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A STABILITY THEOREM FOR EQUILIBRIA OF DELAY DIFFERENTIAL EQUATIONS IN A CRITICAL CASE WITH APPLICATION TO A MODEL OF CELL EVOLUTION

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Abstract. In this paper the stability of the zero equilibrium of a system with time delay is studied. The critical case of a multiple zero root of the characteristic equation of the linearized system is treated by applying a Malkin type theorem and using a complete Lyapunov-Krasovskii functional. An application to a model for malaria under treatment considering the action of the immune system is presented.

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1. Introduction

As the need for more accurate real-life models arose, mathematical modeling through delay differential equations (DDEs) became widespread. This is due to the fact that DDEs models are able to capture latent processes (*i.e.* the time it takes for medicine to take effect, the cell's division cycle, the gestation period).

The study of stability of equilibria of a system of DDEs is often based on the study of the eigenvalues of the linearized system, through the Theorem of linear approximation. A zero eigenvalue represents an especially complex case, which is called a critical case, since that theorem cannot be applied. In the event of a critical case, the stability study becomes problematic.

We start by presenting and proving a theorem for the stability of the zero solution of a DDEs system in a critical case, for a particular class of systems with time delays. This type of systems, for ordinary differential equations, were studied by Malkin in [18] where a theorem for the stability in a critical case is proved. We extend this theorem to the case of DDE systems. The main tool is the use of a complete Lyapunov-Krasovskii functional using some results from [13]. After that, we apply the theorem for an original biological model that depicts cell evolution in Malaria under treatment, with the action of the immune system taken into consideration. Malaria is an infectious disease which spreads through mosquito bites. It is commonly found in tropical regions. The parasites enter the bloodstream and infect erythrocytes. Our model, extending those introduced in [6, 17],

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includes the process of erythropoiesis, the evolution of the parasites, the action of the immune system and the effect of the treatment.

A different model where the same critical case is encountered is the one introduced in [3].

2. A general theorem on a critical case

For general results on stability for delay differential equation we refer to [5, 8, 9, 11].

In what follows, the euclidean norm in the corresponding spaces will be denoted by $||\cdot||$.

Consider the following system with time-delay:

$$\begin{aligned} \dot{x}(t) &= A_0x(t) + \sum_{j=1}^{m} A_j x(t-\tau_j) + F[x(t), x(t-\tau_1), \dots, x(t-\tau_m), y(t)] \\ \dot{y}_i(t) &= G_i[x(t), x(t-\tau_1), \dots, x(t-\tau_m), y(t)],\ 1 \le i \le p, \end{aligned} \tag{2.1}$$

where $A_j \in M_n(\mathbb{R}), 0 \le j \le m$, $\tau_j > 0$ for all $1 \le j \le m, x(t) \in \mathbb{R}^n, y(t) \in \mathbb{R}^p, G_i(0,0,\dots,0,y) = 0, 1 \le i \le p$ and $F(0,0,\dots,0,y) = 0$, $\forall y \in \mathbb{R}^p$. F takes values in $\mathbb{R}^n$. Denote $G = (G_1,\dots,G_p)$. Suppose that F and G are real-analytic and their Taylor expansions around zero contain only powers of the variables with sum greater or equal to two (*i.e.* terms of the form $x_i(t)^r x_j(t)^s, x_i(t)^r x_j(t-\tau_k)^s, x_i(t)^r y_j(t)^s, x_i(t-\tau_k)^r x_j(t)^s, r+s \ge 2$). Then, for every $\delta > 0$, there exist $M_1(\delta)$ and $M_2(\delta)$ with $\lim\limits_{\delta\to 0} M_1(\delta) = \lim\limits_{\delta\to 0} M_2(\delta) = 0$ so that, whenever $||x(t)|| \le \delta, ||x(t-\tau_j)|| \le \delta, 1 \le j \le m, ||y|| \le \delta$,

$$\begin{aligned} &\|F\left(x(t), x(t-\tau_1), \dots, x(t-\tau_m), y(t)\right)\| \\ &\le M_1(\delta)\left(\|x(t)\| + \|x(t-\tau_1)\| + \dots + ||x(t-\tau_m)||\right) \\ &\|G\left(x(t), x(t-\tau_1), \dots, x(t-\tau_m), y(t)\right)\| \\ &\le M_2(\delta)\left(\|x(t)\| + \|x(t-\tau_1)\| + \dots + ||x(t-\tau_m)||\right). \end{aligned} \tag{2.2}$$

Here, the norms in $\mathbb{R}^m$ will be the euclidean norms, $||x||_2 = \sqrt{x_1^2 + \dots + x_m^2}$ and for $\varphi \in C\left([-\tau,0]; \mathbb{R}^{n+p}\right)$ the uniform norm will be $||\varphi||_\infty = \sup\limits_{t\in[-\tau,0]} ||\varphi(t)||_2, \tau = \max\limits_{1\le j\le m} \tau_j$.

