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Nonlinear Models for the Delayed Immune Response to a Viral Infection

Iram Gleria[1] · Adhemar Ranciaro Neto[2] · Askery Canabarro[3]

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Abstract We analyze ordinary differential equations modeling systems of biological interest. We focus on analytical properties of delayed equations that simulate the dynamics between cells of the immune system and a target population. We present the basic features of the linear stability analysis in delayed equations. New analytical results in a four-dimensional system are presented, as well as an analysis of a two-dimensional model.

Keywords Dynamical systems · Mathematical biology · Delayed systems

1 Introduction

In this work. we consider models of ordinary differential equations (ODE) that simulate the dynamics of infectious diseases. The interactions between populations of viruses and the immune system cells are highly non-linear and the details are often unknown. Due introduce to this fact, several ODE models have been proposed, focusing on different aspects of such interactions, aiming the description of the essential features of the problem. Usually, the focus is on the time evolution of the populations of infected and non-infected cells, viruses (sometimes bacteria or other foreign pathogens), and cells of the immune system such as cytotoxic T lymphocytes cells (CTLs), killer cells, antibodies, etc. [1]. If the objective is to replicate empirical data, the use of complex and high-dimensional nonlinear models is mandatory [3]. Unfortunately, there are strong difficulties concerning the estimation of the (several) parameters introduced and the meaning of all the nonlinear interactions proposed. A good alternative is to analyze low-dimensional models and search for those capable of describe the main properties of the immunological system with as few parameters as possible.

Regular one- and two-dimensional systems of ODEs cannot display complex behavior such as chaotic orbits, which are often observed in empirical data [5]. This is the reason why most authors consider models with at least three dimensions. However, even one- and two-dimensional systems may present chaotic behavior through the introduction of time delays. Delayed equations appears in several kinds of problems. To cite a few, in [6], the authors describe continuous deformations in periodic solutions of the one-dimensional Mackey–Glass equation, a standard model for delayed feedback systems [7]. In [8], it is analyzed self-pulsations in laser beams with feedback. Reference [9] considers sigmoid maps, which display a locking behavior observed in several systems, and its relation with the Stern-Brocot tree, a binary tree whose vertices correspond to the positive rational numbers [10, 11]. In [12], some of the authors analyzed the emergence of modulation instability in a lossless fiber with a finite (non-instantaneous) nonlinear response time. In [13], some of the authors analyzed a two-dimensional delayed model for the dynamics of

✉ Iram Gleria
iram@fis.ufal.br

[1] Institute of Physics, Federal University of Alagoas, Alagoas, Brazil

[2] Department of Economics, FEAC, Federal University of Alagoas, Alagoas, Brazil

[3] Center for Polymer Studies and Department of Physics, Boston University, 590 Commonwealth Avenue, Boston, MA, USA

immune cells and a foreign pathogen. The model is based on a previous one proposed in [14, 15] and is given by:

$$\begin{aligned}\dot{T} &= rT - bT^2 - kTE,\\ \dot{E} &= \frac{pT(t-\tau_1)}{1+T(t-\tau_1)^a} + \frac{sE(t-\tau_2)}{1+E(t-\tau_2)} - E,\ a = 1, 2,\end{aligned} \quad (1)$$

where E denotes the concentration of immune cells and T is the population of virus or bacteria. In the first equation, the term $r > 0$ is the reproduction rate and $k > 0$ the efficiency of the immune system in eliminating the virus. The last term is a death rate term b. For the dynamics of E, the first term represents the speed of the processes triggered by T leading to their elimination. The second term represents the auto catalytic effect of immune responses and $-E$ represents a death rate term. In [13], we presented analytical results for $b = 0$, $a = 1$, and several numeric simulations for the case for $a = 2, b \neq 0$, which presents a series of bifurcations evolving to a chaotic regime.

