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Stability Analysis of a Mathematical Model of the Immune Response with Delays

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8.1 Introduction

The immune system is a complex network of cells and signals that has evolved to respond to the presence of pathogens (bacteria, virus, fungi). By pathogen we mean a microbial non-self recognized as a potential threat by the host. Some pathogens preferentially survive and proliferate better inside cells (intracellular pathogens) and others are extracellular (Medzhitov et al. 2002).

The two basic types of immunity are innate and adaptive. The innate response is the first line of defense; this response targets any type of microbial non-self and is non-specific because the strategy is the same irrespective of the pathogen. Innate immunity can suffice to clear the pathogen in most cases, but sometimes it is insufficient. In fact, pathogens may possess ways to overcome the innate response and successfully colonize and infect the host.

When innate immunity fails, a completely different cascade of events ensues leading to adaptive immunity. Unlike the innate response, the adaptive response is tailored to the type of pathogen. Immune responses that clear intracellular pathogens typically involve effector cells (such as cytotoxic T cells, or CTLs) while extracellular pathogens are cleared mostly by effector molecules (e. g. antibodies) involving a different cascade of cells (such as B cells) (Janeway 2001).

There is a natural temporal kinetic that arises as part of these immune responses. The innate immune response develops first occurring on the order of minutes and hours. Adaptive immunity follows innate and occurs on the order of days or weeks. Each has an inherent delay in their development (see next section), and this timing may be crucial in determining success or failure in clearing the pathogen.

8.2 Timing of innate and adaptive immunity

Cells of innate immunity recognize highly conserved structures produced by microbial pathogens. These structures are usually shared by entire classes

of pathogens (Gram-negative bacteria, for example) (Janeway et al. 2002). Once recognition occurs (Akira et al. 2001; Medzhitov et al. 2002; Takeda et al. 2003), the innate immune system is activated and ensues with very rapid kinetics (on the orders of minutes to hours).

The signals induced upon recognition by the innate immune system, in turn, stimulate and orient the adaptive immune response by controlling expression of necessary costimulatory molecules (Janeway 2002). In contrast, adaptive immunity has a tremendous capacity to recognize almost any antigenic structure (i. e., different from our gene repertoire) and because antigen receptors are generated at random (Medzhitov et al. 2000), they bind to antigens regardless of their origin (bacterial, environmental or self). Thus, the adaptive immune system responds to pathogens only after they have been recognized by the innate system (Fearon et al. 1996; Janeway 1989; Medzhitov et al. 1997). It takes at least 3 to 5 days for sufficient numbers of adaptive immune cells to be produced (expansion) (Medzhitov et al. 2000).

Another delay beyond the recognition and expansion phase occurs due to activation and differentiation phases. To complete these phases cells have to circulate and traffick from the lymphatic system through blood to the site of infection (Guermonprez et al. 2002; Zinkernagel 2003). This process takes at least few days (Jenkins et al. 2001).

It is clear timing is a key step in defining immune responses. The time frame for adaptive immunity to efficiently clear a pathogen at a site of infection is generally from 1–3 weeks (Janeway 2001; Jenkins et al. 2001; Lurie 1964). Depending on different factors, such as the type of pathogen, its proliferation rate (virus, bacteria) and tropism (intracellular or extracellular), either faster or slower responses are elicited (Antia et al. 2003; Guermonprez et al. 2002; Harty et al. 2000; Wong et al. 2003). It could be more rapid if memory cells exist (Murali-Krishna et al. 1999; Sprent et al. 2002; Surh et al. 2002; Swain et al. 1999).

The ability to mount an adaptive immune response also allows hosts to recall pathogens they have already encountered, termed a memory response. This facilitates a stronger and more efficient adaptive response whenever a second infection occurs (Sprent et al. 2002). The process of vaccination exploits this idea.

Although several examples exist in the literature of DDE modeling in biosciences and in immunology (see Murray 2002), little research in the experimental setting addresses the specific timing and functional form (kernels) of these kinetics. To begin to study these questions, we first developed a general model of the two-fold immune response, specifically to intracellular bacterial pathogens, incorporating mathematical delays for both innate and adaptive immune response.

Our baseline model tracks five variables: uninfected target cells (X_U), infected cells (X_I), bacteria (B), and phenomenological variables capturing innate (I_R) and adaptive (A_R) immunity. Uninfected target cells (1) have a natural turnover (s_U) and half-life ($\mu_{X_U} X_U$) and can become infected

(mass-action term $\alpha_1 X_U B$).

$$\frac{\mathrm{d}X_U}{\mathrm{d}t} = s_U - \alpha_1 X_U B - \mu_{X_U} X_U \,, \tag{1}$$

Infected cells (2) can be cleared by the adaptive response (mass-action term $\alpha_2 X_I A_R$) or they die (half-life term $\mu_{X_I} X_I$). Here the adaptive response is represented to target intracellular bacteria.

$$\frac{\mathrm{d}X_I}{\mathrm{d}t} = \alpha_1 X_U B - \alpha_2 X_I A_R - \mu_{X_I} X_I \tag{2}$$

The bacterial population (3) has a net proliferation term, represented by a logistic function $\left(\alpha_{20} B \left(1 - \frac{B}{\sigma}\right)\right)$ and is also cleared by innate immunity (mass-action term $\alpha_3 B I_R$).

$$\frac{\mathrm{d}B}{\mathrm{d}t} = \alpha_{20} B \left(1 - \frac{B}{\sigma}\right) - \alpha_3 B I_R \,. \tag{3}$$

Both innate and adaptive responses ((4) and (5), respectively) have a source term and a half-life term.

$$\frac{\mathrm{d}I_R}{\mathrm{d}t} = s_{I_R} + \int_{-\tau_1}^{0} w_1(s)\, f_1\left(B(t+s), I_R(t+s)\right) \mathrm{d}s - \mu_{I_R} I_R \tag{4}$$

$$\frac{\mathrm{d}A_R}{\mathrm{d}t} = s_{A_R} + \int_{-\tau_2}^{0} w_2(s)\, f_2\left(B(t+s), A_R(t+s)\right) \mathrm{d}s - \mu_{A_R} A_R \tag{5}$$

For the innate response, the source term (s_{I_R}) includes a wide range of cells involved in the first wave of defense of the host (such as natural killer cells, polymorphonuclear cells, macrophages and dendritic cells). For the adaptive response, the source term (s_{A_R}) represents memory cells that are present, derived from a previous infection (or vaccination). A zero source implies that this is the first infection with this pathogen (i. e. no memory cells exist). Both responses are enhanced and sustained by signals that we have captured by bacterial load. The amount and type of bacteria present and the duration of infection likely determine the strength and type of immune response.

Two delays are included in the model. The delay for innate immunity, τ_1, occurs on the order of minutes to hours and τ_2 is the delay for adaptive immunity on the order of days to weeks. We assume that both responses are dependent solely on the bacterial load in the previous τ_i time units ($i = 1, 2$) where the kernel functions $w_i(s)$, ($i = 1, 2$) weight the past values of the bacterial load $B(s)$, i. e.:

Case 1

$$f_1\left(B(t+s), I_R(t+s)\right) = B(t+s), \quad s \in [-\tau_1, 0]$$

and

$$f_2\left(B\left(t+s\right), A_R\left(t+s\right)\right) = B\left(t+s\right), \quad s \in [-\tau_2, 0]\,.$$

In a second case, we could consider a different form of the delay. For innate immunity equation we consider the interaction (mass action product) of the bacterial load and the innate response and for adaptive immunity equation the interaction of the adaptive response with infected cells (in the previous τ_i time units, $i = 1, 2$). Therefore

Case 2

$$f_1\left(B\left(t+s\right), I_R\left(t+s\right)\right) = k_{I_R} B\left(t+s\right) I_R\left(t+s\right)$$

and

$$f_2\left(X_I(t+s), A_R(t+s)\right) = k_{A_R} X_I(t+s) A_R(t+s)$$

where k_{I_R} and k_{A_R} are scaling factors. We also consider two different types of functions for the kernels $w_i(s)(i = 1, 2)$, namely exponential or uniform.

As no experimental studies explore delays in any quantitative way, little evidence is available to inform us about the shapes of the delay kernels. However, we explore two biologically plausible cases. In the case of a uniform kernel we assume that the immune response (both innate and adaptive) is uniformly dependent on the previous τ_i time units. This implies that the bacterial load over the entire infection equally influences the response (in the 2nd delay case it implies that the interaction between the response and bacteria equally influences the response).

In the case of an exponential growth kernel, we assume that both immune responses place significant emphasis on the most recent bacterial load and that the influence of bacterial load prior to the most recent history is less significant (in the 2nd delay case it implies that only the most recent history of the interaction between the response and bacteria influences the respective response).

We hypothesis that the shorter the time delay is, the less informative (uniform) is the past history of the infection. Moreover, more recent levels of infection (for example, the number of bacteria in the host in the last few of days) will likely elicit a stronger adaptive immunity response (exponential growth). This leads to our use of a uniform kernel for innate immunity and an exponential growth kernel for adaptive immunity.

To complete the development of the mathematical model, we must estimate values for the parameters and initial conditions, as well as define units. In many cases, previously published data in the literature suggest large ranges in parameter choices: we chose an average value for our model. The values of initial conditions and parameter values are given in Table 8.1 and Table 8.2,

Table 8.1. Initial conditions (cells or bacteria per cm^3 of tissue)

Name	Value	Range
$X_U(0) = X_U^{\text{baseline}}$	$1e^4$	$1e^4 - 1e^5$
$X_I(0) = X_I^{\text{baseline}}$	0	
$B(0) = B_0$	20	
$I_R(0) = I_R^{\text{baseline}}$	$1e^3$	$1e^3 - 1e^4$
$A_R(0) = A_R^{\text{baseline}}$	$1e^2$ OR 0 (for first infections)	$1e^2 - 1e^3$

respectively. Given baseline levels and half-life terms, values of source terms s_U, s_{I_R} and s_{A_R} are determined by the following conditions:

$$s_U \equiv \mu_{X_U} X_U^{\text{baseline}}, \quad s_{I_R} \equiv \mu_{I_R} I_R^{\text{baseline}}, \quad s_{A_R} \equiv \mu_{A_R} A_R^{\text{baseline}}.$$

Thus, for example, changing I_R^{baseline} will affect only s_{I_R} and not μ_{I_R}. To properly define the integrals of equations (4)–(5) (both in delay case 1 and case 2), we need the following initial conditions:

$$\begin{cases} X_I(t) \equiv 0 & \text{for} \quad t \in [-\tau_2, 0] \\ B(t) \equiv B(0) & \text{for} \quad t \in [-\tau_2, 0] \\ I_R(t) \equiv I_R^{\text{baseline}} & \text{for} \quad t \in [-\tau_1, 0] \\ A_R(t) \equiv A_R^{\text{baseline}} & \text{for} \quad t \in [-\tau_2, 0] \end{cases} . \tag{6}$$

Although our model is developed to model human infection regardless of its location, we use a volumetric measure unit (i. e., number of cells per cm^3 of tissue) to possibly compare our results with available experimental data, especially in the respiratory tract and the lung (Holt 2000; Holt et al. 2000; Marino and Kirschner 2004; Marino et al. 2004; Mercer et al. 1994; Stone et al. 1992; Wigginton et al. 2001).