Lemma 2.1. *Suppose that the linear system*

$$\dot{x}(t) = A_0x(t) + \sum_{j=1}^{m} A_j x(t-\tau_j) \tag{2.3}$$

is uniformly asymptotically stable (by [9], Ch.4, Th.4.5, this is equivalent to being exponentially stable). Then there exists a constant $C_1 > 0$ such that the Lyapunov matrix $U(t)$ (see [14]) verifies

$$||U(t)|| \le C_1.$$

Proof. Since, as already mentioned, the asymptotic stability of (2.3) is equivalent to exponential stability, $||x(t)||_2 \le ce^{-\omega t}||\varphi||_\infty$ for some $c, \omega > 0$. Let K be a fundamental matrix solution of (2.3) (see [13]) so $K(0) = I_n$, $K(t) = 0\ \forall t < 0$. The solution of the Cauchy problem (2.3) with an initial data $\varphi \in C([-\tau,0]; \mathbb{R}^n)$ is given by

$$x(t;\varphi) = K(t)\varphi(0) + \sum_{j=1}^{m} \left(\int_{-\tau_j}^{0} K(t-s-\tau) A_j \varphi(s) \right) \mathrm{d}s, \quad t \ge 0.$$

It is known that $||K(t)|| \leq Ce^{-\omega t}$ $\forall t \geq 0$ (see [13], (4)) with constants $C > 0, \omega > 0$ and it follows that

$$U(t) = \int_0^\infty K(s)^T W K(t+s) \mathrm{d}s$$

(T means transpose) is well defined for every $t \in \mathbb{R}$, with

$$W = I_n + \sum_{j=1}^{m} (I_n + \tau_j I_n).$$

Then $U(-t) = U(t)^T$ (see [13]) and, for every $t \geq 0$, one has

$$||U(t)|| \leq C^2 ||W|| \int_0^\infty e^{-\omega s} e^{-\omega(t+s)} \mathrm{d}s = \frac{C^2 ||W|| e^{-\omega t}}{2\omega} \leq \frac{C^2 ||W||}{2\omega} := C_1.$$

□

Theorem 2.2. *Suppose that the linear system (2.3) is uniformly asymptotically stable (by [9], Chap. 4, Thm. 4.5, this is equivalent to being exponentially stable). Then the zero solution of (2.1) is stable. Moreover, if φ is the initial data of (2.1) in $C([-\tau, 0]; \mathbb{R}^{n+p})$ such that, if $\sup\{||\varphi(t)||_2 \mid t \in [-\tau, 0]\} < \delta$, then*

$$\lim_{t \longrightarrow \infty} x_i(t) = 0, i = 1, \ldots, n \textit{ and a finite} \lim_{t \longrightarrow \infty} y_i(t) = \tilde{y_i} \textit{ exists}, 1 \leq i \leq p,$$
$$\textit{with } |\tilde{y_i}| < \epsilon \textit{ if } ||\varphi||_\infty < \delta(\epsilon).$$

Proof. If (2.3) is asymptotically stable then, by [13], there exists a Lyapunov-Krasovskii functional V such that the derivative along (2.3) is

$$\frac{\mathrm{d}}{\mathrm{d}t} V[\xi_t; \varphi] = -||\xi(t)||^2 - \sum_{j=1}^{m} ||\xi(t-\tau_j)||^2 - \sum_{j=1}^{m} \int_{-\tau_j}^{0} ||\xi(t+s)||^2 \mathrm{d}s.$$

Here $\varphi \in C([-\tau, 0]; \mathbb{R}^n)$ is an initial data, ξ is the solution of (2.3) with initial data φ and $\xi_t \in C([-\tau, 0]; \mathbb{R}^n)$ is defined by $\xi_t(s) = \xi(t+s)$ [8, 11].

Then, the derivative of V along the perturbed system

$$\dot{x}(t) = A_0 x(t) + \sum_{j=1}^{m} A_j x(t-\tau_j) + F[x(t), x(t-\tau_1), \ldots, x(t-\tau_m), y(t)] \tag{2.4}$$

is given by (see [13], §4)

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t} V[x_t] \quad = \quad & -||x(t)||^2 - \sum_{j=1}^{m} ||x(t-\tau_j)||^2 - \sum_{j=1}^{m} \int_{-\tau_j}^{0} ||x(t+s)||^2 \mathrm{d}s \\ & + 2F[x(t), x(t-\tau_1), \ldots, x(t-\tau_m), y(t)] \\ & \times [U(0)x(t) + \sum_{j=1}^{m} \int_{-\tau_j}^{0} U^T(s+\tau_j) A_j x(t+s) \mathrm{d}s]. \end{aligned} \tag{2.5}$$

Introduce now

$$\xi(t) = e^{\alpha t} x(t), \tag{2.6}$$

with α a positive constant subject to further determination. According to (2.4)

$$\begin{aligned}
\xi'(t) &= \alpha e^{\alpha t} x(t) + e^{\alpha t} x'(t) \\
&= \alpha e^{\alpha t} x(t) + A_0 e^{\alpha t} x(t) + \sum_{j=1}^{m} A_j e^{\alpha t} x(t-\tau_j) \\
&\quad + e^{\alpha t} F[x(t), x(t-\tau_1), \ldots, x(t-\tau_m), y(t)] \\
&= (\alpha I_n + A_0)\xi(t) + \sum_{j=1}^{m} e^{\alpha \tau_j} A_j \xi(t-\tau_j) \\
&\quad + e^{\alpha t} F[e^{-\alpha t}\xi(t), e^{-\alpha(t-\tau_1)}\xi(t-\tau_1), \ldots, e^{-\alpha(t-\tau_m)}\xi(t-\tau_m), y(t)].
\end{aligned} \tag{2.7}$$

Define

$$\tilde{A} = \alpha I_n + A_0, \quad \tilde{A}_j = e^{\alpha \tau_j} A_j.$$

Since, for $\alpha = 0$, $Re\lambda < 0$ $\forall \lambda$ a root of the characteristic equation of (2.3), the same will be true for the roots of $\det(\lambda I_n - \tilde{A}_0 - \sum_{j=1}^{m} e^{-\lambda \tau_j} \tilde{A}_j) = 0$ if α is small enough.

