\mu_3^2(\Lambda\delta - \mu_1\mu_3)} \right),$
- $\lambda_3 = -K$, that is $\lambda_3 = -\frac{1}{\beta\delta\mu_3} \left[\rho\delta(\Lambda\delta - \mu_1\mu_3) - \beta\mu_3(\gamma\mu_3 - \delta\mu_2) \right].$

If λ_1, λ_2 are real eigenvalues, that is, if $\Lambda^2\delta^2 > 4\mu_3^2(\Lambda\delta - \mu_1\mu_3)$, then, it is immediate that $\lambda_1 < 0$ and $\lambda_2 < 0$, whenever E_1 exists, namely when $\Lambda\delta \geq \mu_1\mu_3$. Moreover, if λ_1 and λ_2 are complex eigenvalues, then $\text{Re}(\lambda_1) = \text{Re}(\lambda_2) = \frac{-\Lambda\delta}{2\mu_3} < 0$, where $\Re$ is the real part of the complex number. Therefore, the equilibrium state E_1 is stable if $\lambda_3 < 0$, that is if

$$\rho\delta(\Lambda\delta - \mu_1\mu_3) - \beta\mu_3(\gamma\mu_3 - \delta\mu_2) > 0 \Leftrightarrow \rho\delta(\Lambda\delta - \mu_1\mu_3) > \beta\mu_3(\gamma\mu_3 - \delta\mu_2)$$

or, equivalently, if

$$\Lambda > \frac{\beta\mu_3}{\rho\delta^2} (\gamma\mu_3 - \delta\mu_2) + \frac{\mu_1\mu_3}{\delta} \quad (1.15)$$

This concludes the proof for non-delayed model.

(b) Let $\tau > 0$. Then the characteristic equation (1.10) computed at the equilibrium point E_1 is given by

$$(\lambda + K) g(\lambda) = 0,$$

where $g(\lambda)$ is the transcendental function, defined by

$$g(\lambda) = \lambda^2 + (\mu_1 + \mu_3)\lambda + \mu_1\mu_3 + e^{-\lambda\tau} \left[\left(\frac{\Lambda\delta}{\mu_3} - \mu_1 - \mu_3 \right) \lambda + \Lambda\delta - 2\mu_1\mu_3 \right].$$

First, we notice that the eigenvalue $\lambda_3 = -K$ is not affected by τ , and has been studied in the previous case $\tau = 0$, so that $\lambda_3 < 0$ if condition (1.15) holds.

Concerning the transcendental function $g(\lambda)$, let us assume the existence condition for E_1 , namely $\Lambda\delta \geq \mu_1\mu_3$. Our aim is to prove that the equilibrium E_1 is locally stable for any positive time delay τ . Following Rouché's Theorem¹¹, if instability occurs for a particular time delay τ , then the characteristic equation evaluated at E_1 must have purely imaginary roots, see, *e.g.*^{12,13,14,15} for analogous stability proofs. Accordingly, in the following, we prove that function g does not

have any pure imaginary roots. Suppose that $\lambda = \pm bi$ are pure imaginary roots of g . Let $m = \mu_1 + \mu_3$ and $n = \mu_1\mu_3$. Therefore,

$$g(bi) = -b^2 + mbi + n + (\cos(b\tau) - i \sin(b\tau)) \left[\left(\frac{\Lambda\delta}{\mu_3} - m \right) bi + \Lambda\delta - 2n \right].$$

Then,

$$g(bi) = 0 \Leftrightarrow \begin{cases} -b^2 + n + (\Lambda\delta - 2n) \cos(b\tau) + b \left(\frac{\Lambda\delta}{\mu_3} - m \right) \sin(b\tau) = 0 \\ mb + b \left(\frac{\Lambda\delta}{\mu_3} - m \right) \cos(b\tau) - \sin(b\tau) (\Lambda\delta - 2n) = 0. \end{cases}$$