In this work we have analytically analyzed only case 1 of the model leaving the analysis of case 2 for a future paper.

The model yields a boundary equilibrium, corresponding to the healthy or uninfected state, and an interior equilibrium, corresponding to an infection scenario. In Sect. 8.3 we have analyzed the main mathematical properties (positivity, boundedness and permanence of solutions) of the model, but a special emphasis is devoted to the local stability analysis (see Sect. 8.4) of the equilibria and particularly of the interior equilibrium. This special attention is due to the fact that the model equations involve distributed delays over finite intervals, and not simply fixed delays or delays over infinite intervals (for which last case the characteristic equation contains the Laplace transform of the delay kernels). Therefore the characteristic equation is dependent on the choice of the delay kernels used in the model, which in the present model, are either uniform or exponential.

Table 8.2. Parameter values

Name	Definition	Range	Units	Reference
μ_{X_U}	Half-life of X_U (like macrophages)	0.011	1/day	(Van Furth et al. 1973)
α_1	Rate of infection	$1e^{-3}$	$B(t)^{-1}$/day	Estimated
α_2	Rate of killing of X_I due to A_R	$1e^{-3}$	$A_R(t)^{-1}$/day	(Flesch and Kaufmann 1990; Lewinsohn et al. 1998; Silver et al. 1998a; Tan et al. 1997; Tsukaguchi et al 1995)
μ_{X_I}	Half-life of X_I	0.011	1/day	(Van Furth et al. 1973)
α_{20}	Growth rate of B	.5	1/day	(North and Izzo 1993; Silver et al. 1998a; Silver et al. 1998b)
σ	Max # of bacteria (threshold)	1e5	$B(t)$	Estimated
α_3	Rate of killing of B due to I_R	$1e^{-4}$	$I_R(t)^{-1}$/day	(Flesch and Kaufmann 1990)
α_4	Rate of killing of B due to A_R	$1e^{-4}$	$A_R(t)^{-1}$/day	Estimated
μ_{I_R}	Half-life of innate immunity cells	.11	1/day	(Sprent et al. 1973)
μ_{A_R}	Half-life of adaptive immunity cells	0.3333	1/day	(Sprent et al. 1973)
τ_1	Delay of innate immunity	[.1, 10]	day	
τ_2	Delay of adaptive immunity	[5, 40]	day	

Furthermore, since the interior equilibrium has components dependent on the range of the delay intervals τ_i, $i = 1, 2$, the characteristic equation will result in a polynomial transcendental equation of exponential type with polynomial coefficients that are dependent on the delay (range) τ_i. In the following of this paper the range of the delay intervals τ_i, $i = 1, 2$, will simply be called the delays τ_1 and τ_2 respectively for innate and adaptive immunity response.

For the polynomial transcendental characteristic equation mentioned above, a geometric stability switch criterion has been derived that enables study of possible stability switches as functions of delays (see Beretta and Kuang 2002). In Sect. 8.5, using the parameter values of Table 8.2 and initial conditions in (6) and Table 8.1, we describe the numerical simulations of the solutions of our model for delay values close to the stability switch values.

A discussion of the mathematical results and of their biological implications for the model is presented in Sects. 8.6 and 8.7.

8.3 Analytical results

The equations of the model are:

$$\begin{aligned}
\frac{\mathrm{d}X_U(t)}{\mathrm{d}t} &= s_U - \alpha_1 X_U(t)B(t) - \mu_{X_U} X_U(t) \\
\frac{\mathrm{d}X_I(t)}{\mathrm{d}t} &= \alpha_1 X_U(t)B(t) - \alpha_2 X_I(t)A_R(t) - \mu_{X_I} X_I(t) \\
\frac{\mathrm{d}B(t)}{\mathrm{d}t} &= \alpha_{20} B(t)\left(1 - \frac{B(t)}{\sigma}\right) - \alpha_3 B(t) I_R(t) \\
\frac{\mathrm{d}I_R(t)}{\mathrm{d}t} &= s_{I_R} + \int_{-\tau_1}^{0} w_1(\theta) B(t+\theta)\,\mathrm{d}\theta - \mu_{I_R} I_R(t) \\
\frac{\mathrm{d}A_R(t)}{\mathrm{d}t} &= s_{A_R} + \int_{-\tau_2}^{0} w_2(\theta) B(t+\theta)\,\mathrm{d}\theta - \mu_{A_R} A_R(t)
\end{aligned} \tag{7}$$

In the following we denote by

$$\Delta(\tau_i) = \int_{-\tau_i}^{0} w_i(\theta)\,\mathrm{d}\theta\,, \quad i = 1, 2\,. \tag{8}$$

We now discuss the main mathematical properties of system (7).

Let $h = \max\{\tau_1, \tau_2\} = \tau_2$ and define

$$x(t) := (X_U(t), X_I(t), B(t), I_R(t), A_R(t)) \in \mathbb{R}^5$$

and $X_t(\theta) = X(t+\theta)\,, \quad \theta \in [-h, 0]$ for all $t \geq 0$. Then (7) can be rewritten as

$$x'(t) = F(x_t) \tag{9}$$

with initial conditions at $t = 0$ given by

$$\Phi \in C([-h, 0], \mathbb{R}^5)$$

where $C([-h, 0], \mathbb{R}^5)$ is the Banach space of continuous functions mapping the interval $[-h, 0]$ into $\mathbb{R}^5$ equipped with the (supremum) norm

$$\| \Phi \| = \sup_{\theta \in [-h, 0]} |\Phi(\theta)|$$

where $|\cdot|$ is any norm in $\mathbb{R}^5$.

For the biological relevance, according to (6) and Table 8.1, we define non-negative initial conditions

$$\Phi(\theta) \geq 0\,, \quad \theta \in [-h, 0]$$

with

$$\Phi_i(0) > 0\,, \quad i = 1, 3, 4, 5 \quad \text{and} \quad \Phi_2(0) = X_I(0) = 0$$

to (7).

Lemma 1. *Any solution* $x(t) = x(\Phi, t)$ *of (7) with* $\Phi(\theta) \geq 0, \theta \in [-h, 0]$, $\Phi(0) > 0$ *(except for* $\Phi_2(0) = 0$*) remains positive whenever it exists, i. e.* $x(t) \in \mathbb{R}^5_+$ *where*

$$\mathbb{R}^5_+ = \{x = (x_1.x_2, x_3, x_4, x_5) \in \mathbb{R}^5 | x_i > 0, i = 1, 2, 3, 4, 5\}$$

Proof. Consider the third equation in (7):

$$\frac{\mathrm{d}B}{\mathrm{d}t} = B(t)\left[\alpha_{20}\left(1 - \frac{B(t)}{\sigma}\right) - \alpha_3 I_R(t)\right]$$

with $B(0) = \Phi_3(0) > 0$. Then

$$B(t) = B(0)\exp\left\{\int_0^t \left[\alpha_{20}\left(1 - \frac{B(s)}{\sigma}\right) - \alpha_3 I_R(s)\right] \mathrm{d}s\right\} > 0\,, \quad t \geq 0 \quad (10)$$

The first equation in (7) gives:

$$\frac{\mathrm{d}X_U}{\mathrm{d}t} > -X_U(t)(\alpha_1 B(t) + \mu_{X_U})\,, \quad X_U(0) = \Phi_1(0) > 0\,,$$

i. e.

$$X_U(t) > X_U(0)\exp\left\{-\int_0^t [\alpha_1 B(s) + \mu_{X_U}]\,\mathrm{d}s\right\} > 0\,, \quad t \geq 0 \qquad (11)$$

Since $X_U(t) > 0, B(t) > 0$ for $t \geq 0$, the second equation in (7) gives

$$\frac{\mathrm{d}X_I}{\mathrm{d}t} > -X_I(t)\left(\alpha_2 A_R(t) + \mu_{X_I}\right)\,, \quad X_I(0) = \Phi_2(0) = 0\,,$$

i. e.

$$X_I(t) > 0 \quad t \geq 0 \qquad (12)$$

Consider the last two equations in (7). Since $B(\theta) = \Phi_3(\theta) \geq 0$ in $[-h, 0]$ and $B(t) > 0$ for $t \geq 0$, we have

$$\frac{\mathrm{d}I_R(t)}{\mathrm{d}t} \geq s_{I_R} - \mu_{I_R} I_R(t)\,, \quad I_R(0) = \Phi_4(0) > 0\,,$$

i. e.

$$I_R(t) \geq I_R(0)\,\mathrm{e}^{-\mu_{I_R} t} + \frac{s_{I_R}}{\mu_{I_R}}(1 - \mathrm{e}^{-\mu_{I_R} t}) > 0\,, \quad t \geq 0\,. \qquad (13)$$

Similarly,

$$\frac{\mathrm{d}A_R(t)}{\mathrm{d}t} \geq s_{A_R} - \mu_{A_R} A_R(t)\,, \quad A_R(0) = \Phi_5(0) > 0\,,$$

i. e.

$$A_R(t) \geq A_R(0)\,\mathrm{e}^{-\mu_{A_R} t} + \frac{s_{A_R}}{\mu_{A_R}}(1 - \mathrm{e}^{-\mu_{A_R} t}) > 0\,, \quad t \geq 0\,. \qquad (14)$$

This completes the proof of positivity. □

Let us consider the boundedness of solutions.