Let V be a Lyapunov-Krasovskii functional constructed as before for the linear system

$$\dot{\xi} = \tilde{A}_0 \xi(t) + \sum_{j=1}^{m} \tilde{A}_j \xi(t-\tau_j).$$

The derivative of V along the solutions of (2.7) is given by

$$\begin{aligned}
\frac{d}{dt} V[\xi_t] = \; & -||\xi(t)||^2 - \sum_{j=1}^{m} ||\xi(t-\tau_j)||^2 - \sum_{j=1}^{m} \int_{-\tau_j}^{0} ||\xi(t+s)||^2 \mathrm{d}s \\
& + 2e^{\alpha t} F\left[e^{-\alpha t}\xi(t), e^{-\alpha t} e^{\alpha \tau_1}\xi(t-\tau_1), \ldots, e^{-\alpha t} e^{\alpha \tau_m}\xi(t-\tau_m), y(t)\right]^T \cdot \\
& \cdot \left[U(0)\xi(t) + \sum_{j=1}^{m} \int_{-\tau_j}^{0} U(s+\tau_j)^T \tilde{A}_j \xi(t+s) \mathrm{d}s \right].
\end{aligned}$$

Take now $\beta < 1$ so that

$$M_1(\beta) \leq \min\left(\frac{1}{C_1(2 + m + \sum_{j=1}^{m} ||\tilde{A}_j||}, \frac{1}{3C_1 \sum_{j=1}^{m} \tau_j ||\tilde{A}_j||} \right). \tag{2.8}$$

Denote, in what follows, $M_1(\beta)$ as M_1 and suppose that the initial data for system (2.1) verifies $sup\{||\varphi(t)||_2 | t \in [-\tau, 0]\} \leq \eta < \beta$. Then, there exists $t_1 \in [0, \tau)$ such that $||\xi(t)||_2 < \beta < 1$ for every $t \in [0, t_1)$ and from the condition imposed to φ one also has $||\xi(t-\tau)||_2 \leq \eta < \beta < 1$ for $t \in [0, t_1)$. Also, $||y(t)|| < \beta$ for $t \in [0, t_1)$.

We show now that if M_1 that verifies (2.8) is small enough one has

$$\frac{\mathrm{d}}{\mathrm{d}t} V[\xi_t] \leq -w(t),$$

with w strictly positively defined, $w(0) = 0$.

Indeed, from the previous estimation of $||U(t)||$ it follows that, for $t \in [0, t_1)$,

$$\begin{aligned}
&||U(0)\xi(t) + \sum_{j=1}^{m} \int_{-\tau_j}^{0} U(s+\tau_j)^T \tilde{A}_j \xi(t+s) \mathrm{d}s|| \\
&\leq C_1 \left(||\xi(t)|| + \sum_{j=1}^{m} ||\tilde{A}_j|| \int_{-\tau_j}^{0} ||\xi(t+s)|| \mathrm{d}s \right),
\end{aligned}$$

and then

$$||e^{\alpha t} F[e^{-\alpha t}\xi(t), e^{-\alpha t} e^{\alpha \tau_1} \xi(t-\tau_1), \ldots, e^{-\alpha t} e^{\alpha \tau_m} \xi(t-\tau_m), y(t)]^T$$

$$\cdot \left[U(0)\xi(t) + \sum_{j=1}^{m} \int_{-\tau_j}^{0} U(s+\tau_j)^T \tilde{A}_j \xi(t+s) \mathrm{d}s \right] ||$$

$$\leq M_1 C_1 \left(||\xi(t)|| + \sum_{j=1}^{m} ||\xi(t-\tau_j)|| \right) \left(||\xi(t)|| + \sum_{j=1}^{m} ||\tilde{A}_j|| \int_{-\tau_j}^{0} ||\xi(t+s)|| \mathrm{d}s \right).$$

Remark that from Schwarz inequality,

$$\left(\int_{-\tau_j}^{0} ||\xi(t+s)|| \mathrm{d}s \right)^2 \leq \tau_j \int_{-\tau_j}^{0} ||\xi(t+s)||^2 \mathrm{d}s,$$

it follows that

$$\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t} V[\xi_t] \leq -||\xi(t)||^2 - \sum_{j=1}^{m} ||\xi(t-\tau_j)||^2 - \sum_{j=1}^{m} \int_{-\tau_j}^{0} ||\xi(t+s)||^2 \mathrm{d}s \\
&\quad +2M_1C_1 ||\xi(t)||^2 + 2M_1C_1 \sum_{j=1}^{m} ||\tilde{A}_j|| ||\xi(t)|| \int_{-\tau_j}^{0} ||\xi(t+s)|| \mathrm{d}s \\
&\quad +2M_1C_1 ||\xi(t)|| \sum_{j=1}^{m} ||\xi(t-\tau_j)|| \\
&\quad +2M_1C_1 \sum_{j=1}^{m} \sum_{k=1}^{m} ||\xi(t-\tau_j)|| ||\tilde{A}_k|| \int_{-\tau_j}^{0} ||\xi(t+s)|| \mathrm{d}s \\
&\leq -||\xi(t)||^2 - \sum_{j=1}^{m} ||\xi(t-\tau_j)||^2 - \sum_{j=1}^{m} \int_{-\tau_j}^{0} ||\xi(t+s)||^2 \mathrm{d}s \\
&\quad +M_1C_1(2 + m + \sum_{j=1}^{m} ||\tilde{A}_j||) ||\xi(t)||^2 + M_1C_1(1 + \sum_{j=1}^{m} ||\tilde{A}_j||) \\
&\quad +3M_1C_1 \sum_{j=1}^{m} \tau_j ||\tilde{A}_j|| \int_{-\tau_j}^{0} ||\xi(t+s)||^2 \mathrm{d}s \\
&= -w(\xi_t)
\end{aligned}$$

