

STABILITY OF A VIRAL INFECTION MODEL WITH STATE-DEPENDENT DELAY, CTL AND ANTIBODY IMMUNE RESPONSES

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ABSTRACT. A virus dynamics model with intracellular state-dependent delay and nonlinear infection rate of Beddington-DeAngelis functional response is studied. The technique of Lyapunov functionals is used to analyze stability of the main interior infection equilibrium which describes the case of both CTL and antibody immune responses activated. We consider first a particular biologically motivated class of discrete state-dependent delays. The general case is investigated next. The stability of the infection-free and the immune-exhausted equilibria is also discussed.

1. Introduction. We are interested in mathematical models of infectious diseases. The diseases are caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi. According to World Health Organization, many viruses (as Ebola virus, Zika virus, HIV, HBV, HCV and others) continue to be a major global public health issues.

In our research we concentrate on models of viral infections. There have been variety of models with and without delays which described dynamics between different viral infections and immune responses. Delays could be concentrated or distributed. We will not describe the historical evolution of such models, just mention that early models [15, 14] contain three variables: susceptible host cells, infected cells and free virus. Next step was to take into account, as written in [27], that “one particular part of the immune system that is very important in the fight against viral infections are the killer T cells or cytotoxic T lymphocytes (CTL).” See also [31] and references therein. There is another adaptive immune response by antibodies. The relative balance of both types of immune response “can be a decisive factor that determines whether patients are asymptomatic or whether pathology is observe” [26]. These lead to introduction of two additional variables of both immune responses [26, 27] (see also [29] and references therein).

The model under consideration contains five variables: susceptible (noninfected) host cells T , infected cells T^* , free virus V , a CTL response Y , and an antibody

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This paper is dedicated to the memory of Igor D. Chueshev.

response A . In case of bilinear nonlinearities and one constant concentrated delay (see, for example, [28]) it has the following form

$$\begin{cases} \dot{T}(t) = \lambda - dT(t) - kT(t)V(t), \\ \dot{T}^*(t) = e^{-\omega h} kT(t-h)V(t-h) - \delta T^*(t) - pY(t)T^*(t), \\ \dot{V}(t) = N\delta T^*(t) - cV(t) - qA(t)V(t), \\ \dot{Y}(t) = \beta T^*(t)Y(t) - \gamma Y(t) \\ \dot{A}(t) = gA(t)V(t) - bA(t). \end{cases} \quad (1)$$

Here the dot over a function denotes the time derivative i.g, $\dot{T}(t) = \frac{dT(t)}{dt}$, all the constants $\lambda, d, k, \delta, p, N, c, q, \beta, \gamma, g, b, \omega$ are positive. As for the immune responses, the fourth equation describes the regulation of CTL response with $pY(t)T^*(t)$ (in the second equation) being the rate of killing of infected cells by lytic immune response. The fifth equation describes the regulation of antibody response with $qA(t)V(t)$ (in the third equation) being the rate of virus neutralization by antibodies [26, p.1744]. In (1), h denotes the delay between the time the virus contacts a target cell and the time the cell becomes actively infected (starts to produce new virions).

In the above model, the standard bilinear incidence rate is used according to the principle of mass action. For more details and references on the models of infectious diseases with more general types of nonlinear incidence rates see e.g. [11, 5]. In [8] a general class of incidence functions is studied for the system without delay. See also [9] for models with finite and infinite distributed delays. In paper [30], following [10, 24, 28], authors assume that the infection rate of the virus dynamics models is given by the Beddington-DeAngelis functional response [1, 2], $\frac{kTV}{1+k_1T+k_2V}$, where $k, k_1, k_2 > 0$ are constants. The Lyapunov asymptotic stability [13] of points of equilibrium is studied for the following model with *constant* concentrated delay

$$\begin{cases} \dot{T}(t) = \lambda - dT(t) - f(T(t), V(t)), \\ \dot{T}^*(t) = e^{-\omega h} f(T(t-h), V(t-h)) - \delta T^*(t) - pY(t)T^*(t), \\ \dot{V}(t) = N\delta T^*(t) - cV(t) - qA(t)V(t), \\ \dot{Y}(t) = \beta T^*(t)Y(t) - \gamma Y(t), \\ \dot{A}(t) = gA(t)V(t) - bA(t). \end{cases} \quad (2)$$

The functional response

$$f(T, V) = \frac{kTV}{1 + k_1T + k_2V}, \quad k, k_1, k_2 > 0, \quad T, V \in R, \quad (3)$$

was introduced by Beddington [1] and DeAngelis et al. [2].

It is evident that the constancy of the delay is an extra assumption which essentially simplifies the analysis, but is not motivated by the biological background of the model. It was a reason (see e.g. [25]) to discuss distributed delay models as an alternative to discrete constant delay ones. We propose another approach.

Our goal is to remove the restriction of the constancy of the delay and investigate the well-posedness and Lyapunov stability of the following virus infection model with Beddington-DeAngelis functional response and *state-dependent delay*. It appears that the analysis essentially differs from the constant delay case. To the best of our knowledge, such models have not been considered before. It is well known that differential equations with state-dependent delay are always nonlinear by its nature (see the review [7] for more details and discussion). We also mention that the constant delay is a particular case of the state-dependent one.

As usual in a delay system with (maximal) delay $h > 0$, for a function $v(t), t \in [a, b] \subset \mathbb{R}, b > a + h$, we denote the history segment $v_t = v_t(\theta) \equiv v(t + \theta), \theta \in [-h, 0]$. We denote the space of continuous functions by $C \equiv C([-h, 0]; \mathbb{R}^5)$ equipped with the sup-norm. In the above notations, we use $u(t) = (T(t), T^*(t), V(t), Y(t), A(t))$ and consider a continuous functional (state dependent delay) $\eta : C \rightarrow [0, h]$. Now we can present the system under consideration

$$\begin{cases} \dot{T}(t) = \lambda - dT(t) - f(T(t), V(t)), \\ \dot{T}^*(t) = e^{-\omega h} f(T(t - \eta(u_t)), V(t - \eta(u_t))) - \delta T^*(t) - pY(t)T^*(t), \\ \dot{V}(t) = N\delta T^*(t) - cV(t) - qA(t)V(t), \\ \dot{Y}(t) = \beta T^*(t)Y(t) - \gamma Y(t), \\ \dot{A}(t) = gA(t)V(t) - bA(t). \end{cases} \tag{4}$$

with the functional response $f(T, V)$ given by (3). We denote by \mathcal{F} the right-hand side of (4) to write the system shortly as $\dot{u}(t) = \mathcal{F}(u_t)$.

The paper is organized as follows. In Section 2, we discuss and choose different sets of initial data and prove the existence and uniqueness of solutions. Next we prove that the sets are invariant. In Section 3 we remind some known results on the stationary points which are most interesting biologically. Section 4 is devoted to the stability properties of the stationary solutions. First, in Subsections 4.1 and 4.2, we study the stability of the main interior equilibrium which describes the case when both CTL and antibody immune responses are activated. We believe this infection equilibrium is the most biologically meaningful in the study of the disease. In Subsections 4.3 and 4.4 we show how our approach could be applied to an infection-free and an immune-exhausted equilibria. We use the technique of Lyapunov functionals [13] and consider first a particular (biologically motivated) case of state-dependent delay. Using this we investigate the general case. A part of the results has been announced in [21].

2. Preliminaries. We first study the basic questions of the existence and uniqueness of solutions to the problem (4). Since two functions T and V are used in (4) at different time moments (current time t and delayed time $t - \eta(u_t)$), we should consider initial values $T(\theta), V(\theta)$ for $\theta \in [-h, 0]$. As usual for such a biological system, one should check the non-negativeness and boundedness of all the coordinates provided initial values are non-negative (see e.g., [12]).

We will study the system (4) with an initial function

$$u_0 = \varphi \equiv (T_0, T_0^*, V_0, A_0, Y_0) \in C_+ \equiv C_+[-h, 0], \tag{5}$$

where $\mathbb{R}_+ \equiv [0, +\infty), C_+ \equiv C_+[-h, 0] \equiv C([-h, 0]; \mathbb{R}_+^5)$.