Lemma 2. *Any solution $x(t) = x(\Phi, t)$ of (7) is bounded.*

Proof. Because of positivity of solutions, the first two equations in (7) give

$$\frac{\mathrm{d}}{\mathrm{d}t}(X_U(t) + X_I(t)) < s_U - \mu\,(X_U(t) + X_I(t))$$

where

$$\mu = \min\{\mu_{X_U}, \mu_{X_I}\}\,.$$

Hence

$$\limsup_{t\to\infty}\,(X_U(t) + X_I(t)) \leq \frac{s_U}{\mu}\,. \tag{15}$$

Positivity of solutions still implies

$$\frac{\mathrm{d}B(t)}{\mathrm{d}t} \leq \alpha_{20} B(t)\left(1 - \frac{B(t)}{\sigma}\right)$$

and therefore

$$\limsup_{t\to\infty} B(t) \leq \sigma\,. \tag{16}$$

Accordingly, there exists a $T_\epsilon > 0$ such that for all $t > T_\epsilon + h$ ($h = \max\{\tau_1, \tau_2\}$) and for sufficiently small $\epsilon > 0, B(t) < \sigma + \epsilon$. Hence, the last two equations in (7) give

$$\frac{\mathrm{d}I_R(t)}{\mathrm{d}t} < s_{I_R} + (\sigma + \epsilon)\Delta(\tau_1) - \mu_{I_R} I_R(t)$$

$$\frac{\mathrm{d}A_R(t)}{\mathrm{d}t} < s_{A_R} + (\sigma + \epsilon)\Delta(\tau_2) - \mu_{A_R} A_R(t)$$

thus implying (by letting $\epsilon \to 0$),

$$\limsup_{t\to\infty} I_R(t) \leq \frac{s_{I_R} + \sigma\Delta(\tau_1)}{\mu_{I_R}} \tag{17}$$

$$\limsup_{t\to\infty} A_R(t) \leq \frac{s_{A_R} + \sigma\Delta(\tau_2)}{\mu_{A_R}} \tag{18}$$

This proves boundedness. □

Definition 1 (Permanence of (7)). *System (7) is permanent (or uniformly persistent) if there exist positive constants $m, M, m < M$, independent of initial conditions and such that for solutions of (7), we have:*

$$\max\left\{\limsup_{t\to\infty} X_U(t), \limsup_{t\to\infty} X_I(t), \limsup_{t\to\infty} B(t), \limsup_{t\to\infty} I_R(t), \limsup_{t\to\infty} A_R(t)\right\} \leq M$$

$$\min\left\{\liminf_{t\to\infty} X_U(t), \liminf_{t\to\infty} X_I(t), \liminf_{t\to\infty} B(t), \liminf_{t\to\infty} I_R(t), \liminf_{t\to\infty} A_R(t)\right\} \geq m \tag{19}$$

Lemma 3. *Provided that*

$$\alpha_{20} > \alpha_3 \frac{s_{I_R} + \sigma\Delta(\tau_1)}{\mu_{I_R}}\,, \tag{20}$$

system (7) is permanent.

Proof. Let us consider the "lim sup" i. e. the first of (19).

From the first equation of (7) and Lemma 1 (positivity), we have:

$$\frac{\mathrm{d}X_U}{\mathrm{d}t} \le s_U - \mu_{X_U} X_U(t)\,,$$

which implies that

$$\limsup_{t\to\infty} X_U(t) \le \frac{s_U}{\mu_{X_U}} := \bar{X}_U\,. \tag{21}$$

From (16), (21) and the second of equations (7), for sufficiently large $t > 0$ and small $\epsilon > 0$, we have

$$\frac{\mathrm{d}X_I(t)}{\mathrm{d}t} < \alpha_1 \left(\frac{s_U}{\mu_{X_U}} + \epsilon\right)(\sigma + \epsilon) - \mu_{X_I} X_I(t)\,,$$

which gives

$$\limsup_{t\to\infty} X_I(t) \le \frac{\alpha_1 \left(\dfrac{s_U}{\mu_{X_U}}\right)\sigma}{\mu_{X_I}} := \bar{X}_I\,. \tag{22}$$

Hence, from (16)–(18), (21), (22) we have

$$\begin{aligned}&\left(\limsup_{t\to\infty} X_U(t), \limsup_{t\to\infty} X_I(t), \limsup_{t\to\infty} B(t), \limsup_{t\to\infty} I_R(t), \limsup_{t\to\infty} A_R(t)\right)\\ &\le (\bar{X}_U, \bar{X}_I, \bar{B}, \bar{I}_R, \bar{A}_R)\end{aligned} \tag{23}$$

where

$$\bar{B} = \sigma\,, \quad \bar{I}_R = \frac{s_{I_R} + \sigma\Delta(\tau_1)}{\mu_{I_R}}\,, \quad \bar{A}_R = \frac{s_{A_R} + \sigma\Delta(\tau_2)}{\mu_{A_R}}\,.$$

If we choose

$$M = \max(\bar{X}_U, \bar{X}_I, \bar{B}, \bar{I}_R, \bar{A}_R)\,,$$

then there exists $M > 0$ such that the first inequality in (19) holds true.

Consider now the "liminf", i. e. the second in (19).

(i) Consider A_R, I_R.
From (13) and (14) we have

$$\liminf_{t\to\infty} I_R(t) \ge \frac{s_{I_R}}{\mu_{I_R}} := \underline{I}_R\,, \quad \liminf_{t\to\infty} A_R(t) \ge \frac{s_{A_R}}{\mu_{A_R}} := \underline{A}_R \tag{24}$$

(ii) Consider B.
From (23), for sufficiently large $t > 0$ and small $\epsilon > 0$ we have

$$\frac{\mathrm{d}B(t)}{\mathrm{d}t} \geq \alpha_{20} B(t) \left(1 - \frac{B(t)}{\sigma}\right) - (\alpha_3 \bar{I}_R + \epsilon) B(t)$$
$$= \alpha_{20} B(t) \left(1 - \frac{\alpha_3 \bar{I}_R + \epsilon}{\alpha_{20}} - \frac{B(t)}{\sigma}\right) .$$

Hence, letting $\epsilon \to 0$

$$\liminf_{t\to\infty} B(t) \geq \left(\frac{\alpha_{20} - \alpha_3 \bar{I}_R}{\alpha_{20}}\right) \sigma := \underline{B} \tag{25}$$

where $\underline{B} > 0$ provided that

$$\alpha_{20} > \alpha_3 \frac{s_{I_R} + \sigma \Delta(\tau_1)}{\mu_{I_R}} (= \alpha_3 \bar{I}_R) .$$

(iii) Consider X_U.
For large $t > 0$, small $\epsilon > 0$ we have

$$\frac{\mathrm{d}X_U(t)}{\mathrm{d}t} \geq s_U - (\alpha_1(\bar{B} + \epsilon) + \mu_{X_U}) X_U$$

from which, letting $\epsilon \to 0$

$$\liminf_{t\to\infty} X_U(t) \geq \frac{s_U}{\alpha_1 \sigma + \mu_{X_U}} := \underline{X}_U \tag{26}$$

(iv) Consider X_I.
For large $t > 0$, small $\epsilon > 0$ we have

$$\frac{\mathrm{d}X_I(t)}{\mathrm{d}t} \geq \alpha_1 (\underline{X}_U - \epsilon)(\underline{B} - \epsilon) - (\alpha_2(\bar{A}_R + \epsilon) + \mu_{X_I}) X_I(t)$$

from which, letting $\epsilon \to 0$, we obtain

$$\liminf_{t\to\infty} X_I(t) \geq \frac{\alpha_1 \underline{X}_U \underline{B}}{\alpha_2 \bar{A}_R + \mu_{X_I}} := \underline{X}_I \tag{27}$$

hence, provided that (20) hods true, (24)–(27) imply that

$$\begin{aligned} &\big(\liminf_{t\to\infty} X_U(t), \liminf_{t\to\infty} X_I(t), \liminf_{t\to\infty} B(t), \liminf_{t\to\infty} I_R(t) , \\ &\liminf_{t\to\infty} A_R(t)\big) \geq (\underline{X}_U, \underline{X}_I, \underline{B}, \underline{I}_R, \underline{A}_R) , \end{aligned} \tag{28}$$

where the constants on the right side of (28) are positive.

Thus, if we choose

$$m = \min(\underline{X}_U, \underline{X}_I, \underline{B}, \underline{I}_R, \underline{A}_R) , \quad m > 0$$

considering that $\liminf x(t) \leq \limsup x(t)$, we have found two positive constants $m, M, m \leq M$ such that (19) hold true. □

Remark 1. As we will see in Theorem 1, if $\Delta(\tau_1) = 0$ the permanence condition (20) becomes the existence condition of the positive equilibrium E_P. Furthermore, if $\Delta(\tau_1) = 0$, then $\underline{B} = B^*$.

Concerning the equilibria of (7), we can give the following result (we omit the computations which can be easily checked):

Theorem 1. *The system (7) gives two non-negative equilibria:*

1. *for all parameter values the boundary equilibrium exists*

$$E_B = \left(X_U^* = \frac{s_U}{\mu_{X_U}}, X_I^* = 0\,,\; B^* = 0, I_R^* = \frac{s_{I_R}}{\mu_{I_R}}, A_R^* = \frac{s_{A_R}}{\mu_{A_R}} \right) \tag{29}$$

on the boundary of the positive cone in R^5 *and*

2. *for* $\alpha_{20} - \alpha_3 \left(s_{I_R}/\mu_{I_R}\right) > 0$ *the positive equilibrium exists*

$$E_P = (X_U^*, X_I^*, B^*, I_R^*, A_R^*)\ .$$

with the following values for each component

$$E_P = \left(\begin{array}{lll} X_U^* = \dfrac{s_U}{\alpha_1 B^* + \mu_{X_U}}, & X_I^* = \dfrac{\alpha_1 B^* X_U^*}{\alpha_2 A_R^* + \mu_{X_I}}, & B^* = \dfrac{\alpha_{20} - \alpha_3 \dfrac{s_{I_R}}{\mu_{I_R}}}{\dfrac{\alpha_{20}}{\sigma} + \alpha_3 \dfrac{\Delta(\tau_1)}{\mu_{I_R}}} \\ I_R^* = \dfrac{s_{I_R} + \Delta(\tau_1) B^*}{\mu_{I_R}}, & A_R^* = \dfrac{s_{A_R} + \Delta(\tau_2) B^*}{\mu_{A_R}} & \end{array} \right) \tag{30}$$

which is interior to the positive cone in R^5.

We observe that the positive equilibrium E_P exists whenever the parameter

$$R_0 := \alpha_{20} - \alpha_3 \frac{s_{I_R}}{\mu_{I_R}} \tag{31}$$

is positive and E_P coincides with the boundary equilibrium E_B as $R_0 = 0$. When $R_0 < 0$ we have only the boundary equilibrium E_B.

