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A Delayed Mathematical Model for the Acute Inflammatory Response to Infection

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Abstract: This paper deals with further developments on a mathematical model recently proposed for the modeling of the acute inflammatory response to infection or trauma. In particular in order to take into account that some interactions have not an immediate effect, we introduce time delays. Specifically the paper deals with the existence of steady states, determining the parameter regimes where the equilibrium points are stable, and the onset of Hopf bifurcation appears. Numerical simulations are performed with the main aim of supporting the analytical results and investigate further dynamics.

Keywords: Wound healing, Time delay, Hopf bifurcation, Asymptotic analysis, Fixed points

1 Introduction

The problem of abnormal organ repair has gained much attention considering that there is a significant shortage of organs available for transplantation. In this context the normal repair process, i.e. wound healing process, assumes an important role. Wound healing is an complex process by which the skin or organ repairs itself after injury [1,2]. Specifically wound healing comprises three sequential, overlapping, phases: the inflammation phase (hemostasis and the actual inflammation), the proliferation phase, and the maturation (remodeling) phase. Hemostasis occurs immediately after tissue injury and can be compared with the acute phase reaction of the innate immune system during infection. The first cells to appear in the wound area are neutrophils which start with the critical task of phagocytosis in order to destroy and remove bacteria, foreign particles and damaged tissue. Phagocytotic activity is crucial for the subsequent processes, because acute wounds that have a bacterial imbalance will not heal. The macrophage becomes the predominant inflammatory cell type in clean noninfected wounds. Every phase of the healing process consists of complex interactions between cells and mediators which tend to regulate the process. Cells participating in wound healing must be activated, i.e. undergo phenotypic alterations of cellular, biochemical, and functional properties.

During the inflamation phase, the immune system performs a fundamental action, see [3,4,5]. The response of the immune system to an infectious agent is subdivided into two main categories: Innate (non-specific) immunity response, which is mediated by granulocytes, macrophages, and NK cells [6]; Adaptive (specific, acquired) immune response, which is mediated by the lymphocytes [7]. The innate immune system is constitutively active and reacts immediately to infection. The adaptive immune response to an invading organism takes some time to develop.

Different mathematical models have been proposed for the modeling of immune system response [8,9]. Specifically mathematical models based on ordinary differential equations [10,11,12,13], partial differential equations [14,15], kinetic theory approach [16,17] and continuum mechanics approach [18]. In the pertinent literature computational models have been also proposed, see [19] and the review paper [20]. However the previous cited models are based on instantaneous interactions thus avoiding to take into account that various phenomena occur with some delay. In order to overcome this issue,

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delayed models have been proposed in population dynamics [21,22], in immunology [23,24], for tumor formation [25,26,27], for economic systems [28,29,30, 31] and specifically in the study of the Solow model [32, 33], of the Dalgaard-Strulik model [34], of the credi risk contagion [35], and in the asset of price [36]. The introduction of time delay allows to enrich the description of the dynamics of a system in particular by changing the stability of the steady state and triggering onset of Hopf bifurcation.

This paper is concerned with further investigations on a mathematical model recently proposed in [37] for the modeling of the acute inflammatory response to infection or trauma. In particular in order to take into account that some interactions have not an immediate effect, we introduce time delays. Specifically the paper deals with the existence of steady states, determining the parameter regimes where the fixed points are stable, and the onset of Hopf bifurcation appears. As known a steady state belongs to the nullclines of the system and it is stable if the real part of each eigenvalue associated with the linearized system at that fixed point is negative. A bifurcation occurs when a change in a parameter alters the number of fixed points and/or their stability.

The contents of the present paper are organized as follows. After this introduction, Section 2 is devoted to the mathematical analysis (existence of steady states and Hopf bifurcation) of the delayed pathogen equation, which shares various properties with the delayed model proposed in Section 3 which consists of a system of two delayed differential equations where the independent variables represent the levels of pathogen and the activated phagocytes (e.g. neutrophils); the model is built up from consideration of direct interactions of fundamental effectors and does not include components of the adaptive immune response, i.e. T-cells and specific antibodies. Numerical simulations are also performed within the Section 3 with the main aim of supporting the analytical results and investigating further nonlinear dynamics. Finally Section 4 is concerned with concluding remarks and further research perspectives.

2 The delayed pathogen equation

It is known that when an individual undergoes an injury, at the wound there exists a sentinel level of immune system cells (local immune response M) able to respond and remove local infections (pathogens P). According to [37] we assume that:

- M is inhibited at the rate k_{mp} when it interacts with P at time t;
- P is inhibited at the rate k_{pm} when it interacts with M at time t;
- s_m models a source of M;
- μ_m models the death of M.