In [16], we analyze a four-dimensional model based in a previous one introduced by Nowak et al. [1], aiming to simulate HIV and SIV (the simian counterpart of HIV) epidemics, and which also apply to hepatitis B (HBV). The Nowak et al. model considers the dynamics of non-infected cells x, infected cells y, and virus load v as follows:

$$\begin{aligned}\dot{x} &= \lambda^* - dx - \beta xy,\\ \dot{y} &= \beta xy - ay,\\ \dot{v} &= ky - uv.\end{aligned} \quad (2)$$

Several three-dimensional models related to (2) are found in literature. We cite as example [2] in which the authors analyze the global stability of three-dimensional models of within-host viral infections of target cells, focusing in the models provided by Nowak and May [1] and Perelson and Nelson [4]. In [17], they analyzed an HIV infection model with time delay due to the CTL immune response. In [18], they also analyzed an HIV-1 infection model and the CTL immune response is investigated. They considered an eclipse stage for the infected cells such that a portion of these cells is reverted to uninfected cells. Ref. [19] studied a viral infection model with delayed immune response. He determined the global stability of the infection-free equilibrium and the local stability of the chronic infection equilibrium. Ref. [20] analyzed oscillations and chaotic behavior triggered by delayed immune response and [21] the dynamics of a model with delayed CTL response and immune circadian rhythm was considered.

Delayed responses are essential for a good description of the immune system as the stimulation generating CTLs need a delay τ, such that the response in time t is a function of the concentration of antigens in time $t-\tau$. We used this fact in [16] to generalize (2), where some of the authors analyzed the following four-dimensional model:

$$\begin{aligned}\dot{x} &= \lambda^* - dx - \beta xy,\\ \dot{y} &= = \beta xv - ay - pyz,\\ \dot{v} &= ky - \beta xv - \mu v,\\ \dot{z}(t) &= cy(t-\tau_1)z(t-\tau_2) - bz(t).\end{aligned} \quad (3)$$

with z the population of the immune competence. In [16], we analyzed (3) numerically, observing a series of bifurcations leading to chaotic behavior that depends upon the value of $\tau_1 = \tau_2 \equiv \tau$, evolving towards a chaotic behavior.

In this paper, we propose an analytical analysis of some ODE models. We consider a two-dimensional model and revisit (3), focusing in analytical properties concerning the stability of its fixed points. Analytical properties of delayed ODEs are hard to determine, and most of the literature focus on numeric solutions, obtained with the help of well-known procedures such as the Runge–Kutta method. The numeric approach is also useful when considering models with partial derivatives, see for example [22] where the authors considered a spatial epidemic model with noise and pattern formation. When we consider time delays, even a linear stability analysis may be cumbersome to implement, as we show in next section. However, many useful informations are obtained from analytical methods; we cite for example the extensive analysis of Nowak [1] and Perelson and May [3].

The objective of this paper is twofold: present novel analytical results in previously studied models and introduce the reader to the difficulties arising in the analysis of ODEs when we consider delayed responses.

The rest of this paper is organized as follows: Section (2) presents a delayed nonlinear two dimensional model and a brief overview of stability analysis in the presence of delays. Section (3) presents novel analytical results for (3). Section (4) concludes.

2 Two-Dimensional Model

Let us propose simple model where the virus population is controlled by the immune system:

$$\begin{aligned}\dot{x} &= rx - \rho xz,\\ \dot{z}(t) &= cx(t-\tau)z - bz,\end{aligned} \quad (4)$$

with x the concentration of virus and z the concentration of the cells of the immune response. The immune system is stimulated by a delayed term proportional to the abundance

of virus $cx(t-\tau)z$. In the absence of the immune competence ($\rho = 0$), the virus populations grows exponentially with rate r. The immune system removes the virus with rate ρxz and they die with rate bz. The system (4) with $\tau = 0$ was originally proposed by [1]. Typical parameter values are $r \approx 50$, $\rho \approx 0.005$, $b \approx 0.01$, $c \approx 0.005$ [1, 16]. With these values the time unit becomes roughly one day.