8.4 Characteristic equation and local stability

System (7) linearized around any of the equilibria gives

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = Lx(t) + \int_{-h}^{0} K(\theta) x(t+\theta)\,\mathrm{d}\theta\,. \tag{32}$$

If we define by $x(t) = \mathrm{col}\,(X_U(t), X_I(t), B(t), I_R(t), A_R(t))$, then by inspection of (7) we get that $L \in \mathrm{R}^{5\times 5}$ is the matrix

$$\boldsymbol{L} = \begin{pmatrix} -\alpha_1 B^* - \mu_{X_U} & 0 & -\alpha_1 X_U^* & 0 & 0 \\ \alpha_1 B^* & -\alpha_2 A_R^* - \mu_{X_I} & \alpha_1 X_U^* & 0 & -\alpha_2 X_I^* \\ 0 & 0 & \left(\alpha_{20} - \alpha_3 I_R^* - \frac{2\alpha_{20}}{\sigma} B^*\right) & -\alpha_3 B^* & 0 \\ 0 & 0 & 0 & -\mu_{I_R} & 0 \\ 0 & 0 & 0 & 0 & -\mu_{A_R} \end{pmatrix} \tag{33}$$

and $K\,(\theta) : [-h, 0] \longrightarrow \mathrm{R}^{5\times 5}$is the matrix function

$$\boldsymbol{K} = \begin{pmatrix} 0\,0 & 0 & 0\,0 \\ 0\,0 & 0 & 0\,0 \\ 0\,0 & 0 & 0\,0 \\ 0\,0 & \tilde{w}_1(\theta) & 0\,0 \\ 0\,0 & w_2(\theta) & 0\,0 \end{pmatrix} \tag{34}$$

where $\tilde{w}_1(\theta) = \begin{cases} w_1(\theta) & \text{in } [-\tau_1\,,\,0] \\ 0 & \text{in } [-\tau_2\,,\,-\tau_1] \end{cases}$. The associated characteristic equation is

$$\det\left(\lambda \boldsymbol{I} - \boldsymbol{L} - \int_{-h}^{0} \boldsymbol{K}\,(\theta)\,\mathrm{e}^{\lambda\theta}\,\mathrm{d}\theta\right) = 0 \tag{35}$$

where $\boldsymbol{I} \in \mathrm{R}^{5\times 5}$ is the identity matrix and λ are the characteristic roots. If we define by

$$F_i\,(\lambda) := \int_{-\tau_i}^{0} w_i(\theta)\,\mathrm{e}^{\lambda\theta}\,\mathrm{d}\theta\,, \quad i = 1, 2 \tag{36}$$

then we get the following explicit structure for the characteristic equation:

$$\begin{vmatrix} \lambda + (\alpha_1 B^* + \mu_{X_U}) & 0 & \alpha_1 X_U^* & 0 & 0 \\ -\alpha_1 B^* & \lambda + (\alpha_2 A_R^* + \mu_{X_I}) & -\alpha_1 X_U^* & 0 & \alpha_2 X_I^* \\ 0 & 0 & \lambda - \left(\alpha_{20} - \alpha_3 I_R^* - \frac{2\alpha_{20}}{\sigma} B^*\right) & \alpha_3 B^* & 0 \\ 0 & 0 & -F_1\,(\lambda) & \lambda + \mu_{I_R} & 0 \\ 0 & 0 & -F_2\,(\lambda) & 0 & \lambda + \mu_{A_R} \end{vmatrix} = 0 \tag{37}$$

It is easy to check that (37) can be written as:

$$\begin{aligned} &[\lambda + (\alpha_1 B^* + \mu_{X_U})]\,[\lambda + (\alpha_2 A_R^* + \mu_{X_I})] \\ &\cdot \det \begin{pmatrix} \lambda - \left(\alpha_{20} - \alpha_3 I_R^* - \frac{2\alpha_{20}}{\sigma} B^*\right) & \alpha_3 B^* & 0 \\ -F_1\,(\lambda) & \lambda + \mu_{I_R} & 0 \\ -F_2\,(\lambda) & 0 & \lambda + \mu_{A_R} \end{pmatrix} = 0\,, \end{aligned}$$

i. e. we have three negative characteristic roots

$$\lambda_1 = -(\alpha_1 B^* + \mu_{X_U}) \quad \lambda_2 = -(\alpha_2 A_R^* + \mu_{X_I}) \quad \lambda_3 = -\mu_{A_R} \tag{38}$$

and the other characteristic roots are solution of:

$$\det \begin{pmatrix} \lambda - \left(\alpha_{20} - \alpha_3 I_R^* - \frac{2\alpha_{20}}{\sigma} B^*\right) & \alpha_3 B^* \\ -F_1(\lambda) & \lambda + \mu_{I_R} \end{pmatrix} = 0 . \tag{39}$$

Thus the study of the characteristic equation (37) is reduced to the study of (39), the remaining characteristic roots being negative.

We remark that $F_2(\lambda)$ does not appear in (39), then the characteristic roots in (39) are independent of the second delay τ_2 of the model, i. e. the term $\int_{-\tau_2}^{0} w(\theta) B(t+\theta) d\theta$ does not play any role in the local stability of the equilibria. This implies that the first delay, that of innate immunity, is determinant in disease outcome. This likely follows because the adaptive response, A_R, does not feedback into (3). Recall this was one formulation of a delay, and in other works we consider others.

Regarding local stability of the boundary equilibrium, we can prove:

Theorem 2. *The boundary equilibrium E_B is:*

1. *asymptotically stable if*

$$\alpha_{20} - \alpha_3 (s_{I_R}/\mu_{I_R}) < 0 ;$$

2. *linearly neutrally stable if*

$$\alpha_{20} - \alpha_3 (s_{I_R}/\mu_{I_R}) = 0 ;$$

with one real vanishing characteristic root, while others characteristic roots are negative;

3. *unstable (with one positive real root) if*

$$\alpha_{20} - \alpha_3 (s_{I_R}/\mu_{I_R}) > 0 .$$

Proof. It follows immediately from (39) (since at the boundary equilibrium $E_B, B^* = 0$ and $I_R^* = (s_{I_R}/\mu_{I_R})$ which gives two characteristic roots: one negative $\lambda = -\mu_{I_R}$ and the other equal to the threshold parameter R_0 for the existence of interior equilibrium E_P:

$$\lambda = \alpha_{20} - \alpha_3 (s_{I_R}/\mu_{I_R}) .$$

□

We now study the local stability of the positive equilibrium E_P. Assume $R_0 > 0$.

At E_P, B^* satisfies

$$\alpha_{20} - \alpha_3 I_R^* - \frac{\alpha_{20}}{\sigma} B^* = 0$$

and therefore (39) reduces to

$$\det \begin{pmatrix} \lambda + \frac{\alpha_{20}}{\sigma} B^* & \alpha_3 B^* \\ -F_1(\lambda) & \lambda + \mu_{I_R} \end{pmatrix} = 0 \,. \tag{40}$$

Therefore the local stability of E_P leads to the equation

$$\lambda^2 + \lambda \left(\mu_{I_R} + \frac{\alpha_{20}}{\sigma} B^* \right) + B^* \left(\mu_{I_R} \frac{\alpha_{20}}{\sigma} + \alpha_3 F_1(\lambda) \right) = 0 \tag{41}$$

where the information of the delay τ_1 is carried by $F_1(\lambda) := \int_{-\tau_1}^{0} w_1(\theta) \mathrm{e}^{\lambda\theta} \, \mathrm{d}\theta$ and is therefore dependent on the choice of the delay kernel $w_1(\theta)$.

8.4.1 Uniform delay kernel

Since $F_1(\lambda)$ regards the delay in immune response it is reasonable, as stated in the introduction, to assume that the delay kernel w_1 is uniform, i. e.

$$w_1(\theta) = A \,, \quad \theta \in [-\tau_1, 0] \,. \tag{42}$$

Then

$$F_1(\lambda) = \frac{A}{\lambda}(1 - \mathrm{e}^{-\lambda\tau_1}) \tag{43}$$

which is defined since $\lambda = 0$ is not a root of (41). In fact, if $\lambda = 0$ then $F_1(0) = \Delta(\tau_1)$ and (41) becomes

$$B^*(\tau_1) \left(\mu_{I_R} \frac{\alpha_{20}}{\sigma} + \alpha_3 \Delta(\tau_1) \right) \neq 0 \,, \quad \forall \tau_1 \geq 0 \,, \tag{44}$$

where by $B^*(\tau_1)$ we emphasize the dependence on delay τ_1, as it is evident from the equilibrium components (30).

Now remark that if $\tau_1 = 0$, then $F_1(\lambda) = 0$ and (41) becomes

$$\lambda^2 + \lambda \left(\mu_{I_R} + \frac{\alpha_{20}}{\sigma} B^*(0) \right) + \mu_{I_R} \frac{\alpha_{20}}{\sigma} B^*(0) = 0 \,, \tag{45}$$

which has two negative roots, i. e. E_P is asymptotically stable at $\tau_1 = 0$.

We have thus the general problem to find the delay values τ_1, if they exist, at which for increasing τ_1 the stability of E_P changes or, in other words, at which E_P undergoes a stability switch.

Since $\lambda = 0$ cannot be a root of (41) for any $\tau_1 \geq 0$ a stability switch for E_P can only occur at delay values τ_1 at which a pair of pure imaginary roots $\lambda = \pm i\omega(\tau_1), \omega(\tau_1) > 0$, crosses the imaginary axis.

Substituting (43) in (41) it is easy to check that (41) takes the form

$$P(\lambda,\tau_1)+Q(\lambda,\tau_1)\mathrm{e}^{-\lambda\tau_1}=0 \tag{46}$$

where P is a third order degree polynomial

$$P(\lambda,\tau_1)=p_3(\tau_1)\lambda^3+p_2(\tau_1)\lambda^2+p_1(\tau_1)\lambda+p_0(\tau_1) \tag{47}$$

with delay dependent coefficients

$$\begin{cases} p_3(\tau_1)=1 \\ p_2(\tau_1)=\mu_{I_R}+\dfrac{\alpha_{20}B^*(\tau_1)}{\overset{\sigma}{(\tau_1)}} \\ p_1(\tau_1)=\dfrac{\mu_{I_R}\alpha_{20}B^*(\tau_1)}{\overset{\sigma}{(\tau_1)}} \\ p_0(\tau_1)=\alpha_3 A\, B^*(\tau_1) \end{cases} \tag{48}$$

and Q is a zeroth order polynomial

$$Q(\lambda,\tau_1)=q_0(\tau_1)=-\alpha_3 A\; B^*(\tau_1)\,. \tag{49}$$

The occurrence of stability switches for equations with delay dependent coefficients of the type (46) has been recently studied by Beretta and Kuang (2002) who have proposed a geometric stability switch criterion. We summarize it below.