Let us introduce the set

$$\begin{aligned} \Omega_C \equiv \{ \varphi \equiv (T_0, T_0^*, V_0, A_0, Y_0) \in C_+[-h, 0], \\ 0 \leq T_0(\theta) \leq \frac{\lambda}{d}, \quad 0 \leq T_0^*(\theta) \leq \frac{k\lambda}{dk_2\delta} e^{-\omega h}, \quad 0 \leq V_0(\theta) \leq \frac{Nk\lambda}{cdk_2} e^{-\omega h}, \\ 0 \leq T_0^*(\theta) + \frac{p}{\beta} Y_0(\theta) \leq \frac{k^2\lambda^2 e^{-2\omega h}}{d^2 ck_2 \min\{\delta; \gamma\}}, \\ 0 \leq V_0(\theta) + \frac{q}{g} A_0(\theta) \leq \frac{Nk\lambda e^{-\omega h}}{dk_2 \min\{c; b\}}, \quad \theta \in [-h, 0] \}. \end{aligned} \tag{6}$$

We consider the following assumption on the state-dependent delay

$$\begin{aligned} (H1_\eta) \quad \forall \psi \in Z^{2,3} \equiv \{ \psi = (\psi^1, \psi^2, \psi^3, \psi^4, \psi^5) \in C_+ : \psi^2(0) = \psi^3(0) = 0 \} \\ \implies \eta(\psi) > 0. \end{aligned} \tag{7}$$

Remark 1. We notice that even more restrictive assumption $\eta(\psi) > 0$ for all $\psi \in C_+$ is biologically well motivated. On the other hand, even this restriction (the so-called “non-vanishing delay”) does not guarantee the uniqueness of solutions with merely continuous data (see [4] for examples).

The first result is the following

Theorem 2. *Let $\eta : C \rightarrow [0, h]$ be a continuous functional (state dependent delay). Then (i) for any initial function $\varphi \in C$ there exist continuous solutions to (4), (5).*

(ii) If additionally, η satisfies $(H1_\eta)$, then for any initial function $\varphi \equiv (T_0, T_0^, V_0, A_0, Y_0) \in \Omega_C$ such that T_0, V_0 are Lipschitz functions, the problem (4), (5) has a unique solution. The solution is globally Lipschitz in time and satisfies*

$$u_t \equiv (T_t, T_t^*, V_t, A_t, Y_t) \in \Omega_C, \quad t \geq 0.$$

Proof of Theorem 2. (i) The existence of continuous solutions is guaranteed by the continuity of the right-hand side of (4) and classical results on delay equations [6, 3].

(ii) Since T_0, V_0 are Lipschitz functions, the uniqueness of continuous solutions follows from the general results on differential equations with state-dependent delay (see the review on ordinary equations [7] for details and references and also [16, 17, 18, 20] for PDEs). Let us show that the set Ω_C is invariant i.e. any solution starting from $\varphi \in \Omega_C$ remains in Ω_C for all $t \geq 0$.

We notice that in the case of constant delay the non-negativeness of all coordinates of a solution follows from the quasi-positivity property of the right-hand side of (4) (see e.g. [22, Theorem 2.1, p.81]). We stress that in the case of state-dependent delay we cannot directly apply [22, Theorem 2.1, p.81] because it relies on the Lipschitz property of the right-hand side of a system, which is not the case for (4). We could use the corresponding extension to the state-dependent delay case [19], but we propose another way here.

To prove the non-negativeness of all coordinates of a solution $u(t) = (T(t), T^*(t), V(t), Y(t), A(t))$ we use the direct analysis of each coordinate. It is easy to see that $T(t) \rightarrow 0+$ implies $\dot{T}(t) \rightarrow \lambda > 0$ which makes impossible for T to become negative. The direct integration shows that coordinates satisfy

$$\begin{aligned} T^*(t) = & T^*(0) e^{-\int_0^t (\delta + pY(s)) ds} \\ & + e^{-\omega h} \int_0^t f(T(\tau - \eta(u_\tau)), V(\tau - \eta(u_\tau))) e^{-\int_\tau^t (\delta + pY(s)) ds} d\tau, \end{aligned} \tag{8}$$

$$V(t) = V(0) e^{-\int_0^t (c + qA(s)) ds} + N\delta \int_0^t T^*(\tau) e^{-\int_\tau^t (c + qA(s)) ds} d\tau, \tag{9}$$

$$Y(t) = Y(0) e^{-\int_0^t (\beta T^*(\tau) - \gamma) d\tau}, \quad A(t) = A(0) e^{-\int_0^t (gV(\tau) - b) d\tau}. \tag{10}$$

Equations (10) show that $Y(0) \geq 0, A(0) \geq 0$ implies $Y(t) \geq 0, A(t) \geq 0$ for all $t \geq 0$. For the constant delay case, equations (8), (9) would imply the similar result for $T^*(t), V(t)$, but for the state-dependent delay we need more care. First, (8) shows the property (for some $t^1 \geq 0$)

$$V(s) \geq 0, s \in [-h, t^1] \quad \text{implies} \quad T^*(s) \geq 0, s \in [0, t^1]. \tag{11}$$

Similarly, (9) gives

$$T^*(s) \geq 0, s \in [0, t^1] \implies V(s) \geq 0, s \in [0, t^1]. \tag{12}$$

Now, let us assume that the non-negativity of T^* or V fails. Properties (11), (12) show that T^* and V should change the sign simultaneously i.e. there exist a (smallest possible) time moment $t^1 \geq 0$ and $\delta^1 > 0$ such that $T^*(t) \geq 0, V(t) \geq 0$ for $t \in (t^1 - \delta^1, t^1]$ and $T^*(t) < 0, V(t) < 0$ for $t \in (t^1, t^1 + \delta^1)$. By the continuity of solutions, $T^*(t^1) = V(t^1) = 0$ which implies (see $(H1_\eta)$) that $u_{t^1} \in Z^{2,3}$ i.e. $\eta(u_{t^1}) > 0$. Hence there exists $\delta^2 > 0$ such that $V(\tau - \eta(u_\tau)) \geq 0$ for $\tau \in (t^1, t^1 + \delta^2)$. By this property and (8), one has $T^*(t) \geq 0$ for $t \in (t^1, t^1 + \delta^2)$. It contradicts the choice of t^1 and completes the proof of the non-negativity of all coordinates.

Let us prove the upper bounds on the coordinates, given in (6). To save the space we formulate an easy variant of the Gronwall's lemma.

Lemma 3. *Let $\ell \in C^1[a, b]$ and $\frac{d}{dt}\ell(t) \leq c_1 - c_2\ell(t), t \in [a, b]$. Then $\ell(a) \leq c_1c_2^{-1}$ implies $\ell(t) \leq c_1c_2^{-1}$ for all $t \in [a, b]$. In the case $b = +\infty$, for any $\varepsilon > 0$ there exists $t_\varepsilon \geq a$ such that $\ell(t) \leq c_1c_2^{-1} + \varepsilon$ for all $t \geq t_\varepsilon$.*

Proof of Lemma 3. We multiply the inequality $\frac{d}{dt}\ell(t) \leq c_1 - c_2\ell(t), t \in [a, b]$ by e^{c_2t} and integrate over $[a, t]$. It leads to $\ell(t) \leq \left(\ell(a) - \frac{c_1}{c_2}\right)e^{-c_2(t-a)} + \frac{c_1}{c_2}$ which completes the proof of Lemma 3. \square