for $t \in [0, t_1)$ when $M_1 = M(\beta)$ is taken according to (2.8) so that it makes w strictly positively defined and of course $w(0) = 0$.

Then $V[\xi_t] \le V[\xi_0]$ for $t \in [0, t_1)$. From general properties related to Lyapunov-Krasovskii functionals, it follows that there exists $N_2 > 0$ so that $||\xi(t)||_2 \le N_2$ in $[0, t_1)$ and N_2 can be made arbitrary small if η is small. (2.6) implies that

$$||x(t)||_2 \le N_2 e^{-\alpha t} \; \forall t \in [0, t_1) \; so \; ||x(t - \tau_j)||_2 \le N_2 e^{\alpha \tau_j} e^{-\alpha t}, \; t \in [0, t_1).$$

The hypothesis on G implies that, $\forall 1 \le i \le p$,

$$||G_i(x(t), x(t - \tau_1), \ldots, x(t - \tau_m), y_i(t))|| \le \tilde{C}_i M_i e^{-\alpha t},$$

with some positive $\tilde{C}_i$ that can be made arbitrary small if η is small. Since

$$y_i(t) - y_i(0) = \int_0^t G_i[x(s), x(s - \tau_1), \ldots, x(s - \tau_m), y_i(s)] \mathrm{d}s, \tag{2.9}$$

it follows that

$$||y_i(t)|| \le ||y_i(0)|| + \frac{\tilde{C}_i M_i}{\alpha}.$$

Take now

$$0 < \varepsilon < \beta$$

and η_ε such that $\tilde{C}_i \le \varepsilon$ and $||y_i(0)|| + \frac{\tilde{C}_i M_i}{\alpha_i} \le \varepsilon$; thus $||\xi(t)||_2 \le \varepsilon, ||\xi(t - s)||_2 \le \varepsilon, ||y(t)|| \le \varepsilon$ for $t \in [0, t_1)$. Since $\varepsilon < \beta$, this last relation must hold for every $t \ge 0$. Indeed, if at some moment t_2 one should have equality to ε, the values will still be smaller than β and all the inequalities that are valid on $[0, t_1)$ still hold, so the values are smaller than ε. It follows that $t_1 = \infty$ and the simple stability is proved. Also $\lim_{t \to \infty} x_i(t) = 0$, $i = 1, \ldots, n$ and from (2.9) there exists a finite $\lim_{t \to \infty} y_i(t), 1 \le i \le p$. One also has $||y_i(t)|| \le ||y_i(0)|| + \frac{\tilde{C}_i M_i}{\alpha_i} < \varepsilon$ if $||\varphi||_\infty < \delta_\varepsilon$, where $\varphi \in C([-\tau, 0], \mathbb{R}^{n+1})$ is the initial data for (2.1). □

3. Cell evolution in Malaria under treatment

One DDE model of malaria can be found in the paper [6]. It contains a simplified equation for erythrocytes' evolution with respect to the model in [7]. We consider a more physiological model for erythropoiesis, following [1, 2, 7, 19]. We only concentrate on the evolution of merozoites during malaria, since their number considerably overcomes that of the gametocytes and their impact is responsible for the damaging effects of the disease. The influence of the immune system in the evolution of malaria is well recognized [15, 17], so it is also considered in the model in the second stage of the illness, the blood stage. The model for the action of the immune system is based on [4, 16, 17].

3.1. The mathematical model

Denote by v_1 the stem-like short-term erythroid cells, by v_2 the uninfected erythrocytes (RBC), by v_3, the concentration of erythropoietin, by v_4 a fictitious variable to be introduced later, by v_5 the number of infected red blood cells (iRBCs), by v_6 the number of free merozoites (extracellular malaria parazites), by v_7 the concentration of immature APCs, by v_8 the concentration of mature APCs, by v_9 the concentration of naive T cells of both CD4+ and CD8+ phenotype, by v_{10} the concentration of active CD4+ T-helper cells, by v_{11} the concentration of active B lymphocytes and CD8+ cytotoxic T-cells and by v_{12} the concentration of antibodies produced by the B cells.

The following equations describe the evolution of the disease induced by Plasmodium falciparum under treatment with Artemisinin.

Recent studies [12] show that Plasmodium falciparum acts on both young and mature erythrocytes. With p the invasion rate, the low of masses results in the presence of the term $-pv_2v_6$ that is accountable for the infection process.

