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VIRAL IN-HOST INFECTION MODEL WITH TWO STATE-DEPENDENT DELAYS: STABILITY OF CONTINUOUS SOLUTIONS

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Abstract. A virus dynamics model with two state-dependent delays and logistic growth term is investigated. A general class of nonlinear incidence rates is considered. The model describes the in-host interplay between viral infection and CTL (cytotoxic T lymphocytes) and antibody immune responses. The wellposedness of the model proposed and Lyapunov stability properties of interior infection equilibria which describe the cases of a chronic disease are studied. We choose a space of merely continuous initial functions which is appropriate for therapy, including drug administration.

Keywords: evolution equation; state-dependent delay; Lyapunov stability; virus infection model

MSC 2020: 93C23, 34K20, 97M60

1. Introduction

At the present time, such virus infections as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and others are referred to global health problems. From Global hepatitis report (WHO, April 2017, see [5]) we know that "a large number of people (about 325 million worldwide in 2015) are carriers of hepatitis B or C virus infections, which can remain asymptomatic for decades," and "viral hepatitis caused 1.34 million deaths in 2015, a number comparable to deaths caused by tuberculosis and higher than those caused by HIV. However, the number of deaths due to viral hepatitis is increasing over time, while mortality caused by tuberculosis and HIV is declining."

By considering biologically-based mathematical models there is a chance to predict whether infections disease would disappear or infectious agent would remain.

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The investigation of different mathematical models can be helpful in understanding pathogenesis, the dynamics of the immune responses and effectiveness of drug treatment. The basic viral infection model was formulated by Perelson and Nelson (see [16]) as

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}T(t) &= \lambda - dT(t) - \beta T(t)V(t),\\
\frac{\mathrm{d}}{\mathrm{d}t}T^*(t) &= \beta T(t)V(t) - aT^*(t),\\
\frac{\mathrm{d}}{\mathrm{d}t}V(t) &= aNT^*(t) - kV(t),
\end{aligned}
\tag{1.1}
$$

where $T(t)$, $T^*(t)$, $V(t)$ represent the concentration (or total number) of non-infected host cells, infected cells and free virions, respectively. The non-infected cells are produced at rate λ, die at rate d and become infected at rate β. Infected cells die at rate a. Free virus is produced by infected cells at rate aN and die at rate k. N is the general count of new virus particles which each infected cell produces during life (the average life span is $1/a$).

Huang (see [9]) proposed the virus dynamics model with the DeAngelis-Beddington functional response

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}T(t) &= \lambda - dT(t) - f(T(t),V(t)),\\
\frac{\mathrm{d}}{\mathrm{d}t}T^*(t) &= f(T(t),V(t)) - aT^*(t),\\
\frac{\mathrm{d}}{\mathrm{d}t}V(t) &= aNT^*(t) - kV(t),
\end{aligned}
\tag{1.2}
$$

where $f(T,V) = \beta TV(1+mT+nV)^{-1}$, $\beta, m \geqslant 0$, $n > 0$, $T, V \in \mathbb{R}$. The next step towards extension of the system was the consideration of immune response which works against virus infection. Antibodies, natural killer cells and T cells are essential components of a normal immune response to virus. Nowak and Bangham in [15] formulated the following model of virus dynamics

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}T(t) &= \lambda - dT(t) - \beta T(t)V(t),\\
\frac{\mathrm{d}}{\mathrm{d}t}T^*(t) &= \beta T(t)V(t) - aT^*(t) - \varrho Y(t)T^*(t),\\
\frac{\mathrm{d}}{\mathrm{d}t}V(t) &= aNT^*(t) - kV(t),\\
\frac{\mathrm{d}}{\mathrm{d}t}Y(t) &= \omega T^*(t)Y(t) - bY(t),
\end{aligned}
\tag{1.3}
$$

where $Y(t)$ is the concentration of CTL cells which died at rate b. Wodarz in [29] summarized this model by adding antibody response,