Since f is non-negative for non-negative arguments (see (3)), we get from the first equation of (4) the estimate $\dot{T}(t) \leq \lambda - dT(t)$. Hence Lemma 3 and $T(0) \leq \frac{\lambda}{d}$ implies $T(t) \leq \frac{\lambda}{d}$ for $t \geq 0$. We use it to estimate the second coordinate, see (3), as follows $f(T, V) \leq \frac{k\lambda V}{d(1+k_2V)} \leq \frac{k\lambda}{dk_2}$. It gives $\dot{T}^*(t) \leq \frac{k\lambda}{dk_2}e^{-\omega h} - \delta T^*(t)$ and Lemma 3 implies the needed bound for T^* in (6). The bound for T^* and the third equation in (4) give $\dot{V}(t) \leq N\delta T^*(t) - cV(t) \leq \frac{Nk\lambda}{dk_2}e^{-\omega h} - cV(t)$. Lemma 3 proves the estimate for V in (6). Next, we use the second and the fourth equations in (4) to get

$$\begin{aligned} \dot{T}^*(t) + \frac{p}{\beta}\dot{Y}(t) &= e^{-\omega h}f(T(t - \eta(u_t)), V(t - \eta(u_t))) - \delta T^*(t) - \frac{\gamma p}{\beta}Y(t) \\ &\leq e^{-\omega h}kT_{max}V_{max} - \min\{\delta; \gamma\} \left(T^*(t) + \frac{p}{\beta}Y(t)\right) \\ &\leq k\frac{\lambda Nk\lambda}{dcdk_2}e^{-2\omega h} - \min\{\delta; \gamma\} \left(T^*(t) + \frac{p}{\beta}Y(t)\right). \end{aligned}$$

Lemma 3 proves the bound for $T^*(t) + \frac{p}{\beta}Y(t)$ in (6). In the similar way, using the third and fifth equations in (4), one gets

$$\dot{V}(t) + \frac{q}{g}\dot{A}(t) \leq N\delta T^*(t) - cV(t) - \frac{bq}{g}A(t) \leq \frac{Nk\lambda}{dk_2}e^{-\omega h} - \min\{c; b\} \left(V(t) + \frac{q}{g}A(t)\right).$$

Lemma 3 implies the last estimate in (6). All solutions are global (defined for all $t \geq -h$). It completes the proof of Theorem 2. \square

Remark 4. We notice our invariant set Ω_C differs from the absorbing set Γ , used in [30] for the constant delay system. Let us denote by Ω_C^ε the set where all the upper bounds in (6) are increased by ε . Then the second part of the Lemma 3 implies that for any $\varepsilon > 0$ the set Ω_C^ε is absorbing for any solution (not necessary starting in Ω_C). Another difference is that all the five coordinates of $\varphi \in \Omega_C$ are continuous functions in contrast to the constant delay case [30], where the second, fourth and fifth coordinates belong to R_+ .

Remark 5. It is well known that continuous solutions to differential equations with state-dependent delay may be non-unique (see examples in [4]). There are two ways to insure the uniqueness of solutions. The first one is to restrict the set of initial functions [7]. The second one is to restrict the class of state-dependent delays [16, 18] and work with continuous initial functions.

If one is interested in continuously differentiable solutions, we could also apply the solution manifold approach [23, 7] to the initial value problem (4), (5). We remind the short notation for the system (4) as $\dot{u}(t) = \mathcal{F}(u_t)$. Let us introduce the following subset of Ω_C (c.f. (6))

$$\Omega_{\mathcal{F}} \equiv \{ \varphi = (T_0, T_0^*, V_0, A_0, Y_0) \in C^1_+[-h, 0]; \quad \varphi \in \Omega_C; \quad \dot{\varphi}(0) = \mathcal{F}(\varphi) \}. \quad (13)$$

The following result is a corollary of Theorem 2.

Theorem 6. *Let $\eta : C \rightarrow [0, h]$ be a continuous functional (state dependent delay), satisfying $(H1_\eta)$. Then for any initial function $\varphi \in \Omega_{\mathcal{F}}$ there exists a unique (continuously differentiable) solution to (4), (5), satisfying*

$$u_t \equiv (T_t, T_t^*, V_t, A_t, Y_t) \in \Omega_{\mathcal{F}}, \quad t \geq 0.$$

One can see that any continuous solution u started at $\varphi \in \Omega_C$, satisfies $u_t \in \Omega_{\mathcal{F}}$ for $t > h$.

3. Stationary solutions. Since the stationary solutions of (4) are the same as for the constant delay system, we keep the notations close to the ones in [30]. We will use the following reproduction numbers for system (4). The basic reproduction number

$$R_0 \equiv \frac{N\lambda k e^{-\omega h}}{c(d + \lambda k_1)}.$$

The CTL reproduction number

$$R_1 \equiv \frac{N\lambda k \beta e^{-\omega h}}{\gamma \delta (Nk + Ndk_2 - k_1 c e^{\omega h})} \left(1 - \frac{1}{R_0} \right).$$

The antibody reproduction number

$$R_2 \equiv \frac{N^2 \lambda k g e^{-\omega h}}{bc(Nk + Ndk_2 - k_1 c e^{\omega h})} \left(1 - \frac{1}{R_0} \right).$$

The CTL competitive reproduction number

$$R_{CTL} \equiv \frac{\lambda \beta^2 k b e^{-\omega h} + k_1 g \delta^2 \gamma^2 e^{\omega h}}{\beta \gamma \delta (g d + k b + k_2 b d + \lambda k_1 g)}.$$

The antibody competitive reproduction number

$$R_A \equiv \frac{N g \delta \gamma}{\beta b c}.$$

All the possible stationary solutions to (4) are described in [30, Theorem 3.1]. To keep the length of our paper reasonable we discuss the three equilibria which are, from our point of view, most interesting biologically. We also correct some misprints in [30, Theorem 3.1].

Lemma 7. (a) *There is the infection-free equilibrium $E^0 = (\frac{\lambda}{d}, 0, 0, 0, 0)$.*

(b) *If $R_0 > 1$, then (4) has the immune-exhausted equilibrium $E^1 = (T_1, T_1^*, V_1, 0, 0)$, where*

$$T_1 = \frac{k_2 N \lambda + c e^{\omega h}}{N k + N d k_2 - k_1 c e^{\omega h}}, \quad T_1^* = \frac{N \lambda k e^{-\omega h}}{\delta (N k + N d k_2 - k_1 c e^{\omega h})} \left(1 - \frac{1}{R_0}\right),$$

$$V_1 = \frac{N^2 \lambda k e^{-\omega h}}{c (N k + N d k_2 - k_1 c e^{\omega h})} \left(1 - \frac{1}{R_0}\right).$$

(c) If $R_{CTL} > 1$ and $R_A > 1$, then (4) has the main inner equilibrium $\widehat{E} = (\widehat{T}, \widehat{T}^*, \widehat{V}, \widehat{Y}, \widehat{A})$. All the coordinates are positive, \widehat{T} is the unique positive root of the quadratic equation

$$d g k_1 \widehat{T}^2 + (d k_2 b + d g - \lambda g k_1 + k b) \widehat{T} - \lambda (g + k_2 b) = 0 \tag{14}$$

and coordinates satisfy

$$\begin{cases} \widehat{T}^* = \frac{\gamma}{\beta}, & \widehat{V} = \frac{b}{g}, & \widehat{A} = \frac{N \delta \gamma g - \beta c b}{\beta q b}, & \widehat{Y} = \frac{\lambda - d \widehat{T} - e^{\omega h} \delta \widehat{T}^*}{e^{\omega h} p \widehat{T}^*}, \\ N \delta \widehat{T}^* = \widehat{V} (c + q \widehat{A}), & \lambda = d \widehat{T} + f(\widehat{T}, \widehat{V}), & (\delta - p \widehat{Y}) \widehat{T}^* e^{\omega h} = f(\widehat{T}, \widehat{V}). \end{cases} \tag{15}$$

These equations connecting the coordinates of the stationary solution will be used below in the study of the stability properties. The proof can be found in [30, Theorem 3.1]. We notice that R_1 and R_2 will be used in Theorem 16 below.