Moreover we introduce a time delay $\tau \geq 0$ into the equation of P as follows:

$$\begin{cases} \dot{M} = s_m - \mu_m M - k_{mp} M P \\ \dot{P} = -k_{pm} M P_\tau \end{cases}$$

where $P_\tau = P(t-\tau)$. Bearing [37] in mind thus we have

$$\dot{P} = k_{pg} P \left(1 - \frac{P}{p_\infty}\right) - \frac{k_{pm} s_m P_\tau}{\mu_m + k_{mp} P}, \tag{1}$$

where k_{pg} is the pathogen growth rate and p_∞ is the carrying capacity of the pathogen population.
In what follows, the above parameters will be assumed nonnegative.

2.1 Steady states and stability analysis

The steady states of Eq. (1) are such that the time derivative $\dot{P}$ vanishes identically. It is immediate to see that the fixed points of Eq. (1) coincide with those for $\tau = 0$. In particular $P_* = 0$ is always a fixed point of Eq. (1). The other fixed points P_* are solution of the following algebraic equation:

$$k_{pg}\left(1 - \frac{P_*}{p_\infty}\right) - \frac{k_{pm} s_m}{\mu_m + k_{mp} P_*} = 0,$$

namely if

$$k_{pg} k_{mp} P_*^2 + k_{pg}\left(\mu_m - k_{mp} p_\infty\right) P_* +$$

$$p_\infty \left(k_{pm} s_m - k_{pg} \mu_m\right) = 0. \tag{2}$$

The discriminant of Eq. (2) reads

$$\Delta = k_{pg}\left[k_{pg}\left(\mu_m + k_{mp} p_\infty\right)^2 - 4 k_{mp} k_{pm} s_m p_\infty\right], \tag{3}$$

then Eq. (1) also admits the fixed point

$$P_* = \left(k_{mp} p_\infty - \mu_m\right)/2k_{mp}$$

if

$$k_{pg} = 4 k_{mp} k_{pm} s_m p_\infty / \left(p_\infty k_{mp} + \mu_m\right)^2,$$

and the fixed point $P_* = p_1$ and $P_* = p_2$, $p_1 < p_2$, with

$$P_* = \frac{k_{pg}\left(k_{mp} p_\infty - \mu_m\right) \pm \sqrt{\Delta}}{2 k_{pg} k_{mp}}$$

if $k_{pg} > 4 k_{mp} k_{pm} s_m p_\infty / \left(p_\infty k_{mp} + \mu_m\right)^2$.
In [37] Reynolds et al. have shown that $P_* = 0$ is stable for $k_{pg} < k_{pm} s_m / \mu_m$, and $P_* = p_2$ is stable whenever it exists. Henceforth, in what follows we will deal only with these two stable fixed points.

Bearing all above in mind, the linearized equation of Eq. (1) around one of these two stable fixed points P_* is

$$\dot{P} = a\,(P - P_*) + b\,(P_\tau - P_*)\,, \tag{4}$$

where if $P_* = 0$ we have

$$a = k_{pg} \quad \text{and} \quad b = -\frac{k_{pm} s_m}{\mu_m}$$

and if $P_* = \dfrac{k_{pg}\,(k_{mp} p_\infty - \mu_m) + \sqrt{\Delta}}{2 k_{pg} k_{mp}}$

$$a = k_{pg}\left[1 - \frac{2P_*}{p_\infty} + \left(1 - \frac{P_*}{p_\infty}\right)^2 \frac{k_{mp} k_{pg} P_*}{k_{pm} s_m}\right]$$

$$\text{and} \quad b = -k_{pg}\left(1 - \frac{P_*}{p_\infty}\right)$$

The associated characteristic equation of (4) reads

$$\lambda - a - b e^{-\lambda \tau} = 0. \tag{5}$$

It is well known that the fixed point P_* of Eq. (1) is locally asymptotically stable if each of the characteristic roots of Eq. (5) has negative real parts. Hence, the marginal stability is determined by the equations $\lambda = 0$ and $\lambda = i\omega$, $\omega > 0$. It is clear that the case $\lambda = 0$ cannot occur because $a + b < 0$. Let $\lambda = i\omega$ be a root of the characteristic equation (5) with $\omega > 0$. Substituting it into (5) and separating the real and imaginary parts yields