$$
\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}T(t) = \lambda - dT(t) - \beta T(t)V(t),\\
&\frac{\mathrm{d}}{\mathrm{d}t}T^*(t) = \beta T(t)V(t) - aT^*(t) - \varrho Y(t)T^*(t),\\
&\frac{\mathrm{d}}{\mathrm{d}t}V(t) = aNT^*(t) - kV(t) - qA(t)V(t),\\
&\frac{\mathrm{d}}{\mathrm{d}t}Y(t) = \omega T^*(t)Y(t) - bY(t),\\
&\frac{\mathrm{d}}{\mathrm{d}t}A(t) = gA(t)V(t) - b'A(t),
\end{aligned}
\tag{1.4}
$$

where $A(t)$ is the concentration of antibodies which died at rate b' and produced by immune cells (proportional to the concentration of viral particles). There are many viral infection models with and without delays (see, e.g., [11], [6], [35], [33], [32], [27], [28], [34], [14], [17], [10] and references therein). The ones that include time delays describe the complicated (non-instant) biological processes more realistically. For the classical theory of (constant) delay equations, see, e.g., monographs [7], [3], [12]. Wang and Liu in [27] considered the viral infection model with one *constant* delay,

$$
\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}T(t) = \lambda - dT(t) - \frac{\beta T(t)V(t)}{1+\gamma V(t)},\\
&\frac{\mathrm{d}}{\mathrm{d}t}T^*(t) = \frac{\beta T(t-\tau)V(t-\tau)\mathrm{e}^{-a\tau}}{1+\gamma V(t-\tau)} - aT^*(t) - \varrho Y(t)T^*(t),\\
&\frac{\mathrm{d}}{\mathrm{d}t}V(t) = aNT^*(t) - kV(t) - qA(t)V(t),\\
&\frac{\mathrm{d}}{\mathrm{d}t}Y(t) = \omega T^*(t)Y(t) - bY(t),\\
&\frac{\mathrm{d}}{\mathrm{d}t}A(t) = gA(t)V(t) - b'A(t).
\end{aligned}
\tag{1.5}
$$

Here τ is the period of time after which the infected cells start to produce new virions. We mention that there is *no* biological reason why the delay(s) should be *constant*. In such a case, the extension to the *state-dependent delay* model is quite natural. In our article, we study a virus infection model with logistic growth term, nonlinear incidence rate and *two state-dependent delays*. State-dependent delays in the model represent a reasonable part of biological models because of more realistic modelling in the systems whose delays may change in accordance with the internal effects of the system. It is important to emphasise that a state-dependent delay system is always *nonlinear* by its nature. It is well understood that the presence of discrete state-dependent delays makes the mathematical analysis of a model quite different from the constant delay cases (see the review on this subject [8]).

To formulate the main system under consideration, we remind an important standard notation. 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 (the state at time t) by $v_t = v_t(\theta) \equiv v(t + \theta)$, $\theta \in [-h, 0]$. We denote the space of continuous functions equipped with the sup-norm by $C \equiv C([-h, 0]; \mathbb{R}^5)$. In the above notation, we use $u(t) = (T(t), T^*(t), V(t), Y(t), A(t))$ and consider two continuous functionals (state dependent delays) $\eta, \alpha\colon C \to [0, h]$. Let us consider the system with two state-dependent delays,

$$
\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}T(t) = rT(t)\Big(1 - \frac{T(t)}{T_K}\Big) - dT(t) - f(T(t), V(t)),\\
&\frac{\mathrm{d}}{\mathrm{d}t}T^*(t) = \mathrm{e}^{-a\tau_1} f(T(t - \eta(u_t)), V(t - \eta(u_t))) - aT^*(t) - \varrho Y(t)T^*(t),\\
&\frac{\mathrm{d}}{\mathrm{d}t}V(t) = aNT^*(t - \alpha(u_t)) - kV(t) - qA(t)V(t),\\
&\frac{\mathrm{d}}{\mathrm{d}t}Y(t) = \omega T^*(t)Y(t) - bY(t),\\
&\frac{\mathrm{d}}{\mathrm{d}t}A(t) = gA(t)V(t) - b'A(t).
\end{aligned}
\tag{1.6}
$$

The logistic growth term (in the first equation of (1.6)) helps us to describe the situation when new target cells are not produced at a constant rate, but created by the proliferation of existing cells which is described by a logistic function $rT(t)(1-T(t)/T_K)$. In (1.6), r is the proliferation rate and T_K is the maximum capacity of cell proliferation.