We consider the class of characteristic equations of the form

$$P(\lambda,\tau)+Q(\lambda,\tau)\mathrm{e}^{-\lambda\tau}=0\,,\quad \tau\in\mathbb{R}_{+0} \tag{50}$$

where P, Q are two polynomials in λ

$$P(\lambda,\tau)=\sum_{k=0}^{n}p_k(\tau)\lambda^k\,;\quad Q(\lambda,\tau)=\sum_{k=0}^{m}q_k(\tau)\lambda^k,\quad n,m\in\mathbb{N}_0\,,\ n>m \tag{51}$$

with coefficients $p_k(\cdot),q_k(\cdot)\colon \mathbb{R}_{+0}\to\mathbb{R}$ which are continuous and differentiable functions of τ.

We assume that

(H1) $P(0,\tau)+Q(0,\tau)=p_0(\tau)+q_0(\tau)\neq 0,\forall\tau\in\mathbb{R}_{+0}$ i. e. $\lambda=0$ is not a root of (50);
(H2) at $\tau=0$ all roots of (50) have negative real parts;
(H3) if $\lambda=i\omega,\omega\in\mathbb{R}$, then

$$P(i\omega,\tau)+Q(i\omega,\tau)\neq 0\,,\quad \forall\tau\in\mathbb{R}_{+0}\,.$$

We now turn to the problem of finding the roots $\lambda=\pm i\omega,\omega\in\mathbb{R}_+$ of (50).

A necessary condition is that

$$F(\omega,\tau)=0 \tag{52}$$

where

$$F(\omega,\tau) := |P(i\omega,\tau)|^2 - |Q(i\omega,\tau)|^2 \,. \tag{53}$$

Let $\omega = \omega(\tau), \tau \in I \subset \mathbb{R}_{+0}$ be a solution of (52). We assume that $\omega = \omega(\tau)$ is a continuous and differentiable function of $\tau \in I$.

For each solution $\omega = \omega(\tau), \tau \in I$, of (50) we find the angle $\theta = \theta(\tau), \tau \in I$ satisfying

$$\begin{cases} \sin\theta(\tau) = \dfrac{-P_R(i\omega,\tau)\,Q_I(i\omega,\tau) + P_I(i\omega,\tau)\,Q_R(i\omega,\tau)}{|Q(i\omega,\tau)|^2} \\ \cos\theta(\tau) = -\dfrac{P_R(i\omega,\tau)\,Q_R(i\omega,\tau) + P_I(i\omega,\tau)\,Q_I(i\omega,\tau)}{|Q(i\omega,\tau)|^2} \end{cases} \tag{54}$$

where, thanks to $(H3)$ we can prove that $\theta(\tau) \in (0, 2\pi)$, $\tau \in I$ and $\theta(\tau)$ is a continuous and differentiable function of $\tau \in I$.

By the functions $\omega = \omega(\tau), \theta = \theta(\tau), \tau \in I$, we define the functions $S_n : I \to \mathbb{R}$ according to

$$S_n(\tau) := \tau - \frac{\theta(\tau) + n2\pi}{\omega(\tau)}\,, \quad n \in \mathbb{N}_0\,, \tag{55}$$

which are continuous and differentiable for $\tau \in I$.

Finally, by any mathematical software such as Maple or Matlab, we draw the curves S_n versus $\tau \in I$ looking for their zeros

$$\tau^* \in I : S_n(\tau^*) = 0\,. \tag{56}$$

In fact, we can prove the following:

Theorem 3. *All the roots $\lambda = \pm i\omega(\tau), \omega(\tau) > 0$ of (50) occur at the delay values τ^* if and only if τ^* is a zero of one of the functions in the sequence S_n, $n \in \mathbb{N}_0$.*

At each $\tau^* \in I$ a pair of roots of (50) $\lambda = \pm i\omega(\tau^*)$ is crossing the imaginary axis according to the sign of

$$\operatorname{sign}\left\{\left.\frac{\mathrm{dRe}\lambda}{\mathrm{d}\tau}\right|_{\lambda=\pm i\omega(\tau^*)}\right\} = \operatorname{sign}\left\{F'_\omega(\omega(\tau^*),\tau^*)\right\}\operatorname{sign}\left\{\left.\frac{\mathrm{d}S_n(\tau)}{\mathrm{d}\tau}\right|_{\tau=\tau^*}\right\}\,. \tag{57}$$

A stability switch occurs at $\tau = \tau^* \in I$ if the total multiplicity on the right side of the imaginary axis changes from 0 to 2 or from 2 to 0 when τ increases through τ^*.

Theorem 4. *If τ^* is the lowest positive zero of the function $S_0(\tau)$ and the transversality condition*

$$sign\left\{\left.\frac{\mathrm{dRe}\lambda}{\mathrm{d}\tau}\right|_{\lambda=\pm i\omega(\tau^*)}\right\} = 1$$

holds, (50) has

(a) all roots with negative real parts if $\tau \in [0, \tau^*)$;
(b) a pair of conjugate pure imaginary roots $\pm i\omega(\tau^*), \omega(\tau^*) > 0$, *crossing the imaginary axis, and all the other roots with negative real part if* $\tau = \tau^*$;
(c) two roots with strictly positive real part if $\tau > \tau^*$;
(d) because of (b), all the roots λ $(\neq \pm i\omega(\tau^*))$ *satisfy the condition* $\lambda \neq im\omega(\tau^*)$, *where* m *is any integer, if* $\tau = \tau^*$.

Hence, at $\tau = \tau^*$ *a Hopf bifurcation occurs (see Hale and Verduyn Lunel, chap. 11, (Hale and Verduyn Lunel 1993))*

Using the parameter values of Table 8.2 in the Introduction we can prove the following:

Theorem 5. *If the uniform delay kernel* w_1 *in (46)–(49) is such that* $A = \dfrac{1}{\tau_1}$, *then in the biological range* $[0.1, 10]$ *there is one stability switch at the delay value*

$$\tau_{1_0}^{+} = 5.6491$$

toward instability, which is also a Hopf bifurcation value.

Proof. We describe the algorithm presented in the previous pages applied to the characteristic equation (46) whose structure is defined in (47), (48) and (49).

1st Step. From (47)–(49) we have

$$P(i\omega, \tau_1) = \left(p_0(\tau_1) - \omega^2 p_2(\tau_1)\right) + i\left(\omega p_1(\tau_1) - \omega^3\right) \tag{58}$$

with

$$P_R(i\omega, \tau_1) = p_0(\tau_1) - \omega^2 p_2(\tau_1), \quad P_I(i\omega, \tau_1) = \omega p_1(\tau_1) - \omega^3 \tag{59}$$

$$Q(i\omega, \tau_1) = q_0(\tau_1) \tag{60}$$

with

$$Q_R(i\omega, \tau_1) = q_0(\tau_1)\,, \quad Q_I(i\omega, \tau_1) = 0\,. \tag{61}$$

Then

$$F(\omega, \tau_1) := |P(i\omega, \tau_1)|^2 - |Q(i\omega, \tau_1)|^2$$

yields

$$F(\omega, \tau_1) = \omega^2[\omega^4 + a_2(\tau_1)\omega^2 + a_1(\tau_1)] = 0 \tag{62}$$

where

$$\begin{cases} a_2(\tau_1) = \mu_{I_R}^2 + \left(\dfrac{\alpha_{20} B^*(\tau_1)}{\sigma}\right)^2 > 0 \\ a_1(\tau_1) = p_1^2(\tau_1) - 2p_0(\tau_1)\, p_2(\tau_1) \\ \qquad = \left[\dfrac{\mu_{I_R}\alpha_{20} B^*(\tau_1)}{\sigma}\right]^2 - 2\alpha_3 A\, B^*(\tau_1)\left(\mu_{I_R} + \dfrac{\alpha_{20} B^*(\tau_1)}{\sigma}\right) \end{cases} \tag{63}$$

It is easy to check that $a_1(\tau_1) < 0$ in $[0, \tau_1^*)$ where

$$\tau_1^* := \frac{2\alpha_3 \left(\mu_{I_R} + \dfrac{\alpha_{20} B^*}{\sigma}\right)}{\left(\dfrac{\mu_{I_R}\alpha_{20}}{\sigma}\right)^2 B^*} = 1.6950 \times 10^5$$

where $B^* = 4.376 \times 10^2$ (we further note that $a_1(\tau_1^*) = 0$ and $a_1(\tau_1) > 0$ in $(\tau_1^*, +\infty)$, i. e. $F(\omega, \tau_1) > 0$ in $(\tau_1^*, +\infty)$ and no stability switch can occur in such a delay range). Since in the biological range $[0.1, 10]$ it is $a_1(\tau_1) < 0$, the only positive root of (62) in the biological range is

$$\begin{cases} \omega_+(\tau_1) = \left[\dfrac{1}{2}\left(-a_2(\tau_1) + \sqrt{a_2^2(\tau_1) - 4a_1(\tau_1)}\right)\right]^{1/2} \\ \tau_1 \in (0, \tau_1^*) = \mathrm{I} \end{cases} \tag{64}$$

(such that $\omega_+(\tau_1^*) = 0$). Furthermore, it's easy to check that

$$F'_\omega(\omega_+(\tau_1), \tau_1) > 0\,. \tag{65}$$

2nd Step. According to (59), (61) we can define the angle $\theta_+(\tau_1)$ as solution of

$$\begin{cases} \sin\theta_+(\tau_1) = -\dfrac{\omega_+ p_1(\tau_1) - \omega_+^3}{|q_0(\tau_1)|} \\ \cos\theta_+(\tau_1) = \dfrac{p_0(\tau_1) - \omega_+^2 p_2(\tau_1)}{|q_0(\tau_1)|} \end{cases} . \tag{66}$$

3rd Step. We define the functions $S_n^+ : \mathrm{I} \to \mathbb{R}$, where $I = [0.1, 10]$, by

$$S_n^+(\tau_1) := \tau_1 - \frac{\theta_+(\tau_1) + n2\pi}{\omega_+(\tau_1)}\,, \quad \tau_1 \in I = (0, \tau_1^*)\,, \quad n \in \mathbb{N}_0\,. \tag{67}$$