The model that takes into consideration the response to the treatment is:

$$\dot{v_i} = f_i(v, v_{\tau_1}, v_{\tau_2}, \cdots, v_{\tau_7}), i = \overline{1,12} \tag{3.1}$$

$$\begin{aligned}
\dot{v}_1 &= -\tfrac{\gamma_0}{1+v_3^{\alpha}}v_1 - (\eta_1+\eta_2)k(v_3)v_1 \\
&\quad -(1-\eta_1-\eta_2)\beta(v_1,v_3)v_1 \\
&\quad +2v_4(1-\eta_1-\eta_2)\beta(v_{1\tau_1},v_{3\tau_1})v_{1\tau_1} + \eta_1 v_4 k(v_{3\tau_1})v_{1\tau_1} \\
\dot{v}_2 &= -\gamma_2 v_2 + \tilde{A}_e k(v_{3\tau_2})v_{1\tau_2} - p\ v_2 v_6 \\
\dot{v}_3 &= -kv_3 + \tfrac{a_1}{1+v_2^r} \\
\dot{v}_4 &= v_4\left(-\tfrac{\gamma_0}{1+v_3^{\alpha}} + \tfrac{\gamma_0}{1+v_{3\tau_1}^{\alpha}}\right) \\
\dot{v}_5 &= pv_2v_6 - \gamma_3 v_5 - pv_{2\tau_3}v_{6\tau_3}S \\
\dot{v}_6 &= (1-c)\beta p v_{2\tau_3}v_{6\tau_3}S - pv_2v_6 l_1(v_{12}) - \mu_M v_6 - b_1 v_6 v_{12} \\
\dot{v}_7 &= d_1 - c_2 v_7 - b_2 v_7 l_2(v_6) \\
\dot{v}_8 &= -c_3 v_8 + b_2 v_7 l_2(v_6) \\
\dot{v}_9 &= d_2 - c_4 v_9 - b_3 v_8 v_9 \\
\dot{v}_{10} &= -c_5 v_{10} - e_1\zeta(v_{10})v_{10}l_2(v_6) + 2e^{-c_5\tau_4}e_1\zeta(v_{10\tau_4})v_{10\tau_4}l_2(v_{6\tau_4}) \\
&\quad +2^{m_1}b_{41}v_{8\tau_6}v_{9\tau_6}l_2(v_{6\tau_6}) \\
\dot{v}_{11} &= -c_6 v_{11} - e_2 v_{10}v_{11}\zeta(v_{10}) + 2e^{-c_6\tau_5}e_2 v_{10\tau_5}v_{11\tau_5}\zeta(v_{10\tau_5}) \\
&\quad +2^{m_2}b_{42}v_{8\tau_7}v_{9\tau_7}l_2(v_{6\tau_7}) \\
\dot{v}_{12} &= -c_7 v_{12}v_6 + e_3 v_{11}\tfrac{v_6}{a_4+v_6}.
\end{aligned}$$

Here $r > 1$, $\beta = \beta_1 - \beta_d$, β_1 being the burst size in absence of treatment and β_d the effect of treatment with Artemisinin. Also, $\tilde{A}_e = A_e(2\eta_2 + \eta_1)$, with A_e the amplification factor. S accounts for the mortality of infected RBCs, and is influenced by treatment (see [6])

It is clear that $E_1 = (0, 0, \hat{v}_3, \hat{v}_4, 0, 0, \hat{v}_7, 0, \hat{v}_9, 0, 0, 0)$ is an equilibrium point, that can be interpreted as closed to the death of the patient.

Let $A = [a_{i,j}]$ be the matrix in the linear approximation around E_1 corresponding to undelayed terms, $B = [b_{i,j}]$ the matrix corresponding to terms with the delay τ_1, $C = [c_{i,j}]$ the matrix that corresponds to the terms with the delay τ_2, $D = [d_{i,j}]$ the matrix that corresponds to the terms with the delay τ_3, $E = [e_{i,j}]$ the matrix that corresponds to the terms with the delay τ_4, $F = [f_{i,j}]$ the matrix that corresponds to the terms with the delay τ_5, $G = [g_{i,j}]$ the matrix that corresponds to the terms with the delay τ_6 and $H = [h_{i,j}]$ the matrix that corresponds to the terms with the delay τ_7 . Then, as can be easily checked, the following nonzero elements appear in the matrices defined above: for $A = \frac{\partial f}{\partial v}$

$$
\begin{aligned}
&a_{11} = -\tfrac{\gamma_0}{1+z_3^{\alpha}} - (\eta_1+\eta_2)k(z_3) - (1-\eta_1-\eta_2)\left[\beta(0,z_3)\right]\\
&a_{22} = -\gamma_2\\
&a_{33} = -k,\\
&a_{43} = \tfrac{\gamma_0 z_4 \alpha z_3^{\alpha-1}}{(1+z_3^{\alpha})^2}\\
&a_{55} = -\gamma_3\\
&a_{66} = -\mu_M\\
&a_{77} = -c_2\\
&a_{88} = -c_3\\
&a_{98} = -b_3 z_9, a_{99} = -c_4\\
&a_{10,10} = -c_5\\
&a_{11,11} = -c_6,
\end{aligned}
$$

for

$$B = \frac{\partial f}{\partial v_{\tau_1}}$$

$$
\begin{aligned}
&b_{11} = 2z_4(1-\eta_1-\eta_2)\beta(0,z_3) + \eta_1 z_4 k(z_3)\\
&b_{43} = -\tfrac{\gamma_0 z_4 \alpha z_3^{\alpha-1}}{(1+z_3^{\alpha})^2},
\end{aligned}
$$

and

$$C = \frac{\partial f}{\partial v_{\tau_2}}$$

$$c_{21} = \tilde{A}_e k(z_3).$$

Accordingly, the characteristic equation will be:

$$det(\lambda I - A - e^{-\lambda\tau_1}B - e^{-\lambda\tau_2}C) = 0,$$

which yields,

$$
\begin{aligned}
&(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22})(\lambda - a_{33})(\lambda - a_{55})\lambda^2(\lambda - a_{66})\\
&\cdot(\lambda - a_{77})(\lambda - a_{88})(\lambda - a_{99})(\lambda - a_{10,10})(\lambda - a_{11,11}) = 0,
\end{aligned}
$$

and one can see that a critical case for stability by the first approximation theory appears.