We consider system (1.6) with the initial conditions

$$
\varphi \equiv u_0 = (T(\cdot), T^*(\cdot), V(\cdot), Y(\cdot), A(\cdot)) \in C \equiv C([-h, 0]; \mathbb{R}^5).
\tag{1.7}
$$

In [34] the authors study the model with one constant delay ($\eta \equiv h$, $\alpha \equiv 0$) and a particular form of the incidence rate (DeAngelis-Beddington functional response $f(T, V) = kTV(1 + k_1T + k_2V)^{-1}$, where $k, k_1, k_2 > 0$ are constants, see [1], [2]). The Lyapunov asymptotic stability (see [13]) of points of equilibrium is studied.

For more details on the general theory of ordinary state-dependent delay equations see, e.g., [4], [8]. To the best of our knowledge the first results on viral infection models with state-dependent delays are presented in [22], [23]. Our study is a natural continuation and an extention of the approach proposed in [22], [23]. In the current study we choose a space of *merely continuous initial functions* which could be appropriate for therapy, including drug administration (see discussions and references in [22]).

The difference between the current study and [22], [23] is not only in the presence of the second *state-dependent* delay, but also in the presence of the logistic nonlinearity in the first equation. This logistic term is more natural in cases of HCV, HBV infections (cf. [24]). We also notice that the introduction of one more state-dependent delay in the model is not just a technical extension of the previous results. The possibility to treat the new state-dependent delay essentially depends not only on the properties of the delay itself, but also on the term where it appears. To the best of our knowledge viral infection models with *multiple state-dependent delays* have not been considered before.

The structure of the paper is the following. Section 2 includes basic results on the wellposedness of the corresponding initial-value problem and study of the stationary solutions. Section 3 contains the main stability results using The Lyapunov stability theory.

2. Preliminaries and basic properties

Due to biological motivations we consider our system with the non-negative initial conditions

$$u_0 = \varphi \equiv (T_0, T_0^*, V_0, Y_0, A_0) \in C_+ \equiv C_+[-h;0], \tag{2.1}$$

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

We introduce the set

$$\begin{aligned} \Omega_C \equiv \Big\{ & \varphi \equiv (T_0, T_0, V_0, A_0, Y_0) \in C_+ \equiv C_+[-h,0], \quad 0 \leqslant T_0(\theta) \leqslant T_{\max}, \\ & 0 \leqslant T_0^*(\theta) \leqslant \frac{\mathrm{e}^{-a\tau_1}\mu T_{\max}}{a}, \quad 0 \leqslant V_0(\theta) \leqslant \frac{\mathrm{e}^{-a\tau_1}\mu T_{\max} N}{k}, \\ & 0 \leqslant T_0(\theta) + \frac{\varrho}{\omega} Y_0(\theta) \leqslant \frac{\mathrm{e}^{-a\tau_1}\mu T_{\max}}{\min\{a,b\}}, \\ & 0 \leqslant V_0(\theta) + \frac{q}{g} A_0(\theta) \leqslant \frac{\mathrm{e}^{-a\tau_1}\mu T_{\max} N}{\min\{k,b'\}}, \quad \theta \in [-h,0] \Big\}, \end{aligned} \tag{2.2}$$

where $T_{\max} \equiv \frac{1}{4} r T_K d^{-1}$.

We assume that the nonlinearity in (1.6) is a function $f\colon \mathbb{R}^2 \to \mathbb{R}$, which satisfies

($\mathrm{H1}_f$) f is a Lipschitz function; $f(0,V) = f(T,0) = 0$; f is strictly increasing in both coordinates and $|f(T,V)| \leqslant \mu |T|$ for all $T \in \mathbb{R}$ and all $V \in \mathbb{R}$.