4. Stability properties. The function $v(x) = x - 1 - \ln x$ for $x > 0$ plays an important role in construction of Lyapunov functionals. One can easily check that $v(x) \geq 0$ and $v(x) = 0$ if and only if $x = 1$. The derivative equals $\dot{v}(x) = 1 - \frac{1}{x}$, which is evidently negative for $x \in (0, 1)$ and positive for $x > 1$. The graph of v explains the use of the composition $v\left(\frac{x}{x^0}\right)$ in the study of the stability properties of an equilibrium x^0 . Another important property is the following estimate

$$\forall \delta \in (0, 1), \quad \forall x \in (1 - \delta, 1 + \delta), \quad \text{one has} \quad \frac{(x - 1)^2}{2(1 + \delta)} \leq v(x) \leq \frac{(x - 1)^2}{2(1 - \delta)}. \tag{16}$$

To check it, one simply observes that all three functions vanish at $x = 1$ and $\left| \frac{d}{dx} \left(\frac{(x-1)^2}{2(1+\delta)} \right) \right| \leq \left| \frac{d}{dx} v(x) \right| \leq \left| \frac{d}{dx} \left(\frac{(x-1)^2}{2(1-\delta)} \right) \right|$ in the δ -neighborhood of $x = 1$.

4.1. Main interior equilibrium. Particular case of a state-dependent delay. We start with the study of the main interior equilibrium. This stationary solution of (4) is described in item (c) of Lemma 7. As before, we denote $u(t) = (T(t), T^*(t), V(t), Y(t), A(t))$. Consider arbitrary $\varphi = (\varphi^1, \varphi^2, \varphi^3, \varphi^4, \varphi^5) \in C$. We are interested in the following particular form of the state-dependent delay

$$\eta(\varphi) = F(\varphi^1(0), \varphi^3(0)). \tag{17}$$

It means that $\eta(u_t) = F(T(t), V(t))$ which looks natural since the delay appears in the nonlinearity f which depends on T and V only (see the second equation in (4)).

Theorem 8. Let $R_{CTL} > 1$ and $R_A > 1$. Assume the state-dependent delay η has the form (17) with a continuous map $F : R_+^2 \rightarrow [0, h]$, satisfies $(H1_\eta)$ (see (7)) and

$$|\eta(\varphi) - \eta(\widehat{\varphi})| = |F(\varphi^1(0), \varphi^3(0)) - F(\widehat{T}, \widehat{V})| \leq c_\eta \left((\varphi^1(0) - \widehat{T})^2 + (\varphi^3(0) - \widehat{V})^2 \right). \tag{18}$$

Then the stationary solution $\widehat{\varphi} = (\widehat{T}, \widehat{T}^*, \widehat{V}, \widehat{Y}, \widehat{A})$ is locally asymptotically stable. For sufficiently small values of c_η , the stationary solution is globally asymptotically stable.

Proof of Theorem 8. Consider the Lyapunov functional

$$\begin{aligned}
 U^1(t) \equiv & \left(T(t) - \widehat{T} - \int_{\widehat{T}}^{T(t)} \frac{f(\widehat{T}, \widehat{V})}{f(\theta, \widehat{V})} d\theta \right) e^{-\omega h} + \widehat{T}^* \cdot v \left(\frac{T^*(t)}{\widehat{T}^*} \right) + \frac{\delta + p\widehat{Y}}{N\delta} \widehat{V} \cdot v \left(\frac{V(t)}{\widehat{V}} \right) \\
 & + \frac{p}{\beta} \widehat{Y} \cdot v \left(\frac{Y(t)}{\widehat{Y}} \right) + \frac{q\widehat{A}}{Ng} \left(1 + \frac{p\widehat{Y}}{\delta} \right) \cdot v \left(\frac{A(t)}{\widehat{A}} \right) + (\delta + p\widehat{Y}) \widehat{T}^* \int_{t-\eta(\widehat{\varphi})}^t v \left(\frac{f(T(\theta), V(\theta))}{f(\widehat{T}, \widehat{V})} \right) d\theta.
 \end{aligned} \tag{19}$$

We use the same notations as in [30] to simplify for the reader the comparison of the computations. In spite of the same Lyapunov functional as in [30], the time derivative of $U^1(t)$ along a solution u of (4) is different due to the state-dependence of the delay in the system. It reads as follows

$$\begin{aligned}
 \frac{d}{dt} U^1(t) = & \left(1 - \frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} \right) e^{-\omega h} (\lambda - dT(t) - f(T(t), V(t))) \\
 & + \left(1 - \frac{\widehat{T}^*}{T^*(t)} \right) (e^{-\omega h} f(T(t - \eta(u_t)), V(t - \eta(u_t))) - \delta T^*(t) - pY(t)T^*(t)) \\
 & + \frac{\delta + P\widehat{Y}}{N\delta} \left(1 - \frac{\widehat{V}}{V(t)} \right) (N\delta T^*(t) - cV(t) - qA(t)V(t)) \\
 & + \frac{p}{\beta} \left(1 - \frac{\widehat{Y}}{Y(t)} \right) (\beta T^*(t)Y(t) - \gamma Y(t)) \\
 & + \frac{q}{Ng} \left(1 + \frac{p\widehat{Y}}{\delta} \right) \left(1 - \frac{\widehat{A}}{A(t)} \right) (gA(t)V(t) - bA(t)) \\
 & + e^{-\omega h} [f(T(t), V(t)) - f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))] \\
 & + \widehat{T}^*(\delta + p\widehat{Y}) \ln \frac{f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))}{f(T(t), V(t))}.
 \end{aligned}$$

Opening parentheses, grouping similar terms and canceling some of them, we obtain

$$\begin{aligned}
 \frac{d}{dt} U^1(t) = & \left(1 - \frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} \right) e^{-\omega h} d (\widehat{T} - T(t)) \\
 & - \widehat{T}^*(\delta + p\widehat{Y}) \left[\frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} - \frac{f(T(t), V(t))}{f(T(t), \widehat{V})} + \frac{e^{-\omega h}}{\delta + p\widehat{Y}} \cdot \frac{f(T(t - \eta(u_t)), V(t - \eta(u_t)))}{T^*(t)} \right. \\
 & \left. + \frac{T^*(t) \cdot \widehat{V}}{\widehat{T}^* \cdot V(t)} + \frac{V(t)}{\widehat{V}} - 3 - \ln \frac{f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))}{f(T(t), V(t))} \right] \\
 & + e^{-\omega h} [f(T(t - \eta(u_t)), V(t - \eta(u_t))) - f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))].
 \end{aligned}$$

To save the space we omit long computations where we intensively used equations (15), for example, $\frac{e^{-\omega h}}{\delta + p\widehat{Y}} = \frac{\widehat{T}^*}{f(\widehat{T}, \widehat{V})}$. Next, we add $\pm \left(1 - \frac{V(t)}{\widehat{V}} \cdot \frac{f(T(t), \widehat{V})}{f(T(t), V(t))} \right)$ into the square brackets to get

$$\begin{aligned}
 \frac{d}{dt} U^1(t) = & \left(1 - \frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} \right) e^{-\omega h} d (\widehat{T} - T(t)) \\
 & - \widehat{T}^*(\delta + p\widehat{Y}) \left[\frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} + \frac{T^*(t) \cdot \widehat{V}}{\widehat{T}^* \cdot V(t)} + \frac{V(t)}{\widehat{V}} \cdot \frac{f(T(t), \widehat{V})}{f(T(t), V(t))} \right.
 \end{aligned}$$

$$\begin{aligned}
 & + \frac{\widehat{T}^*}{T^*(t)} \cdot \frac{f(T(t - \eta(u_t)), V(t - \eta(u_t)))}{f(\widehat{T}, \widehat{V})} - 4 - \ln \frac{f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))}{f(T(t), V(t))} \\
 & + \left\{ \frac{V(t)}{\widehat{V}} - \frac{f(T(t), V(t))}{f(T(t), \widehat{V})} + 1 - \frac{V(t)}{\widehat{V}} \cdot \frac{f(T(t), \widehat{V})}{f(T(t), V(t))} \right\} \\
 & + e^{-\omega h} [f(T(t - \eta(u_t)), V(t - \eta(u_t))) - f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))].
 \end{aligned}$$

For the sum in the braces above, the particular form of the function f (see (3)) and computations give

$$\begin{aligned}
 & \frac{V(t)}{\widehat{V}} - \frac{f(T(t), V(t))}{f(T(t), \widehat{V})} + 1 - \frac{V(t)}{\widehat{V}} \cdot \frac{f(T(t), \widehat{V})}{f(T(t), V(t))} \\
 & = \frac{(V(t) - \widehat{V})^2 k_2 (1 + k_1 T(t))}{\widehat{V} (1 + k_1 T(t) + k_2 \widehat{V}) (1 + k_1 T(t) + k_2 V(t))}. \tag{20}
 \end{aligned}$$