$$a = -b\cos\omega\tau, \quad \omega = -b\sin\omega\tau. \tag{6}$$

Squaring each equation in (6), taking the sum and employing $\sin^2\omega\tau + \cos^2\omega\tau = 1$, we have

$$\omega^2 = b^2 - a^2. \tag{7}$$

It is easy to see that Eq. (7) has one positive solution

$$\omega_0 = \sqrt{b^2 - a^2}$$

if $|b| > |a|$. From (6), one can obtain the value τ_0 corresponding to ω_0 as follows:

$$\tau_0 = \begin{cases} \dfrac{1}{\omega_0}\tan^{-1}\left(\dfrac{\omega_0}{a}\right), & \text{if } a > 0, \\ \dfrac{1}{\omega_0}\tan^{-1}\left(\dfrac{\omega_0}{a}\right) + 2\pi, & \text{if } a < 0. \end{cases}$$

One can also see that the purely imaginary root $i\omega_0$ is simple. If we suppose by contradiction $\lambda = i\omega_0$ to be a repeated root of (5), then differentiating (5) with respect to λ, inserting $\lambda = i\omega_0$, and using (5), leads to $\omega_0 = 0$, which gives a contradiction.

2.2 On the Hopf bifurcation

The conditions under which a Hopf bifurcation occurs at τ_0 are verified except for the transversality condition. Let $\lambda(\tau)$ be the root of (5) near $\tau = \tau_0$ such that $\mathrm{Re}(\lambda(\tau_0)) = 0$ and $\mathrm{Im}(\lambda(\tau_0)) = \omega_0$. Differentiating both sides of Eq. (5) with respect to τ, we have

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = -\frac{1}{\lambda(\lambda - a)} - \frac{\tau}{\lambda}.$$

Thus, we obtain

$$\begin{aligned} sign\left\{\left.\frac{d\,(Re\lambda)}{d\tau}\right|_{\substack{\tau=\tau_0 \\ \omega=\omega_0}}\right\} &= sign\left\{Re\left(\frac{d\lambda}{d\tau}\right)^{-1}_{\substack{\tau=\tau_0 \\ \omega=\omega_0}}\right\} \\ &= sign\left\{\frac{1}{\omega_0^2 + a^2}\right\}. \end{aligned} \tag{8}$$

Since the sign of (8) is positive, when $\lambda = i\omega_0$, the only crossing of the imaginary axis is from left to right as τ increases. Consequently, the stability of the steady state P_* can only be lost and not regained.

Bearing all the above analysis in mind, we can state the main result of this section.

Theorem 1. *Let Δ be defined by Eq. (3).*

1) *If $k_{pg} < k_{pm} s_m / \mu_m$, then the steady state $P_* = 0$ of Eq. (1) is locally asymptotically stable for $\tau < \tau_0$ and unstable for $\tau > \tau_0$, where*

$$\tau_0 = \frac{1}{\omega_0}\tan^{-1}\left(\frac{\omega_0}{k_{pg}}\right), \quad \omega_0 = \sqrt{\left(\frac{k_{pm} s_m}{\mu_m}\right)^2 - k_{pg}^2}.$$

Furthermore, Eq. (1) undergoes a Hopf bifurcation at $P_* = 0$ when $\tau = \tau_0$.

2) *If $k_{pg} > 4 k_{mp} k_{pm} s_m p_\infty / (p_\infty k_{mp} + \mu_m)^2$ and*

$$1 - \frac{P_*}{p_\infty} > \left|1 - \frac{2P_*}{p_\infty} + \left(1 - \frac{P_*}{p_\infty}\right)^2 \frac{k_{mp} k_{pg} P_*}{k_{pm} s_m}\right|,$$

the steady state

$$P_* = p_2 = \left[k_{pg}\,(k_{mp} p_\infty - \mu_m) + \sqrt{\Delta}\right] / 2 k_{pg} k_{mp}$$

of Eq. (1) is locally asymptotically stable for $\tau < \tau_0$ and unstable for $\tau > \tau_0$, where

$$\tau_0 = \begin{cases} \dfrac{1}{\omega_0}\tan^{-1}\tilde{\tau}_0, & \text{if } \alpha > 0, \\ \dfrac{1}{\omega_0}\tan^{-1}\tilde{\tau}_0 + 2\pi, & \text{if } \alpha < 0, \end{cases}$$

and

$$\tilde{\tau}_0 = \frac{\omega_0}{k_{pg}\left[1 - \dfrac{2P_*}{p_\infty} + \left(1 - \dfrac{P_*}{p_\infty}\right)^2 \dfrac{k_{mp} k_{pg} P_*}{k_{pm} s_m}\right]},$$

$$\alpha = 1 - \frac{2P_*}{p_\infty} + \left(1 - \frac{P_*}{p_\infty}\right)^2 \frac{k_{mp}k_{pg}P_*}{k_{pm}s_m},$$

$$\omega_0 = k_{pg}\sqrt{\left(1 - \frac{P_*}{p_\infty}\right)^2 - \alpha^2}.$$

Furthermore, Eq. (1) *undergoes a Hopf bifurcation at* $P_* = p_2$ *when* $\tau = \tau_0$.