Our main assumptions on the *state-dependent* delays η and α are the following (see [18]):

($\mathrm{H}^{\eta}_{\mathrm{ign}}$) exists $\eta_{\mathrm{ign}} > 0$ such that η "ignores" the values of $\varphi(\theta)$ for $\theta \in (-\eta_{\mathrm{ign}}, 0]$, i.e. exists $\eta_{\mathrm{ign}} > 0$: for all $\varphi^1, \varphi^2 \in C$: for all $\theta \in [-h, -\eta_{\mathrm{ign}}] \Rightarrow \varphi^1(\theta) = \varphi^2(\theta) \Rightarrow \eta(\varphi^1) = \eta(\varphi^2)$.

($\mathrm{H}^{\alpha}_{\mathrm{ign}}$) exists $\alpha_{\mathrm{ign}} > 0$ such that α "ignores" the values of $\varphi(\theta)$ for $\theta \in (-\alpha_{\mathrm{ign}}, 0]$, i.e. exists $\alpha_{\mathrm{ign}} > 0$: for all $\varphi^1, \varphi^2 \in C$: for all $\theta \in [-h, -\alpha_{\mathrm{ign}}] \Rightarrow \varphi^1(\theta) = \varphi^2(\theta) \Rightarrow \alpha(\varphi^1) = \alpha(\varphi^2)$.

For more details and discussion on this type of assumptions see [18], [20].

2.1. The wellposedness and the invariance of the set Ω_C. We start with the wellposedness of the initial value problem (1.6), (1.7).

Theorem 2.1. *Let $\eta\colon C \to [0, h]$ and $\alpha\colon C \to [0, h]$ (state-dependent delays) and f be continuous functionals. Then*

(1) *for any initial function $\varphi \in C$ there exist continuous solutions of the system* (1.6), (1.7)*;*

(2) *if additionally η satisfies* ($\mathrm{H}^{\eta}_{\mathrm{ign}}$) *and α satisfies* ($\mathrm{H}^{\alpha}_{\mathrm{ign}}$) *and f satisfies* ($\mathrm{H1}_f$)*, then for any initial function $\varphi = (T_1, T_1^*, V_1, Y_1, A_1) \in \Omega_C$, the system has a unique solution. The solution depends continuously on the initial function and satisfies $u_t = (T_t, T_t^*, V_t, Y_t, A_t) \in \Omega_C$, $t \geqslant 0$.*

R e m a r k 2.2. It is well-known that differential equations with state-dependent delay may possess multiple solutions starting at a continuous initial function, see examples in [4]. There are two ways to get a well-posed initial value problem. The first one (see [26], [8], [19]) is to restrict the space of initial functions to Lipschitz (or more smooth) in-time ones. The second way (see [18], [20]) is to use assumptions of the type ($\mathrm{H}^{\eta}_{\mathrm{ign}}$) to remain in the space C (merely continuous in-time functions). In the current study we apply the second approach (see [18]).

P r o o f of Theorem 2.1. (1) The existence of continuous solutions is guaranteed by the continuity of the right-hand side of the system (1.6) and classical results on the delay equations (see [7], [3]).

(2) For the well-posedness, we use the corresponding extension to the state-dependent delay case which relies on the assumptions ($\mathrm{H}^{\eta}_{\mathrm{ign}}$) and ($\mathrm{H}^{\alpha}_{\mathrm{ign}}$) (see [18]). This approach makes the proof simpler and provides the uniqueness and continuous dependence on initial data. Discussing the invariance of the set Ω_C, we first check that all coordinates of solution $u(t) = (T(t), T^*(t), V(t), Y(t), A(t))$ of our system are non-negative provided such are the initial values. We use the *quasi-positivity* property of the right-hand side of (1.6) (cf. [25], Theorem 2.1, page 81). We emphasize that in the presence of the *state-dependent* delay we cannot directly apply [25], Theorem 2.1, page 81 because it relies on the Lipschitz property of the right-hand

side of a system, which we do *not* have in case of (1.6). Instead, we use the corresponding extension to the state-dependent delay case (see [21]) which relies on the assumptions ($\mathrm{H}^{\eta}_{\mathrm{ign}}$) and ($\mathrm{H}^{\alpha}_{\mathrm{ign}}$).