Now we add $\pm \frac{\widehat{T}^*}{T^*(t)} \cdot \frac{f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))}{f(\widehat{T}, \widehat{V})}$ into the square brackets above and substitute (20) to obtain

$$\begin{aligned}
 & \frac{d}{dt} U^1(t) = \left(1 - \frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} \right) e^{-\omega h} d (\widehat{T} - T(t)) \\
 & - \widehat{T}^* (\delta + p\widehat{Y}) \left[\frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} + \frac{T^*(t) \cdot \widehat{V}}{\widehat{T}^* \cdot V(t)} + \frac{V(t)}{\widehat{V}} \cdot \frac{f(T(t), \widehat{V})}{f(T(t), V(t))} \right. \\
 & \quad \left. + \frac{\widehat{T}^*}{T^*(t)} \cdot \frac{f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))}{f(\widehat{T}, \widehat{V})} \right. \\
 & \quad \left. - 4 - \ln \frac{f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))}{f(T(t), V(t))} + \frac{(V(t) - \widehat{V})^2 k_2 (1 + k_1 T(t))}{\widehat{V} (1 + k_1 T(t) + k_2 \widehat{V}) (1 + k_1 T(t) + k_2 V(t))} \right] \\
 & + e^{-\omega h} \left(1 - \frac{\widehat{T}^*}{T^*(t)} \right) \left[f(T(t - \eta(u_t)), V(t - \eta(u_t))) - f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi}))) \right]. \tag{21}
 \end{aligned}$$

The first four terms in the square brackets above suggest to split the logarithm as follows

$$\begin{aligned}
 & \ln \frac{f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))}{f(T(t), V(t))} = \ln \frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} + \ln \frac{T^*(t) \cdot \widehat{V}}{\widehat{T}^* \cdot V(t)} \\
 & + \ln \left(\frac{V(t)}{\widehat{V}} \cdot \frac{f(T(t), \widehat{V})}{f(T(t), V(t))} \right) + \ln \left(\frac{\widehat{T}^*}{T^*(t)} \cdot \frac{f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))}{f(\widehat{T}, \widehat{V})} \right). \tag{22}
 \end{aligned}$$

Substitution of (22) into (21) implies

$$\begin{aligned}
 & \frac{d}{dt} U^1(t) = \left(1 - \frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} \right) e^{-\omega h} d (\widehat{T} - T(t)) \\
 & - \frac{(V(t) - \widehat{V})^2 \cdot \widehat{T}^* (\delta + p\widehat{Y}) k_2 (1 + k_1 T(t))}{\widehat{V} (1 + k_1 T(t) + k_2 \widehat{V}) (1 + k_1 T(t) + k_2 V(t))} \\
 & - \widehat{T}^* (\delta + p\widehat{Y}) \left[v \left(\frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} \right) + v \left(\frac{T^*(t) \cdot \widehat{V}}{\widehat{T}^* \cdot V(t)} \right) + v \left(\frac{V(t)}{\widehat{V}} \cdot \frac{f(T(t), \widehat{V})}{f(T(t), V(t))} \right) \right]
 \end{aligned}$$

$$\begin{aligned}
 & + v \left(\frac{\widehat{T}^*}{T^*(t)} \cdot \frac{f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))}{f(\widehat{T}, \widehat{V})} \right) \Big] \\
 & + e^{-\omega h} \left(1 - \frac{\widehat{T}^*}{T^*(t)} \right) [f(T(t - \eta(u_t)), V(t - \eta(u_t))) - f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))].
 \end{aligned}
 \tag{23}$$

Here we used the function $v(x) = x - 1 - \ln x$ to save the space. Next, we can rewrite the first term in (23), using (3),

$$\left(1 - \frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} \right) e^{-\omega h} d (\widehat{T} - T(t)) = - (T(t) - \widehat{T})^2 \frac{e^{-\omega h} d(1 + k_2 \widehat{V})}{T(t)(1 + k_1 \widehat{T} + k_2 \widehat{V})}.
 \tag{24}$$

We substitute the last equality into (23) to get

$$\frac{d}{dt} U^1(t) = -D^1(t) + S^1(t),
 \tag{25}$$

where

$$\begin{aligned}
 D^1(t) & \equiv (T(t) - \widehat{T})^2 \cdot \frac{e^{-\omega h} d(1 + k_2 \widehat{V})}{T(t)(1 + k_1 \widehat{T} + k_2 \widehat{V})} \\
 & + \frac{(V(t) - \widehat{V})^2 \cdot \widehat{T}^* (\delta + p \widehat{Y}) k_2 (1 + k_1 T(t))}{\widehat{V} (1 + k_1 T(t) + k_2 \widehat{V}) (1 + k_1 T(t) + k_2 V(t))} \\
 & + \widehat{T}^* (\delta + p \widehat{Y}) \left[v \left(\frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} \right) + v \left(\frac{T^*(t) \cdot \widehat{V}}{\widehat{T}^* \cdot V(t)} \right) + v \left(\frac{V(t)}{\widehat{V}} \cdot \frac{f(T(t), \widehat{V})}{f(T(t), V(t))} \right) \right. \\
 & \left. + v \left(\frac{\widehat{T}^*}{T^*(t)} \cdot \frac{f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))}{f(\widehat{T}, \widehat{V})} \right) \right],
 \end{aligned}
 \tag{26}$$

$$S^1(t) \equiv e^{-\omega h} \left(1 - \frac{\widehat{T}^*}{T^*(t)} \right) \left[f(T(t - \eta(u_t)), V(t - \eta(u_t))) - f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi}))) \right].
 \tag{27}$$

One can see, using $v(x) \geq 0$, that $D^1(t) \geq 0$.

Remark 9. It is easy to check that $D^1(t) = 0$ if and only if $T(t) = \widehat{T}, V(t) = \widehat{V}, T^*(t) = \widehat{T}^*, f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi}))) = f(\widehat{T}, \widehat{V})$. It follows from the property $v(x) = 0$ if and only if $x = 1$.

The sign of $S^1(t)$ is undefined. Our goal is to show that $(-D^1(t) + S^1(t)) \leq 0$, i.e. $\frac{d}{dt} U^1(t) \leq 0$ (see (25)) and $\frac{d}{dt} U^1(t) = 0$ at the stationary point only. To estimate the term $S^1(t)$ we notice that the functional response $f(T, V)$, given by (3), is Lipschitz

$$|f(T, V) - f(\widetilde{T}, \widetilde{V})| \leq L_1^f \cdot |T - \widetilde{T}| + L_2^f \cdot |V - \widetilde{V}|.$$

It implies

$$\begin{aligned}
 & |f(T(t - \eta(u_t)), V(t - \eta(u_t))) - f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))| \\
 & \leq L_1^f \cdot |T(t - \eta(u_t)) - T(t - \eta(\widehat{\varphi}))| + L_2^f \cdot |V(t - \eta(u_t)) - V(t - \eta(\widehat{\varphi}))|.
 \end{aligned}$$

Remark 10. Both coordinates $T(t)$ and $V(t)$ of a solution $u(t)$ of (4) are Lipschitz in time. We denote the corresponding Lipschitz constants for arbitrary solution as L_u^T, L_u^V . It is easy to see that for any δ -neighborhood of the stationary point $\widehat{\varphi}$ the Lipschitz constants of arbitrary solution $|u_t - \widehat{\varphi}| \leq \delta$ (inside of the neighborhood)

is uniformly bounded i.e. $L_u^T \leq L^{T,\delta}, L^V \leq L^{V,\delta}$. Moreover, $L^{T,\delta} \rightarrow 0, L^{V,\delta} \rightarrow 0$ as $\delta \rightarrow 0$.