According to Theorem 2 if $\tau_{1_i}^+$ is a zero of $S_n^+(\tau_1)$ for some $n \in \mathbb{N}_0$, then at $\tau_1 = \tau_{1_i}^+$ there is a pair of pure imaginary roots $\lambda = \pm i\omega_+(\tau_{1_i}^+)$, $\omega_+(\tau_{1_i}^+) > 0$, crossing the imaginary axis according to

$$\begin{aligned} \operatorname{sign}\left\{\left.\frac{\mathrm{dRe}\lambda}{\mathrm{d}\tau_1}\right|_{\lambda=\pm i\omega(\tau_{1_i}^+)}\right\} &= \operatorname{sign}\left\{F'_\omega\left(\omega_+(\tau_{1_i}^+), \tau_{1_i}^+\right)\right\} \operatorname{sign}\left\{\left.\frac{\mathrm{d}S_n^+(\tau_1)}{\mathrm{d}\tau_1}\right|_{\tau_1=\tau_{1_i}^+}\right\} \\ &= \operatorname{sign}\left\{\left.\frac{\mathrm{d}S_n^+(\tau_1)}{d\tau_1}\right|_{\tau_1=\tau_{1_i}^+}\right\} . \end{aligned} \tag{68}$$

In Fig. 8.1 are depicted the graphs of functions $S_n^+(\tau_1)$ versus τ_1 in the biological range $[0.1, 10]$. Only S_0^+ has a zero at $\tau_{1_0}^+ = 5.6491$ which, according to Theorem 2, is a stability switch delay value toward instability. Furthermore, thanks to Theorem 4 we can say that at $\tau_{1_0}^+ = 5.6491$ we have a Hopf bifurcation delay value. □

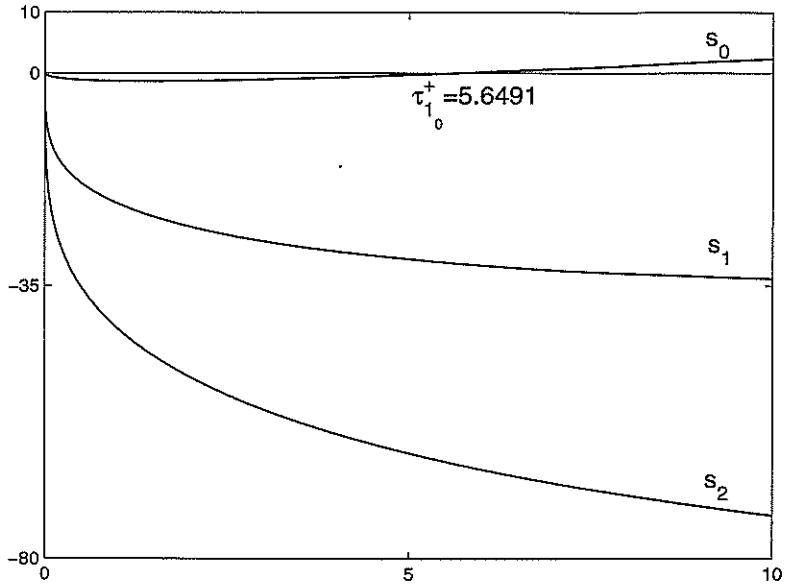

Fig. 8.1. Graphs of functions $S_n^+(\tau_1)$ versus τ_1 in the biological range $[0.1, 10]$. Only S_0^+ has one zero at $\tau_{1_0}^+ = 5.6491$ which is a stability switch delay value toward instability and a Hopf bifurcation delay value

It may be mathematically interesting to consider the functions $S_n^+(\tau_1)$ versus τ_1 even outside of the biological range. As shown in Fig. 8.2 in the range $[0.1, 350]$ for τ_1 the functions S_0^+, S_1^+, S_2^+ present zeros respectively at the delay values $\tau_{1_0}^+ = 5.6491$, $\tau_{1_1}^+ = 91.2267$ and $\tau_{1_2}^+ = 260.4919$. However, by (68) we can see that only $\tau_{1_0}^+$ is a stability switch delay value since between $\tau_{1_0}^+, \tau_{1_1}^+$ the total multiplicity of characteristic roots with positive real part, say

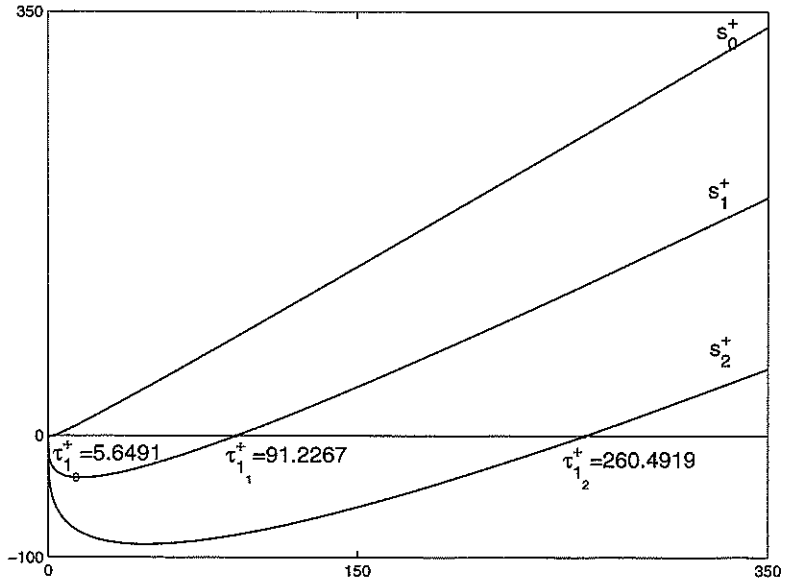

Fig. 8.2. In the range $[0.1, 350]$ are depicted the graphs of the functions S_n^+ versus τ_1. Besides S_0^+ even S_1^+ and S_2^+ have zeros respectively at $\tau_{1_1}^+ = 91.2267$ and $\tau_{1_2}^+ = 260.4919$ but the stability switch occurs at the zero of S_0^+: $\tau_{1_0}^+ = 5.6491$

ρ, is $\rho = 2$ and becomes $\rho = 4$ between $\tau_{1_1}^+$ and $\tau_{1_2}^+$ and finally becomes $\rho = 6$ beyond $\tau_{1_2}^+$. Thus, E_P becomes unstable after $\tau_{1_0}^+$ and it remains unstable on the whole range.

However, we may further observe that, since $\tau_1 \to \tau_1^*$ from left implies $\omega_+(\tau_1) \to 0$, by (66) we see that $\theta_+(\tau_1) \to 2\pi$ and by (67) we have $S_n^+(\tau_1) \to -\infty$ as $\tau_1 \to \tau_1^*$ for each $n \in \mathbb{N}_0$.

Since S_n^+ are continuous and continuously differentiable functions of τ_1, for each S_n^+ which has a zero with positive slope, there exists another one with negative slope. In conclusion, there are only two stability switches which are two external zeros of S_0^+ and which are the external zeros of all the zeros in the sequence S_n^+. The first stability switch from asymptotic stability to instability is at $\tau_{1_0}^+$ and the second stability switch is at the last zero of S_0^+, say at $\tau_{2_0}^+$ from instability to asymptotic stability.

In the interval $(\tau_{1_0}^+, \tau_{2_0}^+)$ the positive equilibrium is unstable. For $\tau_1 > \tau_{2_0}^+$ the positive equilibrium regains its asymptotic stability which is kept for all $\tau_1 \in (\tau_{2_0}^+, +\infty)$.

8.4.2 Exponential delay kernel

If in (41) we assume an exponential delay kernel

$$w_1(\theta) = A\ \mathrm{e}^{k\theta}\ , \quad \theta \in [-\tau_1, 0]\ , \quad A, k \in \mathbb{R}_+ \tag{69}$$

then

$$F_1(\lambda) = \frac{A}{\lambda + k}\left[1 - \mathrm{e}^{-(\lambda+k)\tau_1}\right]\ . \tag{70}$$

If $\lambda = -k$ is not a solution of (41) (if $\lambda = -k$ is a solution the E_P is asymptotically stable) substitution of (70) in (41) leads to (46) where the delay-dependent coefficients (48) are now given by

$$\begin{cases} p_3(\tau_1) = 1 \\ p_2(\tau_1) = k + \mu_{I_R} + \dfrac{\alpha_{20} B^*(\tau_1)}{\sigma} \\ p_1(\tau_1) = k\left(\mu_{I_R} + \dfrac{\alpha_{20} B^*(\tau_1)}{\sigma}\right) + \dfrac{\mu_{I_R}\alpha_{20} B^*(\tau_1)}{\sigma} \\ p_0(\tau_1) = +B^*(\tau_1)\left(\dfrac{k\mu_{I_R}\alpha_{20}}{\sigma} + \alpha_3 A\right) \end{cases} \tag{71}$$

and (49) by

$$q_0(\tau_1) = -\alpha_3 B^*(\tau_1)\, A \mathrm{e}^{-k\tau_1}\ . \tag{72}$$

Even in this case if $\lambda = 0$ we have $F_1(0) = \Delta(\tau_1)$ and (44) shows that $\lambda = 0$ is not a characteristic root for any $\tau_1 \geq 0$. Furthermore, at $\tau_1 = 0$ (45) shows that E_P is asymptotically stable. Hence, again we can ask if increasing τ_1 in the biological range $[0.1, 10]$ there is a delay value at which a stability switch toward instability occurs.

We can follow the same procedure shown for the case of uniform delay kernel, taking into account that the coefficients of (46) are now given by (71) and (72). We omit the detailed computations of steps 1–3. According to Theorems 2 and 3 we can then prove:

Theorem 6. *In the exponential delay kernel (69) we choose* $A = k = \dfrac{\log 2}{\tau_1}$, *then in the biological range* $[0.1, 10]$ *there is one stability switch at the delay value*

$$\tau_{1_0}^{+} = 6.69310$$

toward instability, which is also a Hopf bifurcation delay value.

8.5 Numerical simulations

We simulated the system by numerically solving the differential equations using suitable numerical methods. Our aim was to confirm that the Hopf bifurcations in Theorems 4 and 5 give rise, for increasing delay τ_1, to solutions which show sustained oscillations. We used two different procedures to study the solutions of system (7) with initial conditions (6) and Table 8.1.