Before analyzing this system, let us first consider a general linear system with delays. Denote y a n dimensional vector and consider the dynamics of the following linear system:

$$\dot{y}(t) = \sum_{j=1}^{m} A_j y(t-\tau_j), \tag{5}$$

where each A_j is a $n \times n$ matrix and there are m matrices. Let us suppose a solution of the form $y(t) = e^{\lambda t}\chi$, with constant χ:

$$\left(\lambda I - \sum_{j=1}^{m} A_j e^{-\lambda\tau_j}\right)\chi = 0. \tag{6}$$

Non trivial solutions $\chi \neq 0$ exist if

$$det\left(\lambda I - \sum_{j=1}^{m} A_j e^{-\lambda\tau_j}\right) = 0. \tag{7}$$

The value of λ thus determine the stability of the solutions. If all solutions have negative real part, the solution is asymptotically stable, being unstable if there is at least one solution with positive real part. It is not an easy task to determine such conditions when $\tau \neq 0$. This happens because (4) has infinity complex solutions when $\tau \neq 0$, a consequence of the Picard theorem, which states that, in the neighborhood of an essential singularity $z = a$, the complex function $f(z)$ assumes infinite times any given complex value, except, maybe, some particular value [23]. In spite of the infinity number of solutions, the stability is always determined by a finite number of them. This follows from the following theorem:

Theorem *Given a real number ρ, (7) has a finite number of solutions λ such that $Re\lambda \geq \rho$.*

Bifurcations take place whenever the solution λ crosses the imaginary axis or one or more parameters are altered. Often a turning point, bifurcation occur if λ is real and a Hopf bifurcation if we have a pair of complex conjugated solutions. The Hopf bifurcation theorem was not demonstrated for retarded systems but it is considered as a valid conjecture [24].

Given a non-linear n dimensional system with m delays its stability can be analyzed through the usual linearization procedure around the equilibrium point. Let:

$$\begin{aligned}
\dot{x}_1 &= \sum_{j=1}^{m} f_j^1\left(x_1(t-\tau_j), x_2(t-\tau_j), \cdots\right), \\
&\vdots \\
\dot{x}_n &= \sum_{j=1}^{m} f_j^n\left(x_1(t-\tau_j), x_2(t-\tau_j), \cdots\right).
\end{aligned} \tag{8}$$

We linearize the system around its fixed point $x^* = (x_1^*, x_2^*, \cdots)$ and obtain the Jacobian:

$$\begin{aligned}
\dot{x}_1 &\approx \sum_{j=1}^{m}\left(f_j^1(x_1,\cdots)|_{x^*} + \frac{\partial f_j^1}{\partial x_1}|_{x^*}(x_1(t-\tau_j) - x_1^*)\right. \\
&\quad \left. + \frac{\partial f_j^1}{\partial x_2}|_{x^*}(x_2(t-\tau_j) - x_2^*) + \cdots\right), \\
&\vdots \\
\dot{x}_n &\approx \sum_{j=1}^{m}\left(f_j^n(x_1,\cdots)|_{x^*} + \frac{\partial f_j^n}{\partial x_1}|_{x^*}(x_1(t-\tau_j) - x_1^*)\right. \\
&\quad \left. + \frac{\partial f_j^n}{\partial x_2}|_{x^*}(x_2(t-\tau_j) - x_2^*) + \cdots\right).
\end{aligned} \tag{9}$$

This is a linear system in the variables $y_i \equiv x_i - x_i^*$ with m Jacobian matrices evaluated at the fixed point:

$$A_j = \begin{bmatrix} \frac{\partial f_j^1}{\partial x_1} & \frac{\partial f_j^1}{\partial x_2} & \cdots \\ \vdots & \vdots & \vdots \\ \frac{\partial f_j^n}{\partial x_1} & \frac{\partial f_j^n}{\partial x_2} & \cdots \end{bmatrix}. \tag{10}$$

Let us return to our proposed model (4). The fixed points are

$$\begin{aligned}
&(1) x^* = = \frac{br}{c\rho}, z^* = \frac{r}{\rho}, \\
&(2) x^* = z^* = 0.
\end{aligned} \tag{11}$$