We continue, using the assumptions on the state-dependent delay η (see (17) and (18)),

$$\begin{aligned} &|f(T(t - \eta(u_t)), V(t - \eta(u_t))) - f(T(t - \eta(\widehat{\varphi})), V(t - \eta(\widehat{\varphi})))| \\ &\leq \left(L_1^f L^{T,\delta} + L_2^f L^{V,\delta} \right) \cdot |\eta(u_t) - \eta(\widehat{\varphi})| \\ &\leq \left(L_1^f L^{T,\delta} + L_2^f L^{V,\delta} \right) \cdot c_\eta \left((T(t) - \widehat{T})^2 + (V(t) - \widehat{V})^2 \right). \end{aligned}$$

This and (27) give the estimate

$$|S^1(t)| \leq e^{-\omega h} \left| 1 - \frac{\widehat{T}^*}{T^*(t)} \right| \cdot \left(L_1^f L^{T,\delta} + L_2^f L^{V,\delta} \right) \cdot c_\eta \left((T(t) - \widehat{T})^2 + (V(t) - \widehat{V})^2 \right). \tag{28}$$

Now we can choose small enough δ (see Remark 10) to make the coefficient $e^{-\omega h} \left| 1 - \frac{\widehat{T}^*}{T^*(t)} \right| \cdot \left(L_1^f L^{T,\delta} + L_2^f L^{V,\delta} \right) \cdot c_\eta$ in (28) arbitrary small, which implies (see the form of $D^1(t)$ (26)) the desired property $\frac{d}{dt}U^1(t) = -D^1(t) + S^1(t) < 0$.

Remark 11. It is easy to see from the calculations above that the small value of $|T^*(t) - \widehat{T}^*|$ alone gives $\frac{d}{dt}U^1(t) < 0$. No need to ask the values of $|T(t) - \widehat{T}|, |V(t) - \widehat{V}|$ to be small. On the other hand, the small values of $|T(t) - \widehat{T}|, |V(t) - \widehat{V}|$ give $\frac{d}{dt}U^1(t) < 0$ without the need of small $|T^*(t) - \widehat{T}^*|$. Alternatively, the smaller value of constant c_η (see (18) and (28)) the bigger the set where $\frac{d}{dt}U^1(t) < 0$ holds. The latter implies that in case c_η is sufficiently small, the stationary solution is globally stable. Here the LaSalle invariance principle is applied. In all the cases the values of $A(t)$ and $Y(t)$ have no influence on $\frac{d}{dt}U^1(t)$.

The proof of Theorem 8 is complete. □

4.2. Main interior equilibrium. General case. Now we are interested in continuously differentiable solutions, given by Theorem 6. As we mentioned above, for any solution u , satisfying $u_0 \in \Omega_C$, one has $u_t \in \Omega_{\mathcal{F}}$ for $t > h$.

Theorem 12. *Let $R_{CTL} > 1$ and $R_A > 1$. Assume the state-dependent delay $\eta : C \rightarrow [0, h]$ is continuously differentiable in a μ -neighborhood of the stationary solution $\widehat{\varphi}$ and satisfies (H1 $_\eta$) (see (7)).*

Then the stationary solution $\widehat{\varphi} = (\widehat{T}, \widehat{T}^, \widehat{V}, \widehat{Y}, \widehat{A})$ of (4) is locally asymptotically stable.*

Proof of Theorem 12. Let us introduce the following Lyapunov functional with state-dependent delay along a solution of (4)

$$\begin{aligned} U^{sdd}(t) \equiv & \left(T(t) - \widehat{T} - \int_{\widehat{T}}^{T(t)} \frac{f(\widehat{T}, \widehat{V})}{f(\theta, \widehat{V})} d\theta \right) e^{-\omega h} + \widehat{T}^* \cdot v \left(\frac{T^*(t)}{\widehat{T}^*} \right) + \frac{\delta + p\widehat{Y}}{N\delta} \widehat{V} \cdot v \left(\frac{V(t)}{\widehat{V}} \right) \\ & + \frac{p\widehat{Y}}{\beta} \cdot v \left(\frac{Y(t)}{\widehat{Y}} \right) + \frac{q\widehat{A}}{Ng} \left(1 + \frac{p\widehat{Y}}{\delta} \right) \cdot v \left(\frac{A(t)}{\widehat{A}} \right) + (\delta + p\widehat{Y})\widehat{T}^* \int_{t-\eta(u_t)}^t v \left(\frac{f(T(\theta), V(\theta))}{f(\widehat{T}, \widehat{V})} \right) d\theta. \end{aligned} \tag{29}$$

A particular case of the constant delay functional was considered in [30] (see (19) above). The difference is in the state-dependence of the lower bound of the last integral in (29).

Let us compute the time derivative of the last integral along a continuously differentiable solution

$$\begin{aligned} & \frac{d}{dt} \left(\int_{t-\eta(u_t)}^t v \left(\frac{f(T(\theta), V(\theta))}{f(\widehat{T}, \widehat{V})} \right) d\theta \right) \\ &= v \left(\frac{f(T(t), V(t))}{f(\widehat{T}, \widehat{V})} \right) - v \left(\frac{f(T(t-\eta(u_t)), V(t-\eta(u_t)))}{f(\widehat{T}, \widehat{V})} \right) \cdot \left(1 - \frac{d}{dt} \eta(u_t) \right). \end{aligned}$$

Comparing with the computations of $\frac{d}{dt}U^1(t)$, we see the main difference in the appearance of the term

$$S^{sdd}(t) \equiv -v \left(\frac{f(T(t-\eta(u_t)), V(t-\eta(u_t)))}{f(\widehat{T}, \widehat{V})} \right) \cdot \frac{d}{dt} \eta(u_t). \tag{30}$$

Remark 13. We notice that for any $u \in C^1([-h, b]; R^5)$ one has for $t \in [0, b)$

$$\frac{d}{dt} \eta(u_t) = [(D\eta)(u_t)](\dot{u}_t),$$

where $[(D\eta)(u_t)](\cdot)$ is the Fréchet derivative of η at point u_t . Hence, (for a solution in μ -neighborhood of the stationary solution $\widehat{\varphi}$) the estimate $|\frac{d}{dt} \eta(u_t)| \leq \|(D\eta)(u_t)\|_{L(C;R)} \cdot \|\dot{u}_t\|_C \leq \mu \|(D\eta)(u_t)\|_{L(C;R)}$ guarantees the property

$$\left| \frac{d}{dt} \eta(u_t) \right| \leq \alpha_\mu \text{ with } \alpha_\mu \rightarrow 0 \text{ as } \mu \rightarrow 0. \tag{31}$$

due to the boundedness of $\|(D\eta)(\psi)\|_{L(C;R)}$ as $\mu \rightarrow 0$ (here $\|\psi - \widehat{\varphi}\|_C < \mu$).

The time derivative of $U^{sdd}(t)$ along a continuously differentiable solution u of (4) is computed similar to $\frac{d}{dt}U^1(t)$ in the previous section. We use (15) to get

$$\frac{d}{dt}U^{sdd}(t) = -D^{sdd}(t) + S^{sdd}(t),$$

where

$$\begin{aligned} D^{sdd}(t) \equiv & \left(T(t) - \widehat{T} \right)^2 \cdot \frac{e^{-\omega h} d(1 + k_2 \widehat{V})}{T(t)(1 + k_1 \widehat{T} + k_2 \widehat{V})} \\ & + \frac{(V(t) - \widehat{V})^2 \cdot \widehat{T}^*(\delta + p\widehat{Y}) k_2(1 + k_1 T(t))}{\widehat{V}(1 + k_1 T(t) + k_2 \widehat{V})(1 + k_1 T(t) + k_2 V(t))} \\ & + \widehat{T}^*(\delta + p\widehat{Y}) \left[v \left(\frac{f(\widehat{T}, \widehat{V})}{f(T(t), \widehat{V})} \right) + v \left(\frac{\widehat{T}^*(t) \cdot \widehat{V}}{\widehat{T}^* \cdot V(t)} \right) + v \left(\frac{V(t)}{\widehat{V}} \cdot \frac{f(T(t), \widehat{V})}{f(T(t), V(t))} \right) \right. \\ & \left. + v \left(\frac{\widehat{T}^*}{T^*(t)} \cdot \frac{f(T(t-\eta(u_t)), V(t-\eta(u_t)))}{f(\widehat{T}, \widehat{V})} \right) \right], \end{aligned} \tag{32}$$

and $S^{sdd}(t)$ is defined in (30).