3.2. Analysis of the critical case of cell evolution in Malaria under treatment

We perform a translation to zero by $p_i = v_i - \hat{v}_i$, for $i = 3, 4, 7, 9$. The new system becomes

$$\dot{p_i} = \tilde{f}_i(p, p_{\tau_1}, p_{\tau_2}, \cdots, p_{\tau_7}), i = \overline{1, 12},$$

where

$$\dot{p}_4 = (p_4+\hat{v}_4)\left(-\frac{\gamma_0}{1+(p_3+\hat{v}_3)^\alpha}+\frac{\gamma_0}{1+\left(p_{3\tau_1}+\hat{v}_3\right)^\alpha}\right)=\tilde{f}_4\left(p_3,p_4,p_{3\tau_1}\right).$$

The matrices of partial derivatives into zero are as before,

$$\begin{aligned}\tilde{A} &= \frac{\partial \tilde{f}}{\partial p} = [\tilde{a}_{ij}]\\ \tilde{B} &= \frac{\partial \tilde{f}}{\partial p_{\tau_1}} = [\tilde{b}_{ij}]\\ \tilde{C} &= \frac{\partial \tilde{f}}{\partial p_{\tau_2}} = [\tilde{c}_{ij}].\end{aligned}$$

The characteristic equation for the zero solution of the new system is exactly the one for $\tilde{E}$.
We have:

$$\frac{\partial \tilde{f}_4}{\partial p_3}(0) = \frac{\hat{v}_4\gamma_0\alpha\hat{v}_3^{\alpha-1}}{(1+\hat{v}_3^\alpha)^2}$$

$$\frac{\partial \tilde{f}_4}{\partial p_{3\tau_1}}(0) = -\frac{\hat{v}_4\gamma_0\alpha\hat{v}_3^{\alpha-1}}{(1+\hat{v}_3^\alpha)^2}$$

Since we do not have the linear part equal to zero, the Theorem 2.2 is not directly applicable. We will bring the system to the canonical form to which Theorem 2.2 can be applied.
We take $\xi = \alpha_1 p_1 + \alpha_2 p_2 \cdots + \alpha_{12} p_{12}$ where $\dot{p} = \tilde{A}p$.
Then

$$\dot{\xi} = \alpha_1 \dot{p}_1 + \alpha_2 \dot{p}_2 \cdots + \alpha_{12}\dot{p}_{12},$$

so

$$\begin{aligned}\dot{\xi} &= \alpha_1\tilde{a}_{11}p_1 + \alpha_2\tilde{a}_{22}p_2 + (\alpha_3\tilde{a}_{33}+\alpha_4\tilde{a}_{43})p_3 + \alpha_5\tilde{a}_{55}p_5 + \alpha_6\tilde{a}_{66}p_6\\ &\quad + \alpha_7\tilde{a}_{77}p_7 + (\alpha_8\tilde{a}_{88}+\alpha_9\tilde{a}_{98})p_8 + \alpha_9\tilde{a}_{99}p_9 + \alpha_{10}\tilde{a}_{10,10}p_{10} + \alpha_{11}\tilde{a}_{11,11}p_{11}.\end{aligned}$$

Then, if one imposes $\dot{\xi}=0$, it follows that:

$$\alpha_3\tilde{a}_{33}+\alpha_4\tilde{a}_{43}=0$$

$$\alpha_8\tilde{a}_{88}+\alpha_9\tilde{a}_{98}=0.$$

We take $\alpha_4 = 1$, then $\alpha_3 = -\frac{\tilde{a}_{43}}{\tilde{a}_{33}}$.
Since $\alpha_8 = 0$, $\alpha_9 = 0$ and $\alpha_7 = 0$.
Remark that

$$\dot{p}_{3\tau_1} = \tilde{a}_{33}p_{3\tau_1} + \tilde{R}_{3\tau_1},$$

with $\tilde{R}_{3\tau_1}$ containing terms of order higher or equal to two.
Take

$$\xi_1 = \alpha_3 p_3 + p_4 - \frac{\tilde{b}_{43}}{\tilde{a}_{33}}p_{3\tau_1}.$$

Then,

$$\begin{aligned}\dot{\xi}_1 &= \tilde{b}_{43}p_{3\tau_1} - \frac{\tilde{b}_{43}}{\tilde{a}_{33}}\dot{p}_{3\tau_1} + \tilde{R}_4^{(1)} \\ &= \tilde{b}_{43}p_{3\tau_1} - \frac{\tilde{b}_{43}}{\tilde{a}_{33}}\left(\tilde{a}_{33}p_{3\tau_1} + \tilde{R}_{3\tau_1}\right) + \tilde{R}_4^{(1)} \\ &= \tilde{R}_4^{(2)}(p, p_{\tau_1}),\end{aligned}$$

where $\tilde{R}_4^{(1)}$ and $\tilde{R}_4^{(2)}$ contain only terms of order higher or equal to two. Take

$$p_4 = \xi_1 - \alpha_3 p_3 + \frac{\tilde{b}_{43}}{\tilde{a}_{33}}p_{3\tau_1}.$$