Let us consider fixed point (1). We have terms with a delay $\tau_1 = 0$ and others with delay $\tau_2 = \tau$:

$$J \equiv \sum_{j=1}^{2} A_j e^{-\lambda\tau_j} = \begin{bmatrix} 0 & \frac{-br}{c} \\ ce^{-\lambda\tau} & -b \end{bmatrix}, \tag{12}$$

which leads to the following characteristic equation $det(J - \lambda I) = 0 \Rightarrow \lambda(\lambda + b) + bre^{-\lambda\tau} = 0$. If $\tau = 0$ it is straightforward to obtain $\lambda = \left(-b \pm \sqrt{b^2 - 4br}\right)/2$. It is easy to show that if $b > 4r$, we have two real negative solutions and the equilibrium is a stable node, being unstable if $b < 4r$.

For $b = 4r$, we have an improper node (non hyperbolic fixed point). When $\tau \neq 0$, we must analyze the behavior of

$$\lambda^2 + \lambda b + bre^{-\lambda\tau}. \tag{13}$$

Writing $\lambda = p + Iq$, with $I = \sqrt{-1}$, we first observe that: if $q \neq 0$ then (13) has no roots for $p > 0$. Non-oscillatory solutions, if present, are thus always stable. If $q \neq 0$, substituting $\lambda = p + Iq$ in (13) leads to:

$$\begin{aligned} &Im\left(\lambda^2 + \lambda b + bre^{-\lambda\tau}\right)/q = 0, \\ &\quad \Rightarrow \left(2pq + qb - bre^{-\lambda\tau}\sin q\tau\right)/q = 0, \end{aligned} \tag{14}$$

which implies

$$\begin{aligned} \frac{2p+b}{\tau br} = \frac{e^{-\lambda\tau}\sin q\tau}{q\tau} \Rightarrow \frac{2p+b}{\tau br} \leq e^{-\lambda\tau} \leq 1, \\ \Rightarrow p \leq b\frac{\tau r - 1}{2}. \end{aligned}$$

From the above equation, we see that if $\tau < 1/r \Rightarrow p < 0$ and the equilibrium will be stable. Note that, if $\tau > 1/r$, we may or may not observe solutions with $p > 0$.

It is worth to note that the trivial equilibrium (2) is always unstable, for any τ. In fact, its Jacobian matrix is given by:

$$J = \begin{bmatrix} r & 0 \\ ce^{-\lambda\tau} & -b \end{bmatrix}, \tag{15}$$

whose eigenvalues are $r > 0, -b$. Thus, with null delay, the system converges with damped oscillations for the interior equilibrium, that is, the immune system will not be able to deplete the infection, with a steady solution with a finite population of viruses. When a delayed response is considered, the same behavior takes place if $\tau < 1/r$. For larger delays, we may (or may not) observe the outbreak of sustainable oscillations and chaos.

System (4) has the drawback to present a null equilibrium, meaning no immune cell in the absence of virus. We can fix this by introduction of a term d as follows:

$$\begin{aligned} \dot{x} &= rx - \rho xz, \\ \dot{z}(t) &= d + cx(t-\tau) - bz, \end{aligned} \tag{16}$$

which leads to two equilibrium points:

$$\begin{aligned} &(1)x^* = = 0, z^* = \frac{d}{b}, \\ &(2)x^* = \frac{br/\rho - d}{c}, z^* = \frac{r}{\rho}. \end{aligned} \tag{17}$$

The fixed point (1) has a finite concentration of immune cells even in the the absence of virus. The Jacobian matrix is:

$$J = \begin{bmatrix} r - \rho s/b & 0 \\ ce^{-\lambda\tau} & -b \end{bmatrix}, \tag{18}$$

with eigenvalues $\lambda = -b, r - \rho d/b, \forall\tau$. Thus, the equilibrium is stable provided $r/\rho < d/b$. Note that d/b is the equilibrium concentration of immune cells in the absence of virus, and r/ρ is the equilibrium in the presence of virus. In real cases, the condition $r/\rho < d/b$ is thus very reasonable. For the second fixed point, the Jacobian is:

$$J = \begin{bmatrix} 0 & -\rho(\frac{br/\rho - d}{c}) \\ ce^{-\lambda\tau} & -b \end{bmatrix}, \tag{19}$$

whose characteristic equation is $\lambda^2 + \lambda b + c\rho e^{-\lambda\tau}(\frac{br/\rho - d}{c})$.For null delay, the solution is $\lambda = \left(-b \pm \sqrt{b^2 - 4\rho c(\frac{br/\rho - d}{c})}\right)/2$ which always have negative real parts, guaranteeing the stability of the fixed point. Note that for null delays, the system presents two stable equilibria if $r/\rho < d/b$. Depending on the initial virus load, the system oscillates for the null virus equilibrium, otherwise there will be a persistent infection. For $\tau \neq 0$, a similar procedure as in the previous case led to the conclusion that, if $\tau < b/(br - \rho d)$, λ will have negative real parts. In (4), the critical delay was $\tau < 1/r$, therefore the introduction of d leads to an increase in the delay value that guarantees stability.

3 Four-Dimensional Model

Here, we consider the model (3) which was numerically analyzed in [16] for the case $\tau_1 = \tau_2$. In this model, free virus v attack uninfected cells x at a rate β. λ^* is the production rate of cells and d its death rate. Once infected, the cell becomes an infected cell y, which dies at rate a and are eliminated by the immune response at rate p. Immune cells are produced at rate c, proportional to the abundance of infected cells, and dies at rate b. Typical numeric values are $\lambda^* = 10^5$, $d = 0.1$, $a = 0.5$, $\beta = 2 \times 10^{-7}$, $k = 100$, $u = 5$, $c = 0.2$, $b = 0.05$, and $\rho = 1$ (considering one day as the time unit). As observed in [16], the delayed response induced sustainable oscillations, in which the virus load reaches a minimum value orders of magnitude smaller than those obtained from an instantaneous response. A sequence of bifurcations occurs with increasing response times which can evolve towards a chaotic behavior. To visualize typical chaotic orbits obtained from numeric solutions

of this system, we refer the reader to [16]. Here, we focus on some analytical properties not presented in this reference.

We analyze the local stability of system (3), whose fixed points are:

$$
\begin{aligned}
&(1)x^* = \lambda^*/d,\ y^* = 0,\ v^* = 0,\ z^* = 0, \\
&(2)x^* = = \frac{-\mu a}{\beta(a-k)},\ y^* = \frac{\lambda^*\beta(a-k)+da\mu}{\beta(a-k)a},\ v^* = -\frac{\lambda^*\beta(a-k)+da\mu}{a\mu\lambda^*},\ z^* = 0, \\
&(3)x^* = R,\ y^* = b/c,\ v^* = -\frac{-\lambda^*+dR}{\beta R},\ z^* = -\frac{-c\lambda^*+cdR+ab}{\rho b}, \\
&\quad R = \frac{1}{2}\left(\frac{-kd\beta-dc\mu+\beta c\lambda^* \pm \sqrt{(}(-kd\beta-dc\mu+\beta c\lambda^*)^2+4\beta dc^2\mu\lambda^*)}{\beta dc}\right).
\end{aligned}
\tag{20}
$$

Fixed point (1) corresponds to a system with no virus, no infected cells, and no lymphocytes. There are terms with no delay and terms with delay τ in the Jacobian matrices. The terms f_j^i are:

$$
\begin{aligned}
&f_1^1 = \lambda^* - dx - \beta xv;\ f_1^2 = \beta xv - ay - \rho yz, \\
&f_1^3 = ky - uv - \beta xv;\ f_1^4 = -bz, \\
&f_2^1 = f_2^2 = f_2^3 = 0;\ f_2^4 = cy(t-\tau)z(t-\tau),
\end{aligned}
\tag{21}
$$

and the Jacobian is:

$$
\sum_{j=1}^{2} A_j e^{-\lambda\tau_j} = \begin{bmatrix} -d & 0 & -\beta\lambda^*/d & 0 \\ 0 & -a & \beta\lambda^*/d & 0 \\ 0 & k & -u-\beta\lambda^*/d & 0 \\ 0 & 0 & 0 & -b \end{bmatrix}. \tag{22}
$$