First, we observe that $D^{sdd}(t)$ and $D^1(t)$ have similar forms, while $S^{sdd}(t)$ and $S^1(t)$ are essentially different. Moreover, in general case, we can not use (17), (18).

Our goal is to prove that there is a neighborhood of $\widehat{u} \in C$, where $\frac{d}{dt}U^{sdd}(t) < 0$ (except the point \widehat{u}). We notice that $D^{sdd}(t) \geq 0$, while the sign of $S^{sdd}(t)$ is undefined. We will show that there is a neighborhood of the stationary point, where $|S^{sdd}(t)| < D^{sdd}(t)$.

Let us consider the following auxiliary functionals $D^{(5)}(x)$ and $S^{(5)}(x)$, defined on R^5 , where we simplify notations $x = (x^{(1)}, x^{(2)}, x^{(3)}, x^{(4)}, x^{(5)}) \in R^5$ for $x^{(1)} = T, x^{(2)} = T^*, x^{(3)} = V, x^{(4)} = T(t - \eta), x^{(5)} = V(t - \eta)$

$$D^{(5)}(x) \equiv \left(\frac{f(\widehat{T}, \widehat{V})}{f(x^{(1)}, \widehat{V})} - 1 \right)^2 + \left(\frac{x^{(2)} \cdot \widehat{V}}{\widehat{T}^* \cdot x^{(3)}} - 1 \right)^2 + \left(\frac{x^{(3)} \cdot f(x^{(1)}, \widehat{V})}{\widehat{V} \cdot f(x^{(1)}, x^{(3)})} - 1 \right)^2 + \left(\frac{\widehat{T}^* \cdot f(x^{(4)}, x^{(5)})}{x^{(2)} \cdot f(\widehat{T}, \widehat{V})} - 1 \right)^2 + c^{(1)} \cdot (x^{(1)} - \widehat{T})^2 + c^{(2)} \cdot (x^{(3)} - \widehat{V})^2, \quad c^{(1)}, c^{(2)} > 0. \tag{33}$$

$$S^{(5)}(x) \equiv \alpha \cdot v \left(\frac{f(x^{(4)}, x^{(5)})}{f(\widehat{T}, \widehat{V})} \right), \quad \alpha \geq 0. \tag{34}$$

The reason to consider functions $D^{(5)}(x)$ and $S^{(5)}(x)$ comes from the property (16) of the function v . One sees that $D^{(5)}(x) = 0$ if and only if $x = (\widehat{T}, \widehat{T}^*, \widehat{V}, \widehat{T}, \widehat{V})$. Now we change the coordinates in R^5 to the spherical ones

$$\begin{cases} x^{(1)} = \widehat{T} + r \cos \xi_4 \cos \xi_3 \cos \xi_2 \cos \xi_1, \\ x^{(2)} = \widehat{T}^* + r \cos \xi_4 \cos \xi_3 \cos \xi_2 \sin \xi_1, \\ x^{(3)} = \widehat{V} + r \cos \xi_4 \cos \xi_3 \sin \xi_2, \\ x^{(4)} = \widehat{T} + r \cos \xi_4 \sin \xi_3, \\ x^{(5)} = \widehat{V} + r \sin \xi_4, \end{cases} \quad r \geq 0, \xi_1 \in [0, 2\pi), \xi_i \in [-\pi/2, \pi/2], i = 2, \dots, 5. \tag{35}$$

One can check that the form of $D^{(5)}(x)$ (see (33)) gives the multiplier r^2 in front of the sum, i.e. $D^{(5)}(x) = r^2 \cdot \Phi(r, \xi_1, \dots, \xi_5)$, where $\Phi(r, \xi_1, \dots, \xi_5)$ is continuous and $\Phi(r, \xi_1, \dots, \xi_5) \neq 0$ for $r \neq 0$. The last property is proved, for example, assuming the opposite $\Phi(r^0, \xi_1^0, \dots, \xi_5^0) = 0$ for $r^0 \neq 0$, which contradicts (16). Hence, the classical extreme value theorem (the Bolzano-Weierstrass theorem) shows that the continuous Φ on a closed neighborhood of \widehat{u} has a minimum $\Phi_{min} > 0$. It gives $D^{(5)}(x) \geq r^2 \cdot \Phi_{min}$.

Now the similar arguments for $S^{(5)}(x)$ shows that $|S^{(5)}(x)| \leq \alpha_\mu \cdot r^2$ where the constant $\alpha_\mu \rightarrow 0$ as $\mu \rightarrow 0$ (see (31)). Finally, we can choose a small enough $\mu > 0$ to satisfy $\alpha_\mu < \Phi_{min}$ which proves that $\frac{d}{dt} U^{sdd}(t) \leq -cr^2 \cdot (\Phi_{min} - \alpha_\mu) < 0$.

The proof of Theorem 12 is complete. □

Remark 14. One sees that $S^{(5)}(x)$ depends on $x^{(4)}, x^{(5)}$ only (34). On the other hand, the variables $x^{(4)}, x^{(5)}$ are used in $D^{(5)}(x)$ in one term $\left(\frac{\widehat{T}^* \cdot f(x^{(4)}, x^{(5)})}{x^{(2)} \cdot f(\widehat{T}, \widehat{V})} - 1 \right)^2$ only. It is important to mention that the term in $D^{(5)}(x)$ is not enough to bound $|S^{(5)}(x)|$ i.e.

$$|S^{(5)}(x)| \equiv \left| \alpha \cdot v \left(\frac{f(x^{(4)}, x^{(5)})}{f(\widehat{T}, \widehat{V})} \right) \right| \not\leq \left(\frac{\widehat{T}^* \cdot f(x^{(4)}, x^{(5)})}{x^{(2)} \cdot f(\widehat{T}, \widehat{V})} - 1 \right)^2. \tag{36}$$

The sum of all terms in (33) is needed to bound $|S^{(5)}(x)|$. To see it, one should compare the sets where each functional vanishes. Denote the zero-sets as $Z_{S^{(5)}}$ and Z_{rhs} (for the right-hand side of (36)). Then one sees that $Z_{S^{(5)}}$ is not a subset of Z_{rhs} . Moreover, in any neighborhood of the point $(x^{(2)}, x^{(4)}, x^{(5)}) = (\widehat{T}^*, \widehat{T}, \widehat{V}) \in R^3$ one can find points where the right-hand side of (36) is zero, while the the left-hand side is positive. Clearly, the coordinates of such points should satisfy $f(x^{(4)}, x^{(5)}) \neq f(\widehat{T}, \widehat{V}), \widehat{T}^* \cdot f(x^{(4)}, x^{(5)}) = x^{(2)} \cdot f(\widehat{T}, \widehat{V})$.

4.3. The infection-free equilibrium. Particular case of a state-dependent delay. The case when a solution tends to this equilibrium reflects the complete recovery from the viral infection disease. This stationary solution is described in item (a) of Lemma 7. We are interested in the particular form (17) of the state-dependent delay and consider continuous solutions as in Section 4.1.

Theorem 15. *Let $R_0 \leq 1$. Assume the state-dependent delay η has the form (17) with a continuous map $F : \mathbb{R}_+^2 \rightarrow [0, h]$, satisfies $(H1_\eta)$ (see (7)) and*

$$|\eta(\varphi) - \eta(\varphi^0)| = |F(\varphi^1(0), \varphi^3(0)) - F(T^0, 0)| \leq c_\eta^0 ((\varphi^1(0) - T^0)^2 + (\varphi^3(0))^2). \tag{37}$$

Then the stationary solution $\varphi^0 = E^0 = (\frac{\lambda}{d}, 0, 0, 0, 0)$ is locally asymptotically stable. For sufficiently small values of c_η^0 , the stationary solution is globally asymptotically stable.