Let $A = \Lambda\delta - 2n$ and $B = \frac{\Lambda\delta}{\mu_3} - m$. Therefore,

$$\begin{cases} -b^2 + n = -A \cos(b\tau) - bB \sin(b\tau) \\ mb = -bB \cos(b\tau) + A \sin(b\tau). \end{cases}$$

Squaring both equations and then summing, we get

$$(-b^2 + n)^2 + (mb)^2 = A^2 + b^2 B^2,$$

that is

$$b^4 + (m^2 - 2n - B^2) b^2 + n^2 - A^2 = 0.$$

Introducing $m = \mu_1 + \mu_3$ and $n = \mu_1\mu_3$, we obtain

$$b^4 + (\mu_1^2 + \mu_3^2 - B^2) b^2 + \mu_1^2 \mu_3^2 - A^2 = 0,$$

which means that $u = b^2$ is a positive root of the polynomial

$$f(u) = u^2 + (\mu_1^2 + \mu_3^2 - B^2)u + \mu_1^2 \mu_3^2 - A^2.$$

In view of using the Descarte's rule of signs, we also consider

$$f(-u) = u^2 - (\mu_1^2 + \mu_3^2 - B^2)u + \mu_1^2 \mu_3^2 - A^2,$$

and analyze the coefficient of u in $f(-u)$,

$$\begin{aligned} \mu_1^2 + \mu_3^2 - B^2 &= \mu_1^2 + \mu_3^2 - \left[\frac{\Lambda\delta}{\mu_3} - (\mu_1 + \mu_3) \right]^2 \\ &= - \left(\frac{\Lambda\delta}{\mu_3} \right)^2 + 2 \frac{\Lambda\delta}{\mu_3} (\mu_1 + \mu_3) - 2\mu_1\mu_3 \\ &= 2(\Lambda\delta - \mu_1\mu_3) - \frac{\Lambda\delta^2}{\mu_3^2} (\Lambda\delta - 2\mu_1\mu_3), \end{aligned}$$

where $\Lambda\delta - \mu_1\mu_3 \geq 0$ whenever E_1 exists. We see that, if $\Lambda\delta < 2\mu_1\mu_3$ then $\mu_1^2 + \mu_3^2 - B^2 > 0$ and $f(u)$ has one negative root, at least, of the form $u = b^2$, which is a contradiction.

Thus, we conclude that g does not have any purely imaginary root, and then E_1 is locally stable, for any positive time delay τ . The proof is then completed. $\square$

1.3.3 Local stability of E_3

Consider now the equilibrium state E_3 without ISC cells, which has been determined in Theorem 1.2.1 as

$$n_1(t) = \frac{\mu_2}{\gamma}, \quad n_2(t) = \frac{\mu_1\mu_2 - \Lambda\gamma}{\alpha\mu_2}, \quad n_3(t) = 0.$$

The characteristic equation of system (1.2), referred to the equilibrium state E_3 , is given by

$$\mu_2 \left(\lambda^2 + \frac{\Lambda\gamma}{\mu_2} \lambda + \Lambda\gamma - \mu_1\mu_2 \right) (-\delta\mu_2 e^{-\lambda\tau} + \gamma\lambda + \gamma\mu_3) = 0. \quad (1.16)$$

Theorem 1.3.4. [Local stability of the equilibrium state E_3] *The equilibrium state E_3 is unstable, for any time delay $\tau \geq 0$.*

Proof. Independently of the delay τ , the characteristic equation (1.16) possesses the roots

$$\lambda_1 = \frac{-\gamma\Lambda + \sqrt{\gamma^2\Lambda^2 + 4\mu_2^2(\mu_1\mu_2 - \gamma\Lambda)}}{2\mu_2}, \quad \lambda_2 = \frac{-\gamma\Lambda - \sqrt{\gamma^2\Lambda^2 + 4\mu_2^2(\mu_1\mu_2 - \gamma\Lambda)}}{2\mu_2}, \quad (1.17)$$

resulting from the first factor in (1.16). The third eigenvalue, say λ_3 , is also real and is given by the root of the last factor in (1.16), so that λ_3 depends on the delay τ .