From the characteristic equation $det(J - \lambda I) = 0$, we obtain:

$$
(\lambda^2 d + (du + \lambda^*\beta + ad)\lambda - \lambda^*\beta(k-a) + dau)(b+\lambda)(1+\lambda/d) = 0,
$$

which leads to $\lambda = -d, -b$. Since $d, b > 0$ the stability is determined by the roots of:

$$
-\frac{du+\lambda^*\beta+ad}{2d} \pm \frac{\sqrt{(du+\lambda^*\beta+ad)^2 - 4d(-\lambda^*\beta(k-a)+dau).}}{2d}
$$

Let $\lambda_1 = p + iq, \lambda_2 = p - iq$ solutions of this equation. $\lambda_1\lambda_2$ leads to $p^2+q^2 = \frac{-\lambda^*\beta(k-a)+dau}{d}$. Therefore, $\lambda^*\beta(a-k) + dau > 0$ is a necessary condition for complex roots. In this case, the real part of both λ_1, λ_2 are negative since $\lambda_1 + \lambda_2 = -(du + \lambda^*\beta + ad) < 0$.

Let us now consider real solutions. It is easy to see that it is not possible to obtain both solutions as positive numbers. Then we have two situations: if $\lambda_1\lambda_2 > 0$ both solutions are negative, and the fixed point is stable, which happens when $\lambda^*\beta(a-k) + dau > 0$. Note that $\lambda^*\beta(a-k) + dau < 0$ is sufficient for real solutions, the fixed point being unstable in this case. Stability can be obtained, for example, diminishing k, the growth rate of virus, increasing a or v, the mortality rate of infected cells and virus, respectively, etc.

For the fixed point (2), the following Jacobian matrix is obtained:

$$
\sum_{j=1}^{2} A_j e^{-\lambda\tau_j} = \begin{bmatrix} \frac{\beta\lambda^*}{ua} & 0 & \frac{ua}{a-k} & 0 \\ -\frac{\lambda^*\beta(a-k)+dau}{ua} & -a & -\frac{ua}{a-k} & -\rho\frac{\lambda^*\beta(a-k)+dau}{\beta a(a-k)} \\ \frac{\lambda^*\beta(a-k)+dau}{ua} & k & \frac{uk}{a-k} & 0 \\ 0 & 0 & 0 & -b + ce^{-\lambda\tau}\frac{\lambda^*\beta(a-k)+dau}{\beta a(a-k)} \end{bmatrix}, \tag{23}
$$

whose characteristic equation is:

$$
\frac{(\lambda^3 A + B\lambda^2 + C\lambda + D)(Ece^{-\lambda\tau} - F(\lambda+b)}{ua^2(a-k)^2\beta} = 0, \tag{24}
$$

where:

$$
\begin{aligned}
&A = au(k-a);\ B = \left(\beta\lambda^*(a-k)^2 + uak(a+u) - ua^3\right); \\
&C = u^2a^2d + \lambda^*\beta(u+a)(a-k)^2;\ D = u^2a^2d(a-k) + ua\lambda^*\beta(a-k)^2; \\
&E = \left(\lambda^*\beta(k-a) - dau\right);\ F = \beta a(k-a)
\end{aligned}
$$

We consider $a \neq k$ to avoid singularities. Before we proceed with the analysis of (24), let us consider the equation $\lambda^3 A + B\lambda^2 + C\lambda + D$ with solutions $\lambda_i; i = 1, 2, 3$. The well-known Girard formulas states that:

$$\lambda_1\lambda_2\lambda_3 = \lambda^*\beta(a-k) + aud, \quad (25)$$

$$\lambda_1\lambda_2 + \lambda_2\lambda_3 + \lambda_1\lambda_3 = \frac{(k-a)^2(a+u)\beta\lambda^* + u^2a^2d}{ua(k-a)},$$

$$\lambda_1 + \lambda_2 + \lambda_3 = \frac{\beta\lambda^*(k-a)^2 + ua(a^2 - k(a+u))}{ua(k-a)}.$$