Considering the general case for delay equations (7) i. e. of exponential delay kernels for innate and adaptive immune responses,

$$\begin{aligned} &w_i(\theta) = A_i e^{K_i \theta}\,, \quad \theta \in [-\tau_1, 0]\,, \quad i = 1, 2 \\ &A_i, K_i \in \mathbb{R}_+ \end{aligned}$$

in system (7) we define the new variables

$$\begin{aligned} u_I(t) &:= \int_{-\tau_1}^{0} w_1(\theta) B(t+\theta)\,\mathrm{d}\theta \\ u_A(t) &:= \int_{-\tau_2}^{0} w_2(\theta) B(t+\theta)\,\mathrm{d}\theta \end{aligned} \tag{73}$$

By the transformation $s = t + \theta$ (73) give

$$\begin{aligned} u_I(t) &:= \int_{t-\tau_1}^{t} w_1(s-t) B(s)\,\mathrm{d}s \\ u_A(t) &:= \int_{t-\tau_2}^{t} w_2(s-t) B(s)\,\mathrm{d}s \end{aligned} \tag{74}$$

which is straightforward checking that they satisfy the equations

$$\begin{aligned} \frac{\mathrm{d}u_I}{\mathrm{d}t} &= A_1 B(t) - A_1\,\mathrm{e}^{-K_1\tau_1} B(t-\tau_1) - K_1 u_I(t) \\ \frac{\mathrm{d}u_A}{\mathrm{d}t} &= A_2 B(t) - A_2\,\mathrm{e}^{-K_2\tau_2} B(t-\tau_2) - K_2 u_A(t) \end{aligned}$$

hence, system (7) is transformed into

$$\begin{aligned}
\frac{\mathrm{d}X_U(t)}{\mathrm{d}t} &= s_U - \alpha_1 X_U(t)B(t) - \mu_{X_U} X_U(t) \\
\frac{\mathrm{d}X_I(t)}{\mathrm{d}t} &= \alpha_1 X_U(t)B(t) - \alpha_2 X_I(t)A_R(t) - \mu_{X_I} X_I(t) \\
\frac{\mathrm{d}B(t)}{\mathrm{d}t} &= \alpha_{20} B(t)\left(1 - \frac{B(t)}{\sigma}\right) - \alpha_3 B(t) I_R(t) \\
\frac{\mathrm{d}I_R(t)}{\mathrm{d}t} &= s_{I_R} + u_I(t) - \mu_{I_R} I_R(t) \\
\frac{\mathrm{d}A_R(t)}{\mathrm{d}t} &= s_{A_R} + u_A(t) - \mu_{A_R} A_R(t) \\
\frac{\mathrm{d}u_I(t)}{\mathrm{d}t} &= A_1 B(t) - A_1 \mathrm{e}^{-K_1\tau_1} B(t-\tau_1) - K_1 u_I(t) \\
\frac{\mathrm{d}u_A(t)}{\mathrm{d}t} &= A_2 B(t) - A_2 \mathrm{e}^{-K_2\tau_2} B(t-\tau_2) - K_2 u_A(t)
\end{aligned} \tag{75}$$

with initial conditions given by (6) and Table 8.1, and particularly B takes i.c. on the interval $[-\tau_2, 0]$, i. e.

$$B(s) = \Phi_3(s)\,, \quad s \in [-\tau_2, 0]\,, \tag{76}$$

thus defining at $t = 0$ the initial conditions for u_I and u_A in (75) by

$$\begin{aligned}
u_I(0) &= \int_{-\tau_1}^{0} w_1(s)\Phi_3(s)\,\mathrm{d}s \\
u_A(0) &= \int_{-\tau_2}^{0} w_2(s)\Phi_3(s)\,\mathrm{d}s\,.
\end{aligned} \tag{77}$$

Hence, system (7) is transformed into an equivalent system of delay differential equations (75) with fixed delay τ_1, τ_2, where "equivalent" means that such a new system has the same characteristic equation and same equilibria (regarding the original variables (X_U, X_I, B, I_R, A_R)) as the original system (7) (we leave to the reader to check it). Note that the case of uniform delay kernel for innate response I_R is simply obtained by setting $K_1 = 0$ in (75).

Such a new system (75) may be solved by any delay differential equations solver. We used the Matlab *dde23* by Shampine and Thompson. The second way is by directly approximating the solution of the distributed delay system through the trapezoidal rule for the equations and the (composite) trapezoidal quadrature formula for the integrals. The overall order of accuracy of the method is 2 (Baker and Ford 1988).

We have performed simulations for both cases of uniform (see Figs. 8.3, 8.4) and exponential (see Figs. 8.5, 8.6) delay kernels for the innate response and for τ_1 values below the Hopf threshold $\tau_{1_0}^+$ and for $\tau_1 > \tau_{1_0}^+$, showing in this last case that sustained oscillations occurred.

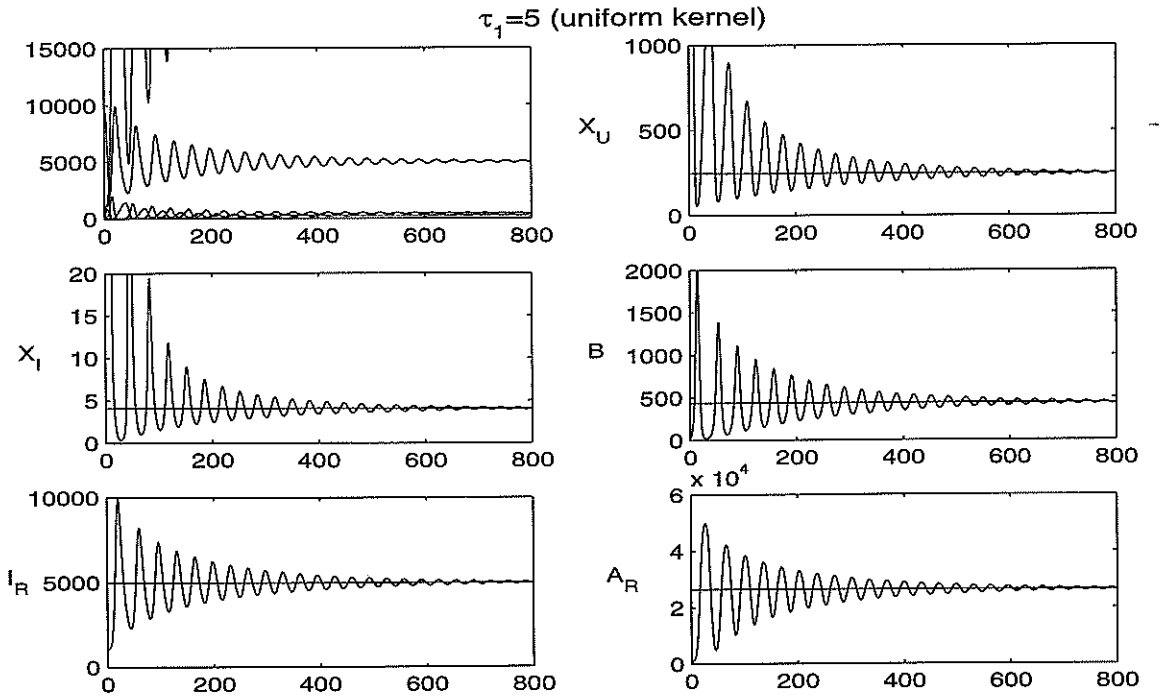

Fig. 8.3. Simulations of solutions of system (7) in case of uniform delay kernel for the innate response with $A_1 = 1$. The delay τ_1 is chosen below the threshold $\tau_{1_0}^+$ of Theorem 4. The top left figure shows the behaviour of all the variables together. The straight lines represent the equilibrium components. The delay kernel for the adaptive response is uniform with $A_2 = 1$ and τ_2 is kept fixed at the value 20

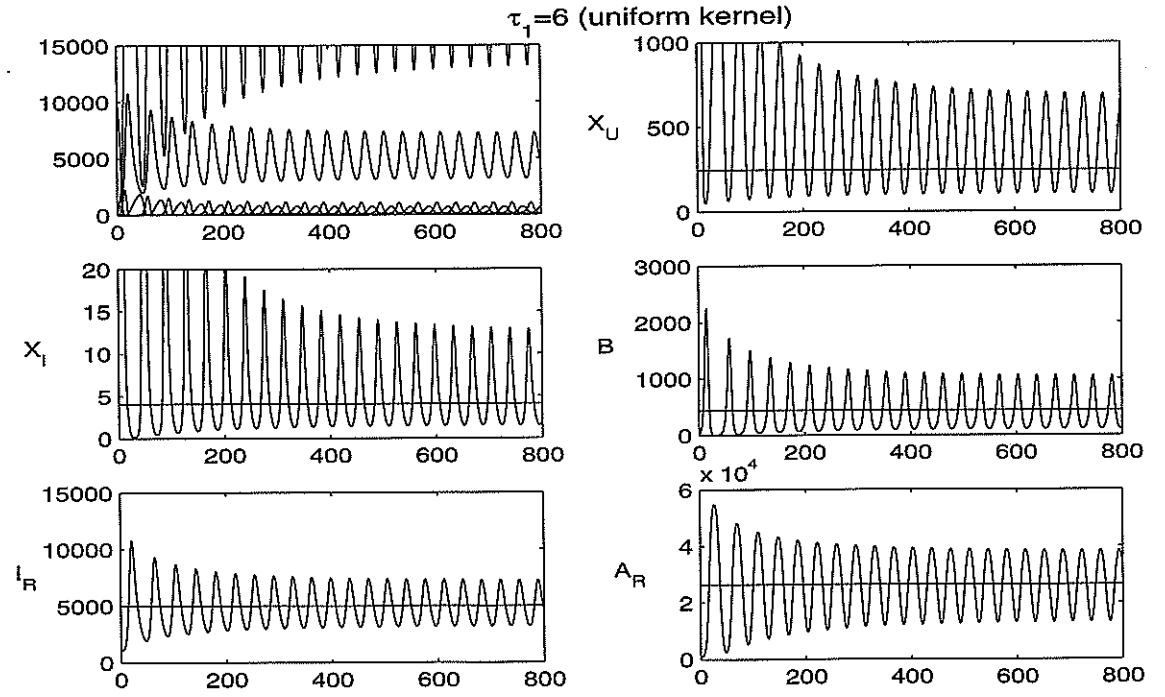

Fig. 8.4. Simulations of solutions of system (7) in case of uniform delay kernel for the innate response with $A_1 = 1$. The delay τ_1 is chosen above the threshold $\tau_{1_0}^+$ of Theorem 4. The delay kernel for the adaptive response is uniform with $A_2 = 1$ and τ_2 is kept fixed at the value 20