3 The delayed model with the immune system response

In this section we couple the pathogen equation analyzed in the previous section with the role of phagocytic immune system cells (neutrophils and macrophages). Bearing paper [37] in mind, we modify the model proposed in [37] by introducing two time delays $\tau_1 \geq 0$ and $\tau_2 \geq 0$ as follows:

$$\dot{P} = k_{pg}P\left(1 - \frac{P}{p_\infty}\right) - \frac{k_{pm}s_m P_{\tau_1}}{\mu_m + k_{mp}P} - k_{pn}N^*P, \qquad (9)$$

$$\dot{N^*} = \frac{s_{nr}\left(k_{nn}N^*_{\tau_2} + k_{np}P_{\tau_2}\right)}{\mu_{nr} + \left(k_{nn}N^* + k_{np}P\right)} - \mu_n N^*, \qquad (10)$$

where P and N^* represent the levels of pathogen and activated phagocytes, respectively and

- k_{pn} is the rate at which N^* consume P;
- s_{nr} is the source of resting phagocytes;
- μ_{nr} is the decay rate of resting phagocytes;
- k_{nn} is the activation of resting phagocytes by previously activated phagocytes and their cytokines;
- μ_n is the decay rate of activated phagocytes;
- k_{np} is the activation rate of resting phagocytes by pa thogen.

It is worth stressing that with respect paper [37], the above model is derived by considering the delayed equations $\dot{P} = -k_{pm}MP_{\tau_1}$ and $\dot{N^*} = \left(k_{nn}N^* + k_{np}P\right)_{\tau_2} N_R - \mu_n N^*$, where N_R is the population of the resting phagocytes.

3.1 Steady states and stability analysis

The steady states of system (9)-(10) are obtained by setting $\dot{P} = \dot{N^*} = 0$, $P_{\tau_1} = P$ and $N^*_{\tau_2} = N^*$ for all t. Therefore, when there is no time delay, i.e. $\tau_1 = \tau_2 = 0$, we recover the model considered in Section 2.2 of paper [37], and in particular there exists the fixed point $(P, N^*) = (0,0)$ (health steady state). It is important to note that the delayed model admits also a steady state $(P, N^*) \neq (0,0)$ which represents the inflammation steady state (septic death state); this state will be analyzed in the next subsection by performing numerical simulations.

Linearization of system (9)-(10) in the neighborhood of the trivial steady state produces the system

$$\dot{P} = k_{pg}P - \frac{k_{pm}s_m}{\mu_m}P_{\tau_1},$$

$$\dot{N^*} = -\mu_n N^* + \frac{s_{nr}k_{np}}{\mu_{nr}}P_{\tau_2} + \frac{s_{nr}k_{nn}}{\mu_{nr}}N^*_{\tau_2}.$$

So the associated characteristic equation is given by

$$\begin{vmatrix} k_{pg} - \lambda - \dfrac{k_{pm}s_m}{\mu_m}e^{-\lambda\tau_1} & 0 \\ \dfrac{s_{nr}k_{np}}{\mu_{nr}}e^{-\lambda\tau_2} & -\mu_n - \lambda + \dfrac{s_{nr}k_{nn}}{\mu_{nr}}e^{-\lambda\tau_2} \end{vmatrix} = 0,$$

namely

$$D(\lambda, \tau_1, \tau_2) \equiv D_1(\lambda, \tau_1) \cdot D_2(\lambda, \tau_2) = 0, \qquad (11)$$

where

$$D_1(\lambda, \tau_1) = \lambda - k_{pg} + \frac{k_{pm}s_m}{\mu_m}e^{-\lambda\tau_1},$$

$$D_2(\lambda, \tau_2) = \lambda + \mu_n - \frac{s_{nr}k_{nn}}{\mu_{nr}}e^{-\lambda\tau_2}.$$

It is known from [37] that, when $\tau_1 = \tau_2 = 0$, the corresponding eigenvalues of (11) are real and given by $\lambda = (k_{pg}\mu_m - k_{pm}s_m)/\mu_m$ and $\lambda = (s_{nr}k_{nn} - \mu_n\mu_{nr})/\mu_{nr}$. In what follows we assume that the inequality $s_{nr}k_{nn} < \mu_n\mu_{nr}$ holds true. Consequently, in absence of delays, the steady state $(0,0)$ of system (9)-(10) is locally asymptotically stable if $k_{pg} < k_{pm}s_m/\mu_m$.

