A NOTE ON THE QUALITATIVE BEHAVIOUR OF AN ODE MODEL RELATED TO ENDOTOXIN TOLERANCE

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The present paper analyses the qualitative behavior of a 2nd order differential equations system modeling the immune system response.

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1. Introduction

Endotoxin tolerance of the immune system has been a topic of major interest for over one decade ([1], [6], [7]). Appropriate mathematical models have been derived for studying the inflammation triggered by endotoxin release at different concentration levels ([3], [5], [8]).

In this paper, we consider the following ODE model for the dynamics of the endotoxin induced inflammatory response of the immune system:

$$\begin{aligned} \frac{\mathrm{d}x_1}{\mathrm{d}t} &= -x_1 + \frac{x_1^n + E_1^n}{x_1^n + 1}\,\frac{1}{F_1 x_2 + 1}\,A(t) \\ \frac{\mathrm{d}x_2}{\mathrm{d}t} &= -x_2 + \frac{x_2^m + E_2^m}{x_2^m + 1}\,A(t) \end{aligned} \tag{1}$$

Here x_1 is the concentration of TNF-α, x_2 represents the "brake effect" of the anti-inflammatory cytokines production, while $A(t)$ is the function standing for the concentration of endotoxin. The experimental data shows that $A(t) > 1$. The coefficients E_1, E_2 are the kinetic constants associated with the mass action rates of reaction and F_1 is the proportionality factor between the TNF-α and the break. All these coefficients are naturally strictly positive, $E_1, E_2 \in (0, 1)$, $F_1 \geq 1$.

The above system of differential equations is a typical enzymatic reaction model, under the Michaelis-Menten hypothesis ([2]).

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In this paper, we focus on the "brake effect" of the anti-inflammatory cytokines production, showing that it leads to a unique, biologically consistent steady-state point, under natural assumptions on the process coefficients. Furthermore, we discuss - based both on closed formulas and simulation results - how this effect influences the steady-state concentration of the TNF-α.

In this note, we shall discuss the case $n = 2$, $m = 1$.

2. The nature of the positive equilibrium

The Existence and Uniqueness Theorem can be applied to the Cauchy problem associated to (1), since the system has rational coefficients.

Subsequently we will show that the system (1) has a unique positive equlibrium point, which is asymptotically stable and a global attractor for the first quadrant.

We start by determining the positive equilibrium points for the ODE model (1). Under the assumption $A(t)$ is constant, $A > 1$, for a sufficiently large time horizon, the equilibria of the system are given by:

$$\begin{aligned} 0 &= -x_1 + \frac{x_1^2 + E_1^2}{x_1^2 + 1}\,\frac{1}{F_1 x_2 + 1}\,A \\ 0 &= -x_2 + \frac{x_2 + E_2}{x_2 + 1}\,A \end{aligned} \tag{2}$$

From the second equation in (2), we get

$$-x_2^2 + (A-1)x_2 + AE_2 = 0.$$

This quadratic equation has a unique positive solution,

$$\tilde{x}_2 \in (A-1\ ,\ A).$$

The first equation in (2) rewrites equivalently

$$-(F_1\tilde{x}_2 + 1)x_1^3 + Ax_1^2 - (F_1\tilde{x}_2 + 1)x_1 + AE_1^2 = 0$$

Let $f(x_1)$ denote the left-hand side of the above equation. Then, its derivative, $f^{'}$ is

$$f^{'}(x_1) = -3(F_1\tilde{x}_2 + 1)x_1^2 + 2Ax_1 - (F_1\tilde{x}_2 + 1). \tag{3}$$

One can show that $f^{'}(x_1) < 0$, since $\tilde{x}_2 \in (A-1\ ,\ A)$. Hence, f is strictly decreasing and the first equation in (2) has a unique real solution $\tilde{x}_1$. Moreover, the equilibrium point of the system (1) verifies

$$\tilde{x}_1 \in (0,1)\,, \quad \tilde{x}_2 \in (A-1, A). \tag{4}$$

With the considerations above, the next result follows.

Theorem 2.1. *The system (1) has a unique equilibrium point in the first quadrant* $\mathbf{R}_+^2$. *This equilibrium point is an asymptotically stable, global attractor in* $\mathbf{R}_+^2$.