From Theorem 1.2.1, item 4), it is immediate that the discriminant in (1.17) is positive whenever E_3 exists. Consequently, independently of the delay τ , the eigenvalues λ_1, λ_2 are real and such that

$$\lambda_1 > 0 \quad \text{and} \quad \lambda_2 < 0$$

and the equilibrium state E_3 is unstable, whenever it exists, for any time delay. $\square$

1.4 GLOBAL STABILITY OF THE EQUILIBRIUM STATES

The global stability of the equilibrium states is an important topic when studying evolutionary systems. This is a difficult topic, in general, and we limit our

analysis in this work to the global stability of the equilibrium state E_0 , see the first item of Theorem 1.2.1, since this corresponds to the easiest case.

In view of using LaSalle's invariance principle¹⁶, we construct a Lyapunov function associated to our differential system (1.2), for the equilibrium state E_0 , $V: \mathcal{D} \subset \mathbb{R}^3 \mapsto \mathbb{R}$, with $\mathcal{D}$ being the interest set given in (1.4). Then, we prove that

- $V(n_1(t), n_2(t), n_3(t)) \geq 0$, for all $(n_1(t), n_2(t), n_3(t)) \in \mathcal{D}$;
- $\dot{V}(n_1(t), n_2(t), n_3(t)) < 0$, for all $(n_1(t), n_2(t), n_3(t)) \neq E_0$;
- $\dot{V}|_{\text{sys}(2)}(n_1(t), n_2(t), n_3(t)) = 0$, if and only if $(n_1(t), n_2(t), n_3(t)) = E_0$.

We state the global stability of the equilibrium E_0 under two assumptions that prevent the blow up of the solution. Namely, we assume that the density of SAPC cells is bounded from above by the corresponding density of E_0 , and also that the ratio between the death rates of SRTC cells and ISC cells dominates the ratio of their proliferative rates resulting from their interaction with SAPC cells. In the sequel, we consider the following assumptions, which are in agreement with the biological features of the model,

$$n_1(t) \leq \frac{\Lambda}{\mu_1}, \quad \frac{\mu_2}{\mu_3} > \frac{\gamma}{\delta},$$

and our result is stated in the following theorem.

Theorem 1.4.1. [Global stability of the equilibrium state E_0] *The equilibrium state E_0 is globally asymptotically stable if $\frac{\delta\Lambda}{\mu_1\mu_3} < 1$.*

Proof. Consider the continuously differentiable function $V: \mathcal{D} \subset \mathbb{R}^3 \mapsto \mathbb{R}$ defined by

$$V(n_1(t), n_2(t), n_3(t)) = n_2(t) + n_3(t). \quad (1.18)$$

It is immediate that

$$V(n_1(t), n_2(t), n_3(t)) \geq 0, \text{ for all } (n_1(t), n_2(t), n_3(t)) \in \mathcal{D}.$$

Along the solutions of system (1.2), we have

$$\begin{aligned} \dot{V}(t) &= \left[\gamma n_2(t) n_1(t) - \rho n_2(t) n_3(t) - \mu_2 n_2(t) \right] + \left[\delta n_3(t - \tau) n_1(t - \tau) - \mu_3 n_3(t) \right] \\ &= \gamma n_2(t) n_1(t) - \mu_2 n_2(t) + \delta n_3(t - \tau) n_1(t - \tau) - \mu_3 n_3(t) - \rho n_2(t) n_3(t). \end{aligned}$$