Now we prove the upper bounds given in (2.2) (see the definition of the set Ω_C). We need the following simple property.

Lemma 2.3 ([23]). *Let $l \in C^1[a,b)$ and satisfies $\frac{\mathrm{d}}{\mathrm{d}t} l(t) \leqslant c_1 - c_2 l(t)$, $t \in [a,b)$. Then from the fact that $l(a) \leqslant c_1 c_2^{-1}$ it follows that $l(t) \leqslant c_1 c_2^{-1}$ for all $t \in [a,b)$. In the case $b = \infty$ for all $\varepsilon > 0$ exists $t_\varepsilon \geqslant a$: $l(t) \leqslant c_1 c_2^{-1} + \varepsilon$ for all $t \geqslant t_\varepsilon$.*

The proof of Lemma 2.3 is simple and can be found in [23].

Since f is a non-negative function for non-negative arguments, we obtain the estimate $\frac{\mathrm{d}}{\mathrm{d}t} T(t) \leqslant rT(t)(1 - T(t)/T_K) - dT(t)$ (see the first equation in (1.6)). The graph of the function $rT(1 - T/T_K)$ is a parabola which reaches its maximum at the vertex $(\frac{1}{2}T_K, \frac{1}{4}rT_K)$. So we can use Lemma 2.3 with $c_1 = \frac{1}{4}rT_K$ and $c_2 = d$. From the inequality $T(0) \leqslant \frac{1}{4}rT_K d^{-1}$ we obtain that $T(t) \leqslant \frac{1}{4}rT_K d^{-1}$ for $t \geqslant 0$. We use this inequality to estimate the second coordinate $T^*(t)$. We also note that $|f(T,V)| \leqslant \mu|T| \leqslant \mu T_{\max}$. Therefore, $\frac{\mathrm{d}}{\mathrm{d}t} T^*(t) \leqslant \mathrm{e}^{-a\tau_1}\mu T_{\max} - aT^*(t)$ and Lemma 2.3 gives the necessary upper bound in (2.2).

From the boundedness of $T^*(t)$ and the third equation of the system we have

$$\frac{\mathrm{d}}{\mathrm{d}t} V(t) \leqslant aNT^*(t - \alpha(u_t)) - kV(t) \leqslant \mathrm{e}^{-a\tau_1}\mu T_{\max} N - kV(t).$$

Lemma 2.3 proves the estimate for V in (2.2). Next, we use the second and fourth equation to obtain

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t} T^*(t) + \frac{\varrho}{\omega}\frac{\mathrm{d}}{\mathrm{d}t} Y(t) &\leqslant \mathrm{e}^{-a\tau_1} f(T(t - \eta(u_t)), V(t - \eta(u_t))) - aT^*(t) - \frac{\varrho b}{\omega} Y(t) \\ &\leqslant \mathrm{e}^{-a\tau_1}\mu T_{\max} - \min\{a,b\}\Big(T^*(t) + \frac{\varrho}{\omega} Y(t)\Big). \end{aligned}$$

Lemma 2.3 proves the boundedness for $T^*(t) + \varrho\omega^{-1}Y(t)$ in (2.2). Similarly, using the third and fifth equations of the system, we get

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t} V(t) + \frac{q}{g}\frac{\mathrm{d}}{\mathrm{d}t} A(t) &\leqslant aNT^*(t - \alpha(u_t)) - kV(t) - \frac{q}{g} b' A(t) \\ &\leqslant \mathrm{e}^{-a\tau_1}\mu T_{\max} N - \min\{k, b'\}\Big(V(t) + \frac{q}{g} A(t)\Big). \end{aligned}$$

The last estimate in (2.2) follows from Lemma 2.3. It gives the invariance of the set Ω_C. All the solutions are global (defined for all $t \geqslant -h$) due to the boundedness (the invariance of Ω_C). $\square$