Letting the time delays τ_1 and τ_2 varied, the trivial fixed point of system (9)-(10) may lose its stability. In order to consider the effects of the time delay, we need to investigate the boundary of the stability region determined by the equations $\lambda = 0$ and $\lambda = i\omega$ $(\omega > 0)$. Letting $\lambda = 0$ in (11), one has that $D(0, \tau_1, \tau_2) \neq 0$ having assumed that $k_{pg}\mu_m - k_{pm}s_m < 0$. Thus, only the case $\lambda = i\omega$ $(\omega > 0)$ needs to be analyzed.

3.1.1 Case $\tau_1 > 0$ and $\tau_2 = 0$

Eq. (11) becomes $D(\lambda, \tau_1, 0) \equiv D_1(\lambda, \tau_1) \cdot D_2(\lambda, 0) = 0$. Let $\lambda = i\omega$ $(\omega > 0)$ be a root of $D(\lambda, \tau_1, 0) = 0$. Since $D_2(i\omega, 0) \neq 0$, $\lambda = i\omega$ has to solve $D_1(\lambda, \tau_1) \equiv \lambda - k_{pg} + (k_{pm}s_m/\mu_m)e^{-\lambda\tau_1} = 0$, i.e. $D_1(i\omega, \tau_1) = 0$. Setting $a = k_{pg}$, $b = -k_{pm}s_m/\mu_m$ and $\tau = \tau_1$, we note that this equation writes as $\lambda - a - be^{-\lambda\tau} = 0$, which is Eq. (5). According to the analysis performed in the previous section, the following result holds.

Proposition 1.*Let $\tau_1 > 0$, $\tau_2 = 0$ and $k_{pg} < k_{pm}s_m/\mu_m$. The steady state $(P,N^*) = (0,0)$ of system (9)-(10) is locally asymptotically stable for $\tau_1 < \tau_0^1$ and unstable for $\tau_1 > \tau_0^1$, where*

$$\tau_0^1 = \frac{1}{\omega_0}\tan^{-1}\left(\frac{\omega_0}{k_{pg}}\right) \quad \text{and} \quad \omega_0 = \sqrt{\left(\frac{k_{pm}s_m}{\mu_m}\right)^2 - k_{pg}^2}.$$

If $\tau_1 = \tau_0^1$ then the system (9)-(10) undergoes a Hopf bifurcation at $(P,N^*) = (0,0)$.

3.1.2 Case $\tau_1 = 0$ and $\tau_2 > 0$

In this case, Eq. (11) is $D(\lambda,0,\tau_2) \equiv D_1(\lambda,0)\cdot D_2(\lambda,\tau_2) = 0$. If $\lambda = i\omega$ $(\omega > 0)$ is a root of $D(\lambda,0,\tau_2) = 0$, then, being $D_1(i\omega,0) \neq 0$, we conclude that $\lambda = i\omega$ is a solution of $D_2(\lambda,\tau_2) \equiv \lambda + \mu_n - (s_{nr}k_{nn}/\mu_{nr})e^{-\lambda\tau_2} = 0$, i.e. $D_2(i\omega,\tau_2) = 0$. Again, we can use Eq. (5) but with $a = -\mu_n$, $b = s_{nr}k_{nn}/\mu_{nr}$ and $\tau = \tau_2$. Contrary to the previous case, we find that the condition $|b| > |a|$ is not satisfied. The fact there is not purely imaginary root satisfying $D(i\omega,0,\tau_2) = 0$ leads to the following result.

Proposition 2.*Let $\tau_1 = 0$, $\tau_2 > 0$. Then the steady state $(P,N^*) = (0,0)$ of system (9)-(10) is locally asymptotically stable.*

3.1.3 Case $\tau_1 > 0$ and τ_2 fixed in its stable interval

We now consider Eq. (11) with τ_2 in its interval of stability, regarding τ_1 as a parameter. Let $\lambda = i\omega$ $(\omega > 0)$ be a root of (11). Then, $D_1(i\omega,\tau_1)\cdot D_2(i\omega,\tau_2) = 0$. From the previous subsection, one has that $D_2(i\omega,\tau_2) \neq 0$, so that we must have $D_1(i\omega,\tau_1) = 0$. It is now straighforward that previous arguments imply the following result.