Proof of Theorem 15. We proceed as in section 4.1. For short we denote $T^0 \equiv \frac{\lambda}{d}$. Define the following Lyapunov functional $U^0(t)$ which was studied in the constant delay case in [30] and we use the value $t - \eta(\varphi^0)$ as the lower limit of the last integral.

$$U^0(t) \equiv \frac{T^0}{1 + k_1 T^0} \cdot v\left(\frac{T(t)}{T^0}\right) + e^{\omega h} T^*(t) + N e^{-\omega h} V(t) + \int_{t - \eta(\varphi^0)}^t f(T(\theta), V(\theta)) d\theta. \tag{38}$$

Here, as before, $v(x) = x - 1 - \ln x$. One can check that (c.f. the part of $D^0(t)$ in [30])

$$\frac{d}{dt} U^0(t) = -D^0(t) + S^0(t),$$

where

$$D^0(t) = \frac{d(T(t) - T^0)^2}{T(t)(1 + k_1 T^0)} - (R_0 - 1) \frac{ce^{\omega h} V(t)(1 + k_1 T(t))}{N(1 + k_1 T(t) + k_2 V(t))} + \frac{ck_2 e^{\omega h}}{N(1 + k_1 T(t) + k_2 V(t))} V^2(t) + pe^{\omega h} Y(t) T^*(t) + \frac{qe^{\omega h}}{N} A(t) V(t),$$

and

$$S^0(t) \equiv f(T(t - \eta(u_t)), V(t - \eta(u_t))) - f(T(t - \eta(\varphi^0)), V(t - \eta(\varphi^0))). \tag{39}$$

See also (27). It is clear that $R_0 \leq 1$ implies $D^0(t) \geq 0$, while the sign of $S^0(t)$ is undefined. The rest of the proof (that $\frac{d}{dt} U^0(t) \leq 0$) follows as in Theorem 8 above. It completes the proof of theorem 15. \square

4.4. The immune-exhausted equilibrium. General case. In this subsection we show how the technique developed in the previous subsections could be applied to another important stationary solution of (4). The immune-exhausted equilibrium could also represent the case of the failure or non activation of immunity. This stationary solution is described in item (b) of Lemma 7.

Theorem 16. *Let $R_1 \leq 1 < R_0$ and $R_2 \leq 1$. Assume the state-dependent delay $\eta : C \rightarrow [0, h]$ is continuously differentiable in a μ -neighborhood of the immune-exhausted stationary solution $\varphi^1 \equiv E^1 = (T_1, T_1^*, V_1, 0, 0)$ and satisfies $(H1_\eta)$ (see (7)). Then the stationary solution φ^1 of (4) is locally asymptotically stable.*

Proof of Theorem 16. Define the following Lyapunov functional $U_{ex}^{sdd}(t)$ which is a state-dependent delay modification of U_2 [30] in the way similar to (29) i.e., the

lower limit of the last integral in $U_{ex}^{sdd}(t)$ below is state-dependent.

$$U_{ex}^{sdd}(t) \equiv \left(T(t) - T_1 - \int_{T_1}^{T(t)} \frac{f(T_1, V_1)}{f(\theta, V_1)} d\theta \right) e^{-\omega h} + T_1^* \cdot v \left(\frac{T^*(t)}{T_1^*} \right) + \frac{V_1}{N} \cdot v \left(\frac{V(t)}{V_1} \right) + \frac{p}{\beta} \cdot Y(t) + \frac{q}{Ng} \cdot A(t) + \delta T_1^* \int_{t-\eta(u_t)}^t v \left(\frac{f(T(\theta), V(\theta))}{f(T_1, V_1)} \right) d\theta. \tag{40}$$

Here, as before, $v(x) = x - 1 - \ln x$. Let us compute the time derivative of $\frac{d}{dt} U_{ex}^{sdd}(t)$ along a solution (we correct some misprints from [30]).

$$\begin{aligned} \frac{d}{dt} U_{ex}^{sdd}(t) &= \left(1 - \frac{f(T_1, V_1)}{f(T(t), V_1)} \right) e^{-\omega h} (\lambda - dT(t) - f(T(t), V(t))) \\ &+ \left(1 - \frac{T_1^*}{T^*(t)} \right) (e^{-\omega h} f(T(t - \eta(u_t)), V(t - \eta(u_t))) - \delta T^*(t) - pY(t)T^*(t)) \\ &+ \frac{1}{N} \left(1 - \frac{V_1}{V(t)} \right) (N\delta T^*(t) - cV(t) - qA(t)V(t)) \\ &+ \frac{p}{\beta} (\beta T^*(t)Y(t) - \gamma Y(t)) + \frac{q}{Ng} (gA(t)V(t) - bA(t)) \\ &+ e^{-\omega h} [f(T(t), V(t)) - f(T(t - \eta(u_t)), V(t - \eta(u_t)))] \\ &+ \delta T_1^* \ln \frac{f(T(t - \eta(u_t)), V(t - \eta(u_t)))}{f(T(t), V(t))} + S_{ex}^{sdd}(t), \end{aligned}$$

where

$$S_{ex}^{sdd}(t) \equiv -v \left(\frac{f(T(t - \eta(u_t)), V(t - \eta(u_t)))}{f(T_1, V_1)} \right) \cdot \frac{d}{dt} \eta(u_t). \tag{41}$$

Now, we proceed with routine computations (opening parentheses, grouping similar terms and canceling some of them) and use equality for the coordinates of the equilibrium $\lambda = dT_1 + f(T_1, V_1)$, $e^{-\omega h} = \delta T_1^* \cdot [f(T_1, V_1)]^{-1}$ and $N\delta T_1^* = cV_1$. We also use computations similar to (24), (20) and split the logarithm on the sum of four terms similar to (22). We will not repeat all the details here.

Finally, we get the following time derivative along a solution of (4)

$$\frac{d}{dt} U_{ex}^{sdd}(t) = -D_{ex}^{sdd}(t) + S_{ex}^{sdd}(t),$$

where $S_{ex}^{sdd}(t)$ is defined in (41) and

$$\begin{aligned} D_{ex}^{sdd}(t) &\equiv (T(t) - T_1)^2 \cdot \frac{e^{-\omega h} d(1 + k_2 V_1)}{T(t)(1 + k_1 T_1 + k_2 V_1)} \\ &+ \frac{p\gamma}{\beta} (R_1 - 1) \cdot Y(t) + \frac{qb}{Ng} (R_2 - 1) \cdot A(t) \\ &+ \delta T_1^* \left[v \left(\frac{T_1^*}{T^*(t)} \cdot \frac{f(T(t - \eta(u_t)), V(t - \eta(u_t)))}{f(T_1, V_1)} \right) + v \left(\frac{T^*(t) \cdot V_1}{T_1^* \cdot V(t)} \right) \right. \\ &+ v \left(\frac{V(t)}{V_1} \cdot \frac{f(T(t), V_1)}{f(T(t), V(t))} \right) + v \left(\frac{f(T_1, V_1)}{f(T(t), V_1)} \right) \\ &\left. + \frac{(V(t) - V_1)^2 \cdot k_2(1 + k_1 T(t))}{V_1(1 + k_1 T(t) + k_2 V_1)(1 + k_1 T(t) + k_2 V(t))} \right]. \tag{42} \end{aligned}$$

We mention that some terms in $D_{ex}^{sdd}(t)$ and $D^{sdd}(t)$ (c.f. (42), (32)) are similar, but the computations use different equalities connecting coordinates of the corresponding equilibria $(T_1, T_1^*, V_1, 0, 0)$ and $(\hat{T}, \hat{T}^*, \hat{V}, \hat{Y}, \hat{A})$. One can see that conditions

$R_1 \leq 1 < R_0$ and $R_2 \leq 1$ imply $D_{ex}^{sdd}(t) \geq 0$. We remind that the reproduction numbers R_0, R_1 and R_2 are defined in Section 3. The rest of the proof (to show that $\frac{d}{dt}U_{ex}^{sdd}(t) \leq 0$) follows the steps of the final part of the proof of Theorem 12. It completes the proof of Theorem 16. \square

Remark 17. We considered different assumptions on the state-dependent delay η . The main assumptions are local. It is interesting to mention that assumption $(H1_\eta)$ is not a restriction for the local behavior in small neighborhoods of equilibria E^1 and \hat{E} .

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