For t large enough, we have $n_3(t) = n_3(t - \tau)$. Using that $n_1(t) \leq \frac{\Lambda}{\mu_1} = \bar{n}_1$, we get

$$\begin{aligned} \dot{V}(t) &\leq \gamma n_2(t) \bar{n}_1 - \mu_2 n_2(t) + \delta n_3(t) \bar{n}_1 - \mu_3 n_3(t) - \rho n_2(t) n_3(t) \\ &\leq \gamma n_2(t) \bar{n}_1 - \mu_2 n_2(t) + \delta n_3(t) \bar{n}_1 - \mu_3 n_3(t) \\ &= \mu_2 \left(\frac{\gamma \bar{n}_1}{\mu_2} - 1 \right) n_2(t) + \mu_3 \left(\frac{\delta \bar{n}_1}{\mu_3} - 1 \right) n_3(t) \end{aligned}$$

Since $\gamma/\delta < \mu_2/\mu_3$, also $\gamma/\mu_2 < \delta/\mu_3$, and we obtain

$$\dot{V}(t) \leq \mu_2 \left(\frac{\delta \bar{n}_1}{\mu_3} - 1 \right) n_2(t) + \mu_3 \left(\frac{\delta \bar{n}_1}{\mu_3} - 1 \right) n_3(t). \quad (1.19)$$

From condition (1.19), it follows that $\dot{V}(t) < 0$ whenever $\frac{\delta \bar{n}_1}{\mu_3} < 1$. Therefore, $\dot{V}$ is negative definite along the trajectories of the solution to our system (1.2). Furthermore, it follows from (1.19), that

$$\dot{V}(n_1(t), n_2(t), n_3(t)) = 0, \text{ if and only if } n_2(t) = n_3(t) = 0,$$

Substituting $n_2(t) = n_3(t) = 0$ into our system (1.2), we get the linear differential equation

$$\dot{n}_1(t) = \Lambda - \mu_1 n_1(t).$$

Since $n_1(t) \leq \Lambda/\mu_1$, we conclude that $n_1(t)$ is an increasing function. Solving the above differential equation, we obtain its solution in the form

$$n_1(t) = e^{-\mu_1 t} \left(n_1(0) - \frac{\Lambda}{\mu_1} \right) + \frac{\Lambda}{\mu_1}$$

so that

$$\lim_{t \rightarrow +\infty} n_1(t) = \frac{\Lambda}{\mu_1}.$$

Therefore,

$$\dot{V}(n_1(t), n_2(t), n_3(t)) = 0, \text{ if and only if } (n_1(t), n_2(t), n_3(t)) = E_0.$$

Thus, V is a Lyapunov function, and the largest compact invariant set in

$$\{(n_1(t), n_2(t), n_3(t)) \in \mathcal{D} : \dot{V} = 0\}$$

is the singleton $\{E_0\}$, since every solution of (1.2) in $\mathcal{D}$ converges towards E_0 as $t \rightarrow \infty$. Therefore, E_0 is the unique accumulation point of the trajectories of the solution to our system (1.2), and by LaSalle's invariance principle¹⁶, the equilibrium point E_0 is globally asymptotically stable whenever $\frac{\delta \Lambda}{\mu_1 \mu_3} < 1$. $\square$

1.5 NUMERICAL RESULTS

In this section, we perform some numerical simulations in view of investigating both the impact of the time delay in the behaviour of the solution and the asymptotic trend of the equilibria determined in the previous sections. To this end, we determine the solution to both systems with and without delay, namely systems (1.2) and (1.1), respectively, and compare the corresponding results. We have integrated the ODE systems (1.1) and (1.2) using the `ode45` solver of the

computing software *Matlab*, see¹⁷. The results will be interpreted in light with the theoretical results of Sections 1.3 and 1.4.

We assume the following initial data

$$(n_1^0, n_2^0, n_3^0) = (0.2, 0.2, 0.2)$$

and two different time delays, namely $\tau \in \{0.4, 0.8\}$. Concerning the input data, we assume the values for the parameters specified in the following two study cases.