Proposition 3.*Let $\tau_1 > 0$, $\tau_2 > 0$ and $k_{pg} < k_{pm}s_m/\mu_m$. The steady state $(P,N^*) = (0,0)$ of system (9)-(10) is locally asymptotically stable for $\tau_1 < \tau_0^1$ and unstable for $\tau_1 > \tau_0^1$, where*

$$\tau_0^1 = \frac{1}{\omega_0}\tan^{-1}\left(\frac{\omega_0}{k_{pg}}\right) \quad \text{and} \quad \omega_0 = \sqrt{\left(\frac{k_{pm}s_m}{\mu_m}\right)^2 - k_{pg}^2}.$$

If $\tau_1 = \tau_0^1$ then system (9)-(10) undergoes a Hopf bifurcation at $(P,N^*) = (0,0)$.

3.1.4 Case τ_1 fixed in its stable interval and $\tau_2 > 0$

This case states that τ_1 is in its stable interval $[0,\tau_0^1)$ and τ_2 is regarded as a parameter. Assume that Eq. (11) has purely imaginary solution of the form $\lambda = i\omega$ $(\omega > 0)$. Then it can be seen that $D_1(i\omega,\tau_1) \neq 0$ since $\tau_1 \in [0,\tau_0^1)$ and $D_2(i\omega,\tau_2) \neq 0$. Consequently, we have the following result.

Proposition 4.*Let $\tau_1 \in [0,\tau_0^1)$, $\tau_2 > 0$ and $k_{pg} < k_{pm}s_m/\mu_m$. Then the steady state $(P,N^*) = (0,0)$ of system (9)-(10) is locally asymptotically stable for $\tau_2 > 0$.*

3.1.5 Case $\tau_1 = \tau_2 = \tau$

Eq. (11) becomes $D(\lambda,\tau) \equiv D_1(\lambda,\tau)\cdot D_2(\lambda,\tau) = 0$. Once again, if $\lambda = i\omega$ $(\omega > 0)$ is such that $D(i\omega,\tau) = 0$, we have that $D_1(i\omega,\tau) = 0$. Applying the analysis of previous subsections, we obtain conditions under which a family of periodic solutions bifurcate from the trivial equilibrium.

Proposition 5.*Let $k_{pg} < k_{pm}s_m/\mu_m$. There exists $\tau_0 > 0$ given by*

$$\tau_0 = \frac{1}{\omega_0}\tan^{-1}\left(\frac{\omega_0}{k_{pg}}\right) \quad \text{and} \quad \omega_0 = \sqrt{\left(\frac{k_{pm}s_m}{\mu_m}\right)^2 - k_{pg}^2}.$$

such that the steady state $(P,N^*) = (0,0)$ of system (9)-(10) is locally asymptotically stable for $\tau < \tau_0$ and unstable for $\tau > \tau_0$. Moreover, for $\tau = \tau_0$, the Hopf bifurcation occurs at $(P,N^*) = (0,0)$.

3.2 Numerical investigations

This section is devoted to further investigations on the model (9)-(10). Specifically by employing numerical solutions we perform the stability analysis and we investigate on the existence of Hopf bifurcation in the other fixed point (P,N^*) of the model (9)-(10) where analytical results have not been reported. Accordingly we perform a sensitivity analysis on the time delays τ_1 and τ_2.

The stability analysis is performed by considering a specific model and in order to compare our model with the model proposed in [37], we set the parameters of the delayed model (9)-(10) as follows:

$$\begin{aligned} &p_\infty = 20\times10^6, k_{pm} = 0.6, s_m = 0.005,\\ &\mu_m = 0.002, k_{mp} = 0.01, k_{pg} = 2.95,\\ &s_{nr} = 0.08, k_{nn} = 0.01, k_{np} = 0.1,\\ &\mu_{nr} = 0.12, k_{nn} = 0.01, k_{np} = 0.1, \mu_n = 0.05. \end{aligned}$$

The first step is to compute the fixed points. As known, the steady states are points where the nullclines intersect. As Figure 1 shows we have two different steady states: the fixed point $E_0 = (0,0)$ whose stability analysis has been performed in the previous section and the fixed point $E_1 = (5\times10^5, 1.6)$. In what follows the numerical investigations focus on the stability analysis of the fixed point E_1.