2.2. Stationary solutions. Now we pay attention to stationary solutions of (1.6). We denote the coordinates of a stationary solution by $u^* = (T_1, T_1^*, V_1, Y_1, A_1)$. Since the stationary solutions of the system do not depend on the type of delay (state-dependent or constant), then we have

$$\begin{aligned} &rT_1\Big(1 - \frac{T_1}{T_K}\Big) - dT_1 - f(T_1, V_1) = 0,\\ &\mathrm{e}^{-a\tau_1} f(T_1, V_1) - aT_1^* - \varrho Y_1 T_1^* = 0,\\ &aNT_1^* - kV_1 - qA_1V_1 = 0,\\ &\omega T_1^* Y_1 - bY_1 = 0,\\ &gA_1V_1 - b'A_1 = 0. \end{aligned} \tag{2.3}$$

Our interest is in the stationary solutions with all positive coordinates (inner equilibria). From the last two equations it follows that $T_1^* = b/\omega$, $V_1 = b'/g$. Then from the third equation we see that $A_1 = (aNbg - k\omega b')/q\omega b'$. Positivity of A_1 follows from the assumption that the constants of the system satisfy the inequality

$$aNbg > k\omega b'. \tag{H2}$$

Substituting $V_1 = b'/g$ in the first equation of (2.3), we obtain

$$rT_1\Big(1 - \frac{T_1}{T_K}\Big) - dT_1 = f\Big(T_1, \frac{b'}{g}\Big), \tag{2.4}$$

$$-\frac{r}{T_K}T_1^2 + (r-d)T_1 = f\Big(T_1, \frac{b'}{g}\Big). \tag{2.5}$$

Our next assumption is

$$f\Big(\frac{r-d}{2r}T_K, \frac{b'}{g}\Big) \leqslant \frac{T_K}{4r}(r-d)^2. \tag{H3}$$

As a kind of motivation, we mention some important examples of nonlinearities f, which satisfy (H3).

Lemma 2.4. *The DeAngelis-Beddington functional response* $f(T,V) = \beta TV/(1+\mu T+\gamma V)$ *and the functional response of Crowley-Martin type (see* [31]*)* $f(T,V) = \beta TV/(1+\mu T)(1+\gamma V)$ *both satisfy* (H3).

P r o o f of Lemma 2.4. We start with the DeAngelis-Beddington functional response. One has

$$-\frac{r}{T_K}T_1^2 + (r-d)T_1 = \frac{\beta T_1 b' g^{-1}}{1 + \mu T_1 + \gamma b' g^{-1}}.$$

We assume that the concentration of non-infected cells is positive (for the obvious biological reason). Hence

$$\begin{aligned}
-\frac{r}{T_K}T_1\Big(1+\mu T_1+\gamma\frac{b'}{g}\Big)+(r-d)\Big(1+\mu T_1+\gamma\frac{b'}{g}\Big)&=\beta T_1\frac{b'}{g},\\
-\frac{r\mu}{T_K}T_1^2+T_1\Big(-\frac{r}{T_K}\Big(1+\gamma\frac{b'}{g}\Big)+\mu(r-d)\Big)+(r-d)\Big(1+\gamma\frac{b'}{g}\Big)-\beta T_1\frac{b'}{g}&=0,\\
D=\Big(\frac{r}{T_K}\Big(1+\gamma\frac{b'}{g}\Big)+\mu(r-d)\Big)^2-\frac{4r\mu}{T_K}\beta\frac{b'}{g},&\\
T_1=\frac{rT_K^{-1}(1+\gamma g^{-1})-\mu(r-d)}{-2r\mu T_K^{-1}}&\\
\pm\frac{\sqrt{(rT_K^{-1}(1+\gamma b'g^{-1})+\mu(r-d))^2-4r\mu T_K^{-1}\beta b'g^{-1}}}{-2r\mu T_K^{-1}}&.
\end{aligned}$$