Case 1. Convergence of the solution to the equilibrium state E_0 . We consider

$$\Lambda = 0.119, \alpha = 0.21, \beta = 2, \gamma = 0.01, \rho = 0.025, \delta = 3, \mu_1 = 0.5, \mu_2 = 0.5, \mu_3 = 0.75.$$

In this case, we have

$$E_0 = (0.238, 0, 0)$$

and

$$\Lambda\gamma - \mu_1\mu_2 = -0.24881 < 0, \quad \Lambda\delta - \mu_1\mu_3 = -0.018 < 0.$$

According to Theorem 1.3.2, the equilibrium state E_0 is locally asymptotically stable for any delay $\tau \geq 0$ and the solutions of systems (1.1) and (1.2) converge to E_0 .

The results of our simulatons are shown in Figure 1.1. We can see that the effects of the delay are visible in the evolution of n_1 and n_3 whereas they are not detectable in the evolution of n_2 . This is due to the fact that n_1 and n_3 depend directly on the delay τ and n_2 does not.

Case 2. Convergence of the solution to the equilibrium state E_1 . We consider

$$\Lambda = 0.1, \alpha = 0.21, \beta = 0.3, \gamma = 0.21, \rho = 0.025, \delta = 0.35, \mu_1 = 0.1, \mu_2 = 0.2, \mu_3 = 0.21.$$

In this case, we have

$$\frac{\mu_3}{\delta} = 0.6, \quad \frac{\Lambda\delta - \mu_1\mu_3}{\beta\mu_3} = 0.222$$

and the equilibrium state E_1 is given by

$$E_1 = (0.6, 0, 0.222).$$

Moreover, we have

$$\Lambda\delta - 2\mu_1\mu_3 = -0.07 < 0, \quad \Lambda - \frac{\beta\mu_3}{\rho\delta^2}(\gamma\mu_3 - \delta\mu_2) + \frac{\mu_1\mu_3}{\delta} = 5.37 > 0.$$

According to Theorem 1.3.3, the equilibrium state E_1 is locally asymptotically stable in both models with and without delay, and the solutions of systems (1.1) and (1.2) approach to E_1 . The results are shown in Figure 1.2. Again, the effects of the delay are visible in the evolution of n_1 and n_3 whereas they are almost undetectable in the evolution of n_2 .

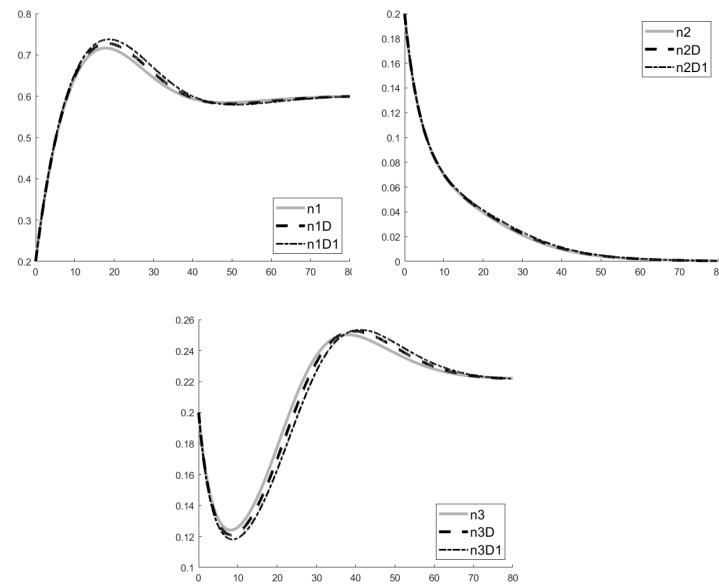


FIGURE 1.1 Solution to system (1.1) without delay (full line) and to system (1.2) with delay $\tau = 0.4$ (D-dashed line), and $\tau = 0.8$ (D1-dotted line). Dynamics of populations n_1 , n_2 and n_3 showing the asymptotic trend to equilibrium E_0 .