Note that we consider $\lambda^*\beta(a-k) + aud < 0$ to avoid negative fixed points (the variables denote concentrations, and a negative concentration is meaningless). So $\lambda_1\lambda_2\lambda_3 < 0$ and $a < k$ leads to $\lambda_1+\lambda_2+\lambda_3 < 0$ and $\lambda_1\lambda_2+\lambda_2\lambda_3+\lambda_1\lambda_3 > 0$. Then, either the three roots are negative or there are two positive roots and one negative. This last case leads to a contradiction: let $\lambda_2, \lambda_3 > 0$ and $\lambda_1 < 0$. Then since $\lambda_1\lambda_2+\lambda_2\lambda_3+\lambda_1\lambda_3 > 0$ we have $\lambda_2\lambda_3 > -\lambda_1(\lambda_2+\lambda_3) > 0$. On the other side, from $\lambda_1 + \lambda_2 + \lambda_3 < 0$ we obtain $-\lambda_2\lambda_3 > \lambda_2^2 + \lambda_3^2$ which is a contradiction.

Let us now analyze the term

$$Ece^{-\lambda\tau} - F(\lambda + b). \quad (26)$$

If $\tau = 0$ the solution is:

$$\lambda = \frac{c(\lambda^*\beta(a-k+adu)) + \beta ab(k-a)}{\beta a(a-k)},$$

which is negative if $c < \frac{\beta ab(a-k)}{\lambda^*\beta(a-k)+adu}$. It is possible to show that this condition is sufficient to guarantee stability even with a non null retard. To see this, write this solutions as

$$c < bF/E; F, E > 0,$$

Let $\lambda = p + iq$ a solution of (26). Therefore:

$$Ece^{-p\tau}cos(q\tau) - Fp - bF = 0,$$
$$-qF - e^{-p\tau}cEsin(q\tau) = 0. \quad (27)$$

Consider $c < bF/E$ and a slightly minor value $c = bF/E - \epsilon, \epsilon > 0$. Substituting in (27):

$$p = e^{-p\tau}cos(q\tau)\left(b - \frac{\epsilon E}{F}\right) - b. \quad (28)$$

It is easy to see that, if $q = 0$ then $p < 0$. Two cases must be considered: (i) $(b - \frac{\epsilon E}{F}) < 0$ and (ii) $(b - \frac{\epsilon E}{F}) > 0$. In case (i) $p < 0$ follows from (28). In case (ii), let (28) be rewritten as:

$$p = (e^{-p\tau} - 1)b - \frac{\epsilon E}{F}e^{-p\tau}. \quad (29)$$

Consider $p > 0$. The right side of (29) is positive iff $e^{-p\tau} > 1$, which implies $p < 0$, a contradiction. Therefore $p < 0, \forall\tau$.

Now let $q \neq 0$. Isolating sin and cos in (27) and using $\cos^2 q\tau + \sin^2 q\tau = 1$:

$$\left(\frac{pF + bF}{e^{-p\tau}E}\right)^2 + \left(\frac{-qF}{e^{-p\tau}cE}\right)^2 = 1 \Rightarrow, \quad (30)$$
$$p^2 + 2pb + q^2 + b^2 = \frac{e^{-2p\tau}c^2E^2}{F^2},$$

which is of the type $f(p) = g(p)$. Consider the cases

$$(i) q^2 + b^2 > \frac{c^2E^2}{F^2},$$
$$(ii) q^2 + b^2 < \frac{c^2E^2}{F^2}.$$

Note that, $f(p=0) = q^2 + b^2$ and $g(p=0) = \frac{c^2E^2}{F^2}$ with $f(p)$ a second order equation and $g(p)$ an exponential. In the first case, we have $f(p) = g(p)$ in a value $p < 0$. This is the same restriction $c < bF/E$. In fact this implies

$$b^2 > \frac{c^2F^2}{E^2} \Rightarrow q^2 + b^2 - c^2E^2/F^2 > 0.$$

In case (ii), it is easy to see that it is *possible* $f(p) = g(p)$ for some $p > 0$.