The first set of simulations refers to the case $\tau_1 = \tau_2 = \tau$. Letting τ varied, we have found that a Hopf bifurcation occurs at $\overline{\tau} = 0.83358$. Indeed as Figure 2 shows, if $\tau < \overline{\tau}$ the fixed point E_1 is asymptotically stable and if $\tau > \overline{\tau}$ the

fixed point E_1 is unstable (the numerical solutions has been obtained for a set of initial conditions near the fixed point E_1). It is worth stressing that in the previous section we have proved analytically that the fixed point E_0 undergoes a Hopf bifurcation.

This set of simulations is susceptible of biological interpretation. Indeed in the equations of P and N^* at time t we have introduced also the role of these cells at time $t-\tau$ in order to take into account different stage of activation. Differently from [37], our results show how it is important during the interactions to take care of the time at which the cells are activated. According to Figure 2, if at time t we have also cells whose activation stage is that at time $t-\tau$, with $\tau < \bar{\tau}$, the system will reach the septic death; if at time t we consider cells whose activation stage is that at time $t-\tau$, with $\tau > \bar{\tau}$, the system can reach the health stage (remember that in this case also the steady state E_0 undergoes a Hopf bifurcation).

The second set of numerical investigations refers to the case $\tau_1 = 0$ and $\tau_2 \geq 0$. As Figure 3 shows, for a set of initial conditions near the fixed point E_1, when $\tau_2 < \bar{\tau}$ the fixed point E_1 is always locally asymptotically stable; for $\tau_2 > \bar{\tau}$ the fixed point E_1 is unstable (in particular the origin is always asymptotically stable as already proved in the previous section). This set of results shows again how the time delay influences the asymptotic behavior of the system: health state or septic death. In the third case, namely when $\tau_1 \geq 0$ and $\tau_2 = 0$, our numerical results show that the fixed point E_1 is always asymptotically stable.

The last set of numerical simulations refers to the sensitivity analysis with respect the parameter k_{pg} and in the case $\tau_1 = \tau_2 = \tau$. In the case $\tau = 0.4$, the Figure 4 shows that for $k_{pg} = 2.7$ the system reaches the steady state E_0 and for $k_{pg} = 2.95$ the system reaches the steady state E_1.

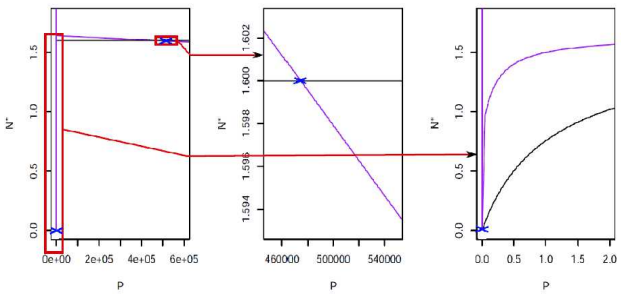

Fig. 1: In the left panel the nullclines of the pathogen (purple line) and of the activated phagocytes (black line). Zooming of the regions where there are the steady states: $E_1 = (5 \times 10^5, 1.6)$ (center panel) and $E_0 = (0,0)$ (right panel).

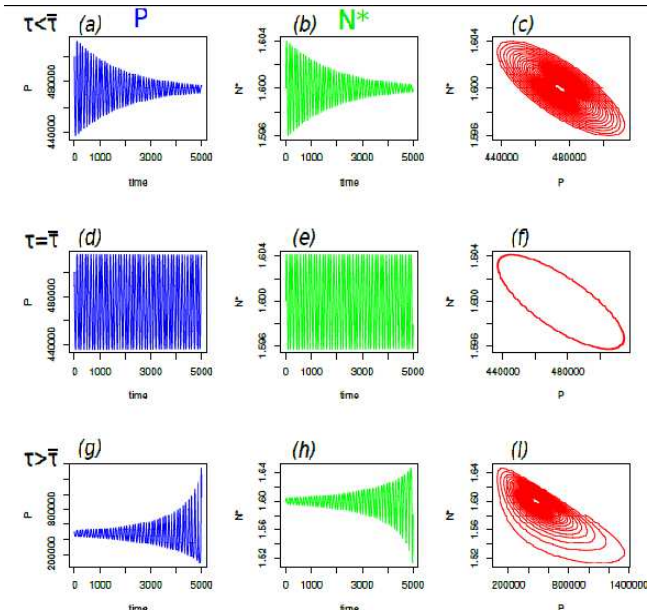

Fig. 2: Numerical solutions of the delayed model (9)-(10) in the case $\tau_1 = \tau_2 = \tau$ and with initial conditions near the steady state $E_1 = (5 \times 10^5, 1.6)$. The first column (a), (b) and (c) shows the time evolution of P (blue line), the second column (b), (e) and (h) shows the time evolution of N^* (green line), the third column (c), (f) and (i) shows the associated phase space diagram of the delayed N^*/P system (red line).