Replace the fourth equation by the equation for $\dot{\xi}_1$ so this equation has zero linear part. Substitute p_4 in the equations of the new system and define

$$\begin{aligned}\tilde{f}_1\left(p_1, p_3, \xi_1, p_{1\tau_1}, p_{3\tau_1}\right) = \; & -\tfrac{\gamma_0}{1+(p_3+\hat{v}_3)^{\alpha}}p_1 - (\eta_1+\eta_2)k(p_3+\hat{v}_3)p_1 \\ & -(1-\eta_1-\eta_2)\beta(p_1, p_3+\hat{v}_3)p_1 \\ & +\big[2(1-\eta_1-\eta_2)\beta(p_{1\tau_1}, p_{3\tau_1}+\hat{v}_{3\tau_1})p_{1\tau_1} \\ & +\eta_1 k(p_{3\tau_1}+\hat{v}_{3\tau_1})p_{1\tau_1}\big]\,\xi_1 \\ & +B_1(p_3, p_{1\tau_1}, p_{3\tau_1}),\end{aligned}$$

with B_1 containing only terms of order greater or equal to two. It follows that the linear part of $\tilde{f}_1$ does not contain ξ_1, neither do the linear part of the rest of the equations. Denote the new system as $\dot{u} = \bar{f}(u, u_{\tau_1}, \ldots, u_{\tau_7})$ with $u = (p_1, p_2, p_3, \xi_1, p_5, \ldots, p_{12})$. Let

$$\hat{A} = \frac{\partial \bar{f}}{\partial u}(0) = [\hat{a}_{i,j}].$$

Now, we take $\xi_2 = \beta_1 u_1 + \beta_2 u_2 + \beta_3 u_3 + \beta_4 \xi_1 + \cdots + \beta_{12}u_{12}$, where $\dot{u} = \hat{A}u$.
So,

$$\dot{\xi}_2 = \beta_1\dot{u}_1 + \beta_2\dot{u}_2 + \beta_3\dot{u}_3 + \beta_4\dot{\xi}_1 + \cdots + \beta_{12}\dot{u}_{12}.$$

Then, since ξ_1 has no linear part in the system in the u-variables, it follows that

$$\begin{aligned}\dot{\xi}_2 = \; & \beta_1\hat{a}_{11}u_1 + \beta_2\hat{a}_{22}u_2 + \beta_3\hat{a}_{33}u_3 + \beta_5\hat{a}_{55}u_5 \\ & +(\beta_6\hat{a}_{66} + \beta_{12}\hat{a}_{12,6})u_6 + \beta_7\hat{a}_{77}u_7 + \beta_8\hat{a}_{88}u_8 + \beta_9\hat{a}_{99}u_9 \\ & +\beta_{10}\hat{a}_{10,10}u_{10} + \beta_{11}\hat{a}_{11,11}u_{11}.\end{aligned}$$

Now, if one imposes $\dot{\xi}_2 = 0$, it follows that:

$$\beta_6\hat{a}_{66} + \beta_{12}\hat{a}_{12,6} = 0.$$

For $\beta_{12} = 1$, it follows that $\beta_6 = -\frac{\hat{a}_{12,6}}{\hat{a}_{66}}$. Then

$$\xi_2 = \beta_6 u_6 + u_{12},$$

so the equation of ξ_2 has no linear part, that is

$$\dot{\xi}_2 = R_4^{(1)},$$

with $R_4^{(1)}$ containing only terms of order greater or equal to two. Take

$$p_{12} = \xi_2 - \beta_6 p_6$$

Replace the twelfth equation by $\dot{\xi}_2$ so this equation has a zero linear term. Substitute p_{12} in the equations of the system in u and define:

$$\begin{aligned} g_6(u_2, u_6, \xi_2, u_{2\tau_3}, u_{2\tau_6}) = (1-c)\beta p u_{2\tau_3} u_{6\tau_3} S - \mu_M u_6 \\ - p u_2 u_6 l_1(\xi_2 - \beta_6 u_6) \\ + b_1 u_6(\xi_2 - \beta_6 u_6). \end{aligned}$$

Remark that the linear part of g_6 does not contain ξ_2. and the other equations do not contain ξ_2 at all. Redenote the other right-hand components of the system in u by the corresponding g. A new system is obtained for $\zeta = (u_1, u_2, u_3, \xi_1, u_5, \dots, u_{11}, \xi_2)$