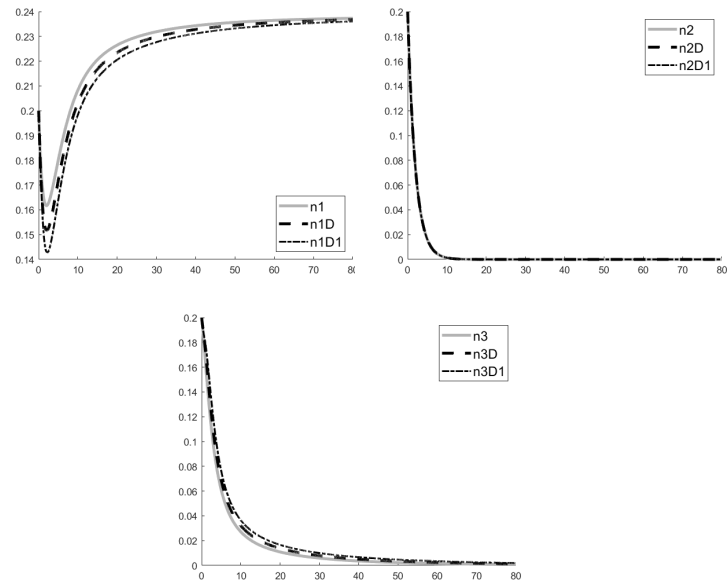


FIGURE 1.2 Solution to system (1.1) without delay (full line) and to system (1.2) with delay $\tau = 0.4$ (D-dashed line) and $\tau = 0.8$ (D1-dotted line). Dynamics of populations n_1 , n_2 and n_3 showing the asymptotic trend to equilibrium E_1 .

1.6 SUMMARY AND PERSPECTIVES

In this work, we consider an existing macroscopic model for autoimmune diseases and introduce a discrete time delay in the dynamics. We determine the equilibrium states of the new model and study their local stability. Then we also investigate the global stability of a biologically meaningful disease-free equilibrium state. We perform some numerical simulations in order to estimate how the solution is influenced by the delay.

Even if the new model introduces the delay only in the terms describing the interactions between SAPCs and ISCs, the simulations show that the solution is affected by the delay confirming the importance of studying the time-delayed generalization model.

Therefore, the delayed model proposed in this work provides a rather comprehensive explanation for the active immune regulation that can have a long time effect in controlling the development of autoimmunity. In particular, the delay describes the cumulative duration of the viral attachment and the interaction between the ISCs and SAPCs.

The work developed in this article did not exhausted the subject here initiated, in the sense that the stability of the unique equilibrium state of co-existence of all populations cells was not studied and the global stability had been studied only for a disease-free equilibrium state. These challenging problems will be considered in a future work.

Another problem that we plan to address is the development and analysis of an extended version of the model considered here, possibly with more than one time delay. We plan to consider a different time delay for the interactions involving SRTCs. In this case, the delay can describe the lag that the self-reactive T cells take to activate their memory. More specifically, there are two types of self-reactive T cells, namely naïve cells and cells with memory. An important characteristic of the naïve self-reactive T cells response is the formation of immunological memory after initial antigen exposure that helps the immune system learn with experience. After the initial interaction, naïve T cells undergo clonal expansion to become activated T cells with memory. See more details in¹⁸. However, according to¹⁹ and references therein, memory T cells show a delayed recruitment to the infected site. The new idea is to consider this time delay in our system and investigate its effects on the local and global behaviour of the solution.

Acknowledgments

This work is part of L. Boudjellal first year PhD program, under the support of CMAT Ph.D. fellowship UMINHO/BID/2021/116.

It is also partially supported by CoSysM3–2022.03091.PTDC from national funds (OE) through FCT/MCTES (<https://doi.org/10.54499/2022.03091.PTDC>) and by the Portuguese FCT Projects UIDB/00013/2020, UIDP/00013/2020

of CMAT-UM, UIDB/04106/2020, UIDP/04106/2020 of CIDMA-UA.

The authors acknowledge the fruitful discussions with Professor Ana Jacinta Soares, from the University of Minho, Portugal.

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