Proof. The existence and uniqueness have been already proved. In order to study the stability, let the vector field $G : \mathbf{R}^2 \to \mathbf{R}^2$,

$$G(x_1, x_2) = \begin{bmatrix} G_1(x_1, x_2) \\ G_2(x_1, x_2) \end{bmatrix} = \begin{bmatrix} -x_1 + \dfrac{x_1^2 + E_1^2}{x_1^2 + 1} \dfrac{1}{F_1 x_2 + 1} A \\ -x_2 + \dfrac{x_2 + E_2}{x_2 + 1} A. \end{bmatrix}$$

Then its associated Jacobian matrix is defined by

$$J_G(x_1, x_2) = \begin{bmatrix} -1 + \dfrac{2x_1(1 - E_1^2)}{(x_1^2 + 1)^2 (F_1 x_2 + 1)} A & * \\ 0 & -1 + \dfrac{1 - E_2}{(x_2 + 1)^2} A. \end{bmatrix} \tag{5}$$

We now prove that, at the equilibrium point $(\tilde{x}_1, \tilde{x}_2)$, the eigenvalues of the Jacobian matrix - which are precisely its diagonal elements - are negative:

$$(\tilde{x}_1^2 + 1)^2 (F_1 \tilde{x}_2 + 1) > (\tilde{x}_1^2 + 1)^2 (\tilde{x}_2 + 1)(\tilde{x}_1^2 + 1)^2 A > 2\tilde{x}_1 (1 - E_1^2) A$$

and

$$\frac{1 - E_2}{(\tilde{x}_2 + 1)^2} A < \frac{1 - E_2}{A} < 1,$$

where we used $E_1, E_2 \in (0, 1)$, $F_1 > 1$, $A > 1$ and (4). Thus, according to standard Lyapunov stability theory [4], $(\tilde{x}_1, \tilde{x}_2)$ is an asymptotically stable equilibrium point.

It remains to show that $(\tilde{x}_1, \tilde{x}_2)$ is also a global attractor in the positive quadrant. Analyzing the sign of the function G_2 on the positive real axis, one can see that $G_2 > 0$ on $(0, \tilde{x}_2)$, while $G_2 < 0$ on $(\tilde{x}_2, \infty)$. Hence $\tilde{x}_2$ is an attractor on $\mathbf{R}_+$ (see, for instance, Chapter 1 in [4]).

By using the inequality $f'(x_1) < 0$, where f has been introduced in (3), and by invoking a similar argument as before by regarding now the sign of $G_1(x_, x_2)$, it results that $(\tilde{x}_1, \tilde{x}_2)$ is a global attractor on $\mathbf{R}_+^2$. □

The behavior described in Theorem is illustrated in Figure 1. The values picked up for the simulation are $A = 8$; $E1 = 0.7$, $E2 = 0.25$; $F1 = 5$, yielding the steady-state values emphasized in the graphic which stand for the equilibrium point: $\tilde{x}_1 = 0.1061$, $\tilde{x}_2 = 7.2749$.

3. **Conclusion**

For the proposed model (1) we proved the existence and uniqueness of the positive equilibrium and its stability - global attractor in $\mathbf{R}_+^2$.

As a main conclusion, for a constant endotoxin level $A(t)$ on a sufficiently large interval, the dynamic interaction *TNF-α — anti-inflammatory cytokines* has a single, biologically consistent, steady-state.

For a further research, one can consider other model parameters, such that $n = 3$ and/or $m = 2$.

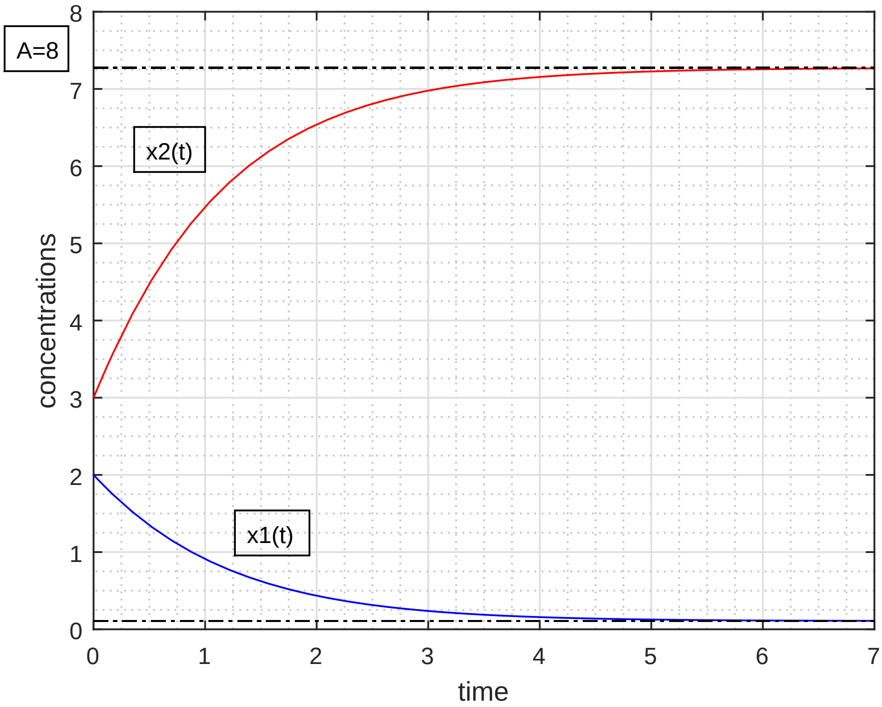

FIGURE 1. Time-domain evolution

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