In short: $\lambda^*\beta(a-k) + aud < 0$ and $a - k < 0$ guarantees a positive fixed point and these conditions plus $c < \frac{\beta ab(a-k)}{\lambda^*\beta(a-k)+aud}$ implies in the stability of fixed points (1) and (2) $\forall\tau$. If $c > \frac{\beta ab(a-k)}{\lambda^*\beta(a-k)+aud}$ depending on the value of q, we may have $p > 0$ and the fixed point loses its stability for some τ. These results are consistent with [16], where we observed, for instantaneous immune response, damped oscillations towards the stationary solution. Retarded response makes stationary solution unstable and sustained outbreaks of the virus load were observed. In fact, with the chosen parameter values of [16] the condition $c < \frac{\beta ab(a-k)}{\lambda^*\beta(a-k)+aud}$ implies $c < 2.6610^{-7}$, which is not satisfied with the choice $c = 0.2$.

Let us consider the fixed point (3):

$$x^* = R, y^* = b/c, v^* = -\frac{-\lambda^* + dR}{\beta R}, z^* = -\frac{-c\lambda^* + cdR + ab}{\rho b}, \quad (31)$$
$$R = \frac{1}{2}\left(\frac{-kd\beta - dc\mu + \beta c\lambda^* \pm \sqrt{((-kd\beta - dc\mu + \beta c\lambda^*)^2 + 4\beta dc^2\mu\lambda^*)}}{\beta dc}\right).$$

We consider $R > 0$. We also consider:

$$v^* = -\frac{-\lambda^* + dR}{\beta R} > 0 \Rightarrow \lambda^* > dR,$$
$$z^* = -\frac{-c\lambda^* + cdR + ab}{\rho b} > 0 \Rightarrow c\lambda^* - cdR - ab > 0.$$

After some algebra, it is possible to show that the above condition is equivalent to $c > \frac{\beta ab(a-k)}{\lambda^*\beta(a-k)+aud}$, which are the conditions upon which the fixed point 2) loses its stability. It is also possible to show that the restriction $v^* > 0$ leads to:

$$\frac{du - \beta\lambda^* - \sqrt{(du+\beta\lambda^*)^2 + 4dukb\beta}}{du} < c < \frac{du - \beta\lambda^* + \sqrt{(du+\beta\lambda^*)^2 + 4dukb\beta}}{du}.$$

An analytical analysis of this equation falls beyond the scope of this paper, as the resulting characteristic equation is a transcendental equation involving a fourth order polynomial. This shows the limitations of a purely analytical approach to analyze delayed ODEs with three or more dimensions. The results presented here are in accord with the numeric analysis performed in [16].

4 Concluding remarks

In this paper, we considered analytical tools to analyze delayed ODEs of biological interest. We studied a two-dimensional system that simulates the dynamics of the immune system cells and a target population of viruses. New analytical results in a four-dimensional system considered in [16] were presented.

Low dimensional ODE models are often used to model biological systems, the focus being on the search for those that describe the main features of the proposed system with as few parameters as possible. As chaotic orbits are often observed in empirical data, most authors consider models with at least three dimensions. However, even one- and two-dimensional models may present chaotic behavior through the introduction of time delays. In this work, we presented some of the difficulties arising in the analytical analysis of delayed equations, focusing in the stability conditions of the equilibrium points. We showed how the conditions for the real part of the eigenvalues be negative, necessary to stability, may be cumbersome to determine when $\tau \neq 0$, even in relatively low-dimensional models. This happens because the corresponding characteristic equation has infinity complex solutions. However, even with an infinity number of solutions, the stability is determined by a finite number of them. Analytical tools are useful to complement numeric solutions such as the ones obtained via Runge-Kutta methods, and may reveal features such as which parameters are fundamental for bifurcations that lead to complex behavior.

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