We deal with $T_1 > \frac{1}{2}T_K(1-d/r)$ to study the stability of the stationary solution. For this case the assumption on the parameters is

$$\begin{aligned}
&\frac{rT_K^{-1}(1+\gamma b'g^{-1})-\mu(r-d)}{-2r\mu T_K^{-1}}\\
&\qquad-\frac{\sqrt{\big(rT_K^{-1}(1+\gamma b'g^{-1})+\mu(r-d)\big)^2-4r\mu T_K^{-1}\beta b'g^{-1}}}{-2r\mu T_K^{-1}}>\frac{T_K}{2}\Big(1-\frac{d}{r}\Big);\\
&\frac{T_K}{r}\sqrt{\Big(\frac{r}{T_K}\Big(1+\gamma\frac{b'}{g}\Big)+\mu(r-d)\Big)^2-\frac{4r\mu}{T_K}\beta\frac{b'}{g}}>1+\gamma\frac{b'}{g};\\
&2(r-d)\Big(1+\gamma\frac{b'}{g}\Big)+\frac{T_K}{r}\mu(r-d)^2-4\beta\frac{b'}{g}>0;\\
&2(r-d)\Big(1+\gamma\frac{b'}{g}+\frac{T_K}{2r}\mu(r-d)\Big)>4\beta\frac{b'}{g}\;\Rightarrow\;\frac{\beta b'}{g+\frac{1}{2}\mu g(r-d)r^{-1}T_K+\gamma b'}\leqslant\frac{r-d}{2}.
\end{aligned}$$

By substituting the form of the functional response in (H3) we get

$$\begin{aligned}
\frac{\frac{1}{2}\beta(r-d)r^{-1}T_Kb'g^{-1}}{1+\mu\frac{1}{2}(r-d)r^{-1}T_K+\gamma b'g^{-1}}&\leqslant\frac{T_K}{4r}(r-d)^2,\\
\frac{\beta b'}{g+\frac{1}{2}\mu g(r-d)r^{-1}T_K+\gamma b'}&\leqslant\frac{r-d}{2}.
\end{aligned}$$

Hence the DeAngelis-Beddington functional response satisfies (H3).

Now we continue with the Crowley-Martin functional response. One has

$$-\frac{r}{T_K}T_1^2+(r-d)T_1=\frac{\beta T_1b'g^{-1}}{(1+\mu T_1)(1+\gamma b'g^{-1})}.$$

As before, we assume $T_1 \neq 0$. Then

$$
\begin{aligned}
-\frac{r}{T_K} T_1 (1+\mu T_1)\Big(1+\gamma\frac{b'}{g}\Big) + (r-d)(1+\mu T_1)\Big(1+\gamma\frac{b'}{g}\Big) &= \beta\frac{b'}{g};\\
-\frac{r\mu}{T_K}\Big(1+\gamma\frac{b'}{g}\Big)T_1^2 + T_1\Big(-\frac{r}{T_K}\Big(1+\gamma\frac{b'}{g}\Big) + \mu(r-d)\Big(1+\gamma\frac{b'}{g}\Big)\Big)&\\
+ (r-d)\Big(1+\gamma\frac{b'}{g}\Big) - \beta\frac{b'}{g} &= 0;
\end{aligned}
$$

$$
D = \Big(\frac{r}{T_K}\Big(1+\gamma\frac{b'}{g}\Big) + \mu(r-d)\Big(1+\gamma\frac{b'}{g}\Big)\Big)^2 - \frac{4r\mu}{T_K}\Big(1+\gamma\frac{b'}{g}\Big)\beta\frac{b'}{g};
$$

$$
\begin{aligned}
T_1 = {}& \frac{rT_K^{-1}(1+\gamma b'g^{-1}) - \mu(r-d)(1+\gamma b'g^{-1})T_K(1+\gamma b'g^{-1})}{-2r\mu T_K^{-1}(1+\gamma b'g^{-1})}\\
&\pm \frac{\sqrt{\big(rT_K^{-1}(1+\gamma b'g^{-1}) + \mu(r-d)(1+\gamma b'g^{-1})\big)^2 - 4r\mu T_K^{-1}(1+\gamma b'g^{-1})\beta b'g^{-1}}}{-2r\mu T_K^{-1}(1+\gamma b'g^{-1})}.
\end{aligned}
$$