$$\dot{\zeta} = g(\zeta, \zeta_{\tau_1}, \dots, \zeta_{\tau_7}) \tag{3.2}$$

$$\begin{aligned}
\dot{u}_1 =& -\tfrac{\gamma_0}{1+(u_3+\hat{v}_3)^\alpha} u_1 - (\eta_1+\eta_2)k(u_3+\hat{v}_3)u_1 - (1-\eta_1-\eta_2)\beta(u_1, u_3+\hat{v}_3)u_1 \\
&+[2(1-\eta_1-\eta_2)\beta(u_{1\tau_1}, u_{3\tau_1}+\hat{v}_3)u_{1\tau_1} + \eta_1 k(u_{3\tau_1}+\hat{v}_3)u_{1\tau_1}]\xi_1 \\
&+B_1(u_3, u_{1\tau_1}, u_{3\tau_1}) \\
\dot{u}_2 =& -\gamma_2 u_2 + \tilde{A}_e k(u_{3\tau_2}+\hat{v}_3)u_{1\tau_2} - p_2 u_6 \\
\dot{u}_3 =& -k(u_3+\hat{v}_3) + \tfrac{a_1}{1+u_2^r} \\
\dot{\xi}_1 =& R_4^{(2)}(u, u_{\tau_1}) \\
\dot{u}_5 =& p u_2 u_6 - \gamma_3 u_5 - p u_{2\tau_3} u_{6\tau_3} S \\
\dot{u}_6 =& (1-c)\beta p u_{2\tau_3} u_{6\tau_3} S - p u_2 u_6 l_1(\xi_2 - \beta_6 u_6) - \mu_M u_6 - b_1 u_6(\xi_2 - \beta_6 u_6) \\
\dot{u}_7 =& d_1 - c_2(u_7+\hat{v}_7) - b_2(u_7+\hat{v}_7)l_2(u_6) \\
\dot{u}_8 =& -c_3 u_8 + b_2(u_7+\hat{v}_7)l_2(u_6) \\
\dot{u}_9 =& d_2 - c_4(u_9+\hat{v}_9) - b_3 u_8(u_9+\hat{v}_9) \\
\dot{u}_{10} =& -c_5 u_{10} - e_1\zeta(u_{10})u_{10}l_2(u_6) + 2e^{-c_5\tau_4} e_1 \zeta(u_{10\tau_4})u_{10\tau_4} l_2(u_{6\tau_4}) \\
&+2^{m_1} b_{41} u_{8\tau_6} u_{9\tau_6} l_2(u_{6\tau_6}) \\
\dot{u}_{11} =& -c_6 u_{11} - e_2 u_{10} u_{11} \zeta(u_{10}) + 2e^{-c_6\tau_5} e_2 u_{10\tau_5} u_{11\tau_5} \zeta(u_{10\tau_5}) \\
&+2^{m_2} b_{42} u_{8\tau_7} u_{9\tau_7} l_2(u_{6\tau_7}) \\
\dot{\xi}_2 =& R_4^{(1)}.
\end{aligned}$$

Compute

$$\bar{A} = \frac{\partial g}{\partial \zeta}$$

$$
\begin{aligned}
&\bar{a}_{11} = -\tfrac{\gamma_0}{1+(u_3+\hat{v}_3)^\alpha} - (\eta_1+\eta_2)k(u_3+\hat{v}_3) - (1-\eta_1-\eta_2)\beta(0,u_3+\hat{v}_3)\\
&\bar{a}_{22} = -\gamma_2\\
&\bar{a}_{33} = -k,\\
&\bar{a}_{55} = -\gamma_3\\
&\bar{a}_{66} = -\mu_M\\
&\bar{a}_{77} = -c_2\\
&\bar{a}_{88} = -c_3\\
&\bar{a}_{98} = -b_3(u_9+\hat{v}_9)_9, \bar{a}_{99} = -c_4\\
&\bar{a}_{10,10} = -c_5\\
&\bar{a}_{11,11} = -c_6,
\end{aligned}
$$

$$\bar{B} = \frac{\partial g}{\partial \zeta_{\tau_1}}$$

$$\bar{b}_{11} = [2(1-\eta_1-\eta_2)\beta(0,u_3+\hat{v}_3) + \eta_1 k(u_3+\hat{v}_3)]\xi_1 + B_1^{'}(u_3,0),$$

$$\bar{C} = \frac{\partial g}{\partial \zeta_{\tau_2}}$$

$$\bar{c}_{21} = \tilde{A}_e k(u_3+\hat{v}_3).$$

Accordingly, the characteristic equation will be:

$$det(\lambda I - \bar{A} - e^{-\lambda\tau_1}\bar{B} - e^{-\lambda\tau_2}\bar{C}) = 0,$$

which yields,

$$
\begin{aligned}
&(\lambda - \bar{a}_{11} - \bar{b}_{11}e^{-\lambda\tau_1})(\lambda - \bar{a}_{22})(\lambda - \bar{a}_{33})(\lambda - \bar{a}_{55})\lambda^2(\lambda - \bar{a}_{66}))\\
&\cdot(\lambda - \bar{a}_{77})(\lambda - \bar{a}_{88})(\lambda - \bar{a}_{99}(\lambda - \bar{a}_{10,10})(\lambda - \bar{a}_{11,11}) = 0.
\end{aligned}
$$

From these calculations we conclude that Theorem 2.2 can be applied to study the stability of the zero solution of system (11) and its conclusions transferred to the study of stability of the equilibrium point E_1 of system (10).

4. Conclusions

A qualitative study of the solutions of models described by delay differential equations is an important step towards the validation of the model. One important property is the stability of equilibrium points. A difficult problem in this direction is the stability study when zero eigenvalues exist in the spectrum of the Jacobian matrix calculated in the equilibrium. This makes the theorem on stability by linear approximation inapplicable. This critical case, discussed in this pape, is not uncommon in DDEs models and gives rise to a number of problems.

Although the theorem we present can be applied to a specific class of systems of DDEs, there is a considerable amount of models which can fit the required type, either in life sciences or in engineering.

The original biological model for which we use the above theorem has a standalone importance. We considered a widely spread disease (with available treatment), which continues to impact human life. The need to have available tools to study such models is undeniable.

It is also worth noticing that the mathematical model we introduced might be adapted to capture other diseases involving blood cells evolution (see [3]).

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