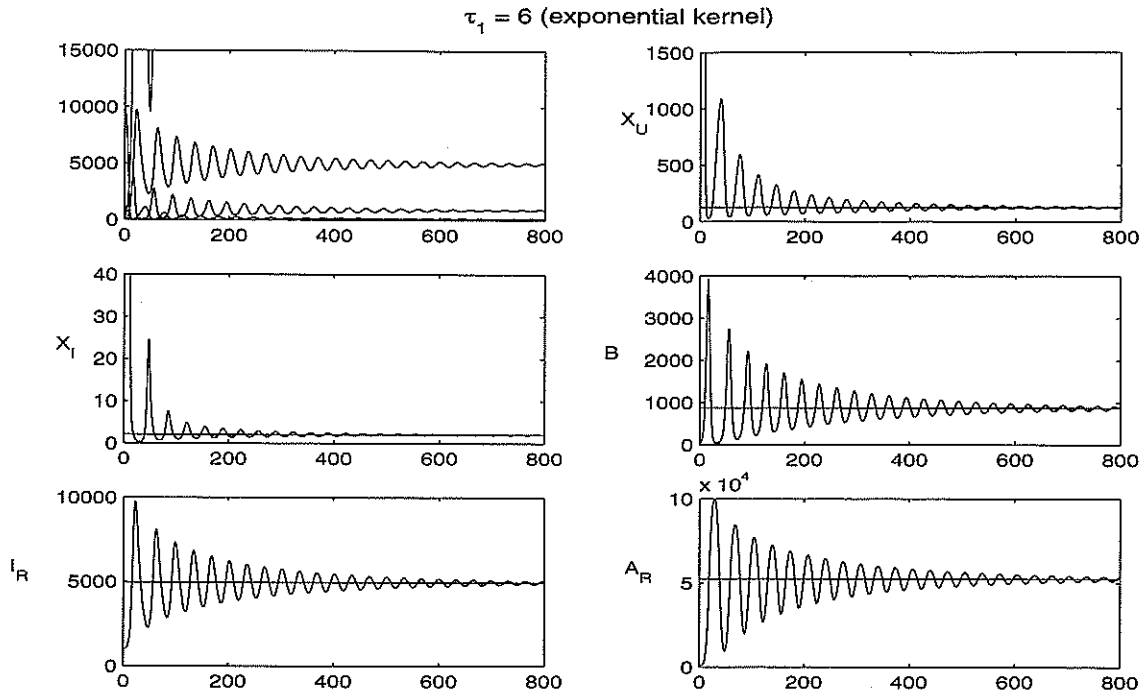

Fig. 8.5. Simulations of solutions of system (7) in case of exponential delay kernel for the innate response with $A_1 = K_1 = \log 2/\tau_1$. The delay τ_1 is chosen below the threshold $\tau_{1_0}^+$ of Theorem 5. The delay kernel for the adaptive response is uniform with $A_2 = 1$ and τ_2 is kept fixed at the value 20

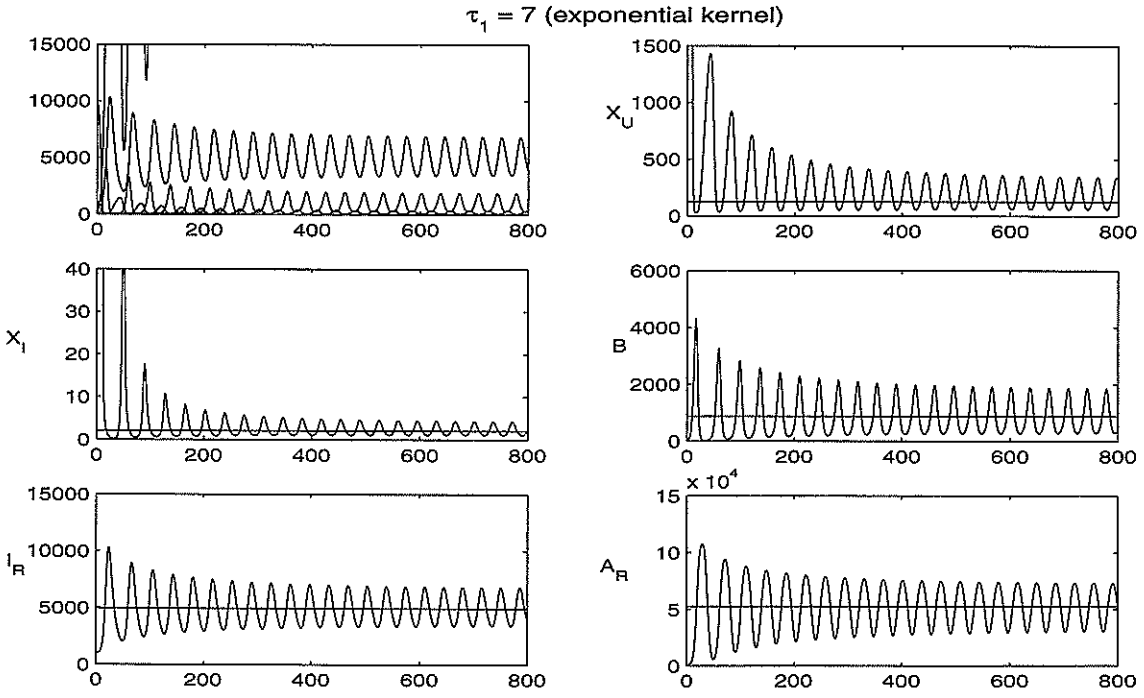

Fig. 8.6. Simulations of solutions of system (7) in case of exponential delay kernel for the innate response with $A_1 = K_1 = \log 2/\tau_1$. The delay τ_1 is chosen above the threshold $\tau_{1_0}^+$ of Theorem 5. The delay kernel for the adaptive response is uniform with $A_2 = 1$ and τ_2 is kept fixed at the value 20

8.6 Discussion

We develop a mathematical model to address timing of the immune system when challenged by intracellular bacterial infection. A baseline model accounts for different killing capabilities of the immune system and incorporates two delays representing the two types of immune responses, namely innate and adaptive immunity for which two different cases of delay interactions are proposed. We have discussed only case 1, remarking however that case 2 can be studied similarly.

The baseline model, case 1, admits a boundary equilibrium E_B or uninfected steady state and only when the threshold parameter R_0 in (31) becomes positive one positive equilibrium E_P bifurcates from E_B (transcritical bifurcation) corresponding to the infected steady state. The local stability of E_B is independent of the delays in the innate (τ_1) and adaptive (τ_2) immune responses. E_B is asymptotically stable whenever the positive equilibrium E_P is not feasible and unstable if E_P exists. The positive equilibrium E_P has components dependent on either the delay τ_1 or on the delay τ_2 although its local stability is independent of τ_2, as it is evident by (40). The study of the characteristic equation leads to (41) where the term $F_1(\lambda)$ takes information of the delay kernel $w_1(\theta)$, $\theta \in [-\tau_1, 0]$ in the innate immune response. This is a crucial point in modelling the immune system since there is little information regarding these delays. Assuming a uniform or exponential delay kernel, (41) takes the form of the polynomial exponential transcendental equation (46) with delay dependent coefficients given by (47)–(49) for uniform delay kernel or by (71)–(72) for an exponential delay kernel. Of course, the change of the numerical value of any parameter in the delay kernel may lead to different outcomes of the stability analysis. We note that at $\tau_1 = 0$ the positive equilibrium E_P is asymptotically stable whereas, increasing τ_1, E_P has a Hopf bifurcation toward sustained oscillations (see Sect. 8.5) at $\tau_{1_0}^+ = 5.6491$ in the case of uniform delay kernel (with $A = \frac{1}{\tau_1}$) or at $\tau_{1_0}^+ = 6.69310$ in the case of exponential delay kernel (with $A = K = \frac{\log 2}{\tau_1}$).

We could attempt to derive global stability results for E_P by Lyapunov functional method, but the presence of a Hopf bifurcation with respect to τ_1 should lead to severe bounds on τ_1. We do not show such computations here but the global stability result for E_P requires values of τ_1, τ_2 close to zero, i. e. useless in understanding the behaviour of the model for large delays. Though we do not discuss the baseline model case 2, it is interesting to note that this model presents many of the properties of the model case 1. In both cases there are two non-negative equilibria E_B and E_P, the second arising when the same threshold parameter R_0 in (31) is positive and again, for the stability of E_B, Theorem 2 holds true. The main difference is in the stability analysis for E_P which is now dependent on both delays τ_1 and τ_2.

8.7 Biological discussion

Our baseline model suggests a key role for innate immunity in establishing a protective response and describes how different delay times and shapes affect the pattern of bacterial growth and its impact on the host. Our study indicates how a delayed innate response (τ_1 larger than 5 days) results in oscillatory behavior, suggesting how trade offs for initial conditions of both the host (for example the baseline level of innate immunity cells, I_R^{baseline}, or the host capability of containing the early stages of infection) and the pathogen (its proliferation rate, α_{20}) determine the final infection outcome. E_B or uninfected steady state represents a successful immune response of the host: bacteria are cleared and the system returns to equilibrium. The model suggests how this scenario is stable, is readily achieved and it is independent from delays either in innate or adaptive responses. Clearance in this case seems more a structural property of the host (initial number of cells and their efficacy in killing) and the pathogenicity of the bacteria (virulence factors). E_P or the infected steady state represents successful colonization of the host by bacteria. Here the innate immunity "memory" plays an important role: the shorter τ_1, the easier infection can be stabilized (τ_1 smaller than the stability switch $\tau_{1_0}^+$). In fact, a small value for τ_1 (on the order of hours) is more biologically consistent and plausible than τ_1 on the order of days. Damped oscillation still lead to an infection scenario: some level of intracellular bacteria always persists (Figs. 8.1 and 8.3). Considering τ_1 larger than the stability switch (see Figs. 8.2 and 8.4), the average of the oscillations is equivalent to the level of bacteria in the oscillations. Although, on average, the two outcomes are similar, a biological difference can be drawn in terms of latent versus chronic infection scenarios. Latent infection represents a damped oscillation where a "peaceful" coexistence between the host and the intracellular bacteria is established. On the other hand, a chronic infection scenario is suggested by a sustained oscillation, where an "unstable" and potentially dangerous coexistence between the host and the pathogen could be driven out of control more easily by either host factor or environmental pressure. As an example consider tuberculosis infection in humans. The adaptive immune response to Mycobacterium tuberculosis infection is the formation of a multicellular immune structure called a granuloma. Recent hypotheses suggest how granuloma are a dynamic entities (Capuano et al. 2003) that contain the spread of the infection to other parts of the body. A continuous trade-off between host immune cells and bacteria numbers exists within the granuloma: waves of infection and bursting of chronically infected cells (releasing intracellular bacteria) are contained by waves of effector cells taking up bacteria and stabilizing infection. The exponential kernel induces larger oscillations in bacterial levels, suggesting how a uniform kernel is more beneficial for the innate response, and also more biologically plausible.

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