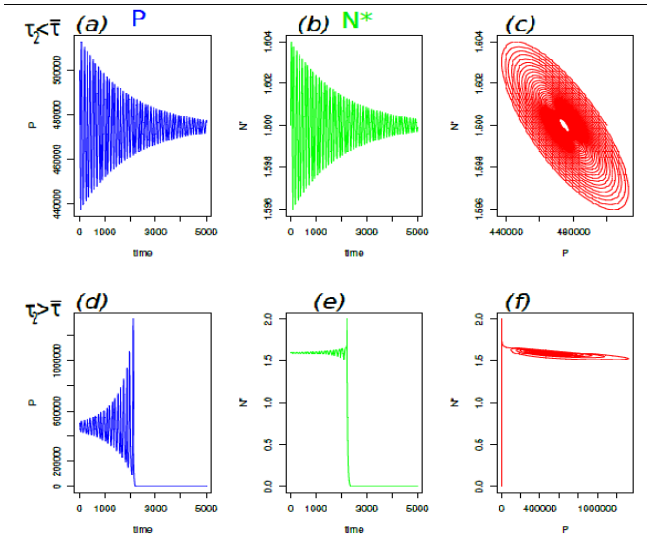

Fig. 3: Numerical solutions of the delayed model (9)-(10) in the case $\tau_1 = 0$ and $\tau_2 \geqslant 0$, and with initial conditions near the steady state $E_1 = (50 \times 10^6, 1.6)$. The first column (a) and (d) shows the time evolution of P (blue line), the second column (b) and (e) shows the time evolution of N^* (green line), the third column (c) and (f) shows the associated phase space diagram of the delayed N^*/P system (red line).

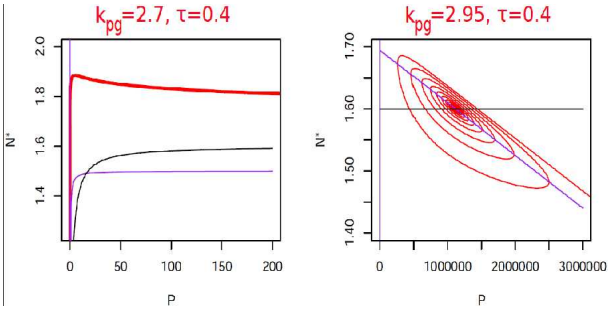

Fig. 4: Phase space diagram of the delayed model (9)-(10) in the case $\tau_1 = \tau_2 = \tau = 0.4$. For $k_{pg} = 2.7$ the system reaches the steady state E_0 (left panel) and for $k_{pg} = 2.95$ the system reaches the steady state E_1 (right panel). The pathogen nullclines are in purple line and the activated phagocytes nullclines are in black line.

4 Conclusions and future perspective

The present paper has been devoted to generalize the mathematical model developed in [37] by inserting two time delays in order to take into account cells with different stage of activation. The asymptotic analysis has been concerned with the stability analysis of the steady states and the sufficient conditions under which a Hopf bifurcation occurs. The analysis has shown how time delays can influence the whole dynamics and in particular the stability of the steady state.

In particular the numerical results and the bifurcation analysis suggest that the magnitude of the time delay plays several important roles in the restoration of health.

It is worth stressing that the biological relevance of the analysis performed in the present paper and the related conclusions are limited by the simplifications present in the proposed delayed model. Therefore the development of a much larger model that is also able to reproduce experimental data is object of future investigations.

Research directions include the derivation of an explicit algorithm for determining the direction of the Hopf bifurcation and the stability of the bifurcating periodic solutions. This step can be pursued by employing the center manifold theory and the normal form method [38]. Further research directions include generalizations of the delayed model proposed in the present paper, which takes into account tissue damage and anti-inflammatory mediators such as cortisol and interleukin-10. Moreover the introduction of the adaptive branch of the immune system is object of further investigations.

Finally the derivation of a mathematical model for the acute inflammatory response to infection based on the thermostatted kinetic theory [39,40] is part of future research perspective.

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