Since $T_1 \geqslant \frac{1}{2}T_K(1-d/r)$, to satisfy (H3), one needs the following condition on the parameters of the system

$$
\begin{aligned}
&\frac{rT_K^{-1}(1+\gamma b'g^{-1}) - \mu(r-d)(1+\gamma b'g^{-1})T_K(1+\gamma b'g^{-1})}{-2r\mu T_K^{-1}(1+\gamma b'g^{-1})}\\
&\quad\pm \frac{\sqrt{\big(rT_K^{-1}(1+\gamma b'g^{-1}) + \mu(r-d)(1+\gamma b'g^{-1})\big)^2 - 4r\mu T_K^{-1}(1+\gamma b'g^{-1})\beta b'g^{-1}}}{-2r\mu T_K^{-1}(1+\gamma b'g^{-1})}\\
&\geqslant \frac{T_K}{2}\Big(1-\frac{d}{r}\Big);\\
&\frac{T_K\sqrt{\big(rT_K^{-1}(1+\gamma b'g^{-1}) + \mu(r-d)(1+\gamma b'g^{-1})\big)^2 - 4r\mu T_K^{-1}(1+\gamma b'g^{-1})\beta b'g^{-1}}}{r(1+\gamma b'g^{-1})} \geqslant 1;
\end{aligned}
$$

$$
2(r-d)\mu\Big(1+\frac{T_K}{2r}(r-d)\mu\Big) - 4\beta\frac{b'\mu}{g(1+\gamma b'g^{-1})} \geqslant 0;
$$

$$
2(r-d)\Big(1+\frac{T_K}{2r}(r-d)\mu\Big) \geqslant 4\beta\frac{b'}{g(1+\gamma b'g^{-1})} \Rightarrow \frac{\beta b'g^{-1}}{(1+\mu\frac{1}{2}(r-d)r^{-1}T_K)T_K} \leqslant \frac{r-d}{2}.
$$

We substitute the form of Crowley-Martin functional response into (H3) to get

$$
\frac{\frac{1}{2}\beta(r-d)r^{-1}T_K b'g^{-1}}{(1+\frac{1}{2}\mu(r-d)r^{-1}T_K)(1+\gamma b'g^{-1})} \leqslant \frac{T_K}{4r}(r-d)^2
$$

or a simpler inequality

$$
\frac{\beta b'g^{-1}}{(1+\frac{1}{2}\mu(r-d)r^{-1}T_K)(1+\gamma b'g^{-1})} \leqslant \frac{r-d}{2}. \tag{2.6}
$$

Hence, we see that the Crowley-Martin functional response satisfies the property (H3), provided (2.6) is valid.

The proof of Lemma 2.4 is complete. □

Now we return to the general case. Since $f(\cdot, b'g^{-1})$ is strictly increasing in the first coordinate, continuous and $f\left(0, b'g^{-1}\right) = 0$, by assumption (H3), the equation (2.5) has the unique positive root satisfying

$$T_1 \in \Big[\frac{T_K}{2}\Big(1-\frac{d}{r}\Big), T_K\Big(1-\frac{d}{r}\Big)\Big]. \tag{2.7}$$

Remark 2.5. It is important to mention that, in the general case, there could be other positive roots (even multiple) of (2.5), satisfying $T_1 < \frac{1}{2}T_K(1-d/r)$. In the current study we are interested in the unique root, satisfying (2.7). This case reflects the situation when more than half of the target organ constitutes of healthy cells. We believe that this equilibrium is the most interesting from the biological point of view.

The first two equations in (2.3) give (recall that T_1^* is already known)

$$Y_1 = \frac{\omega}{\varrho b}\Big(\mathrm{e}^{a\tau_1}\Big(rT_1\Big(1-\frac{T_1}{T_K}\Big) - dT_1\Big) - a\frac{b}{\omega}\Big).$$

The positivity of Y_1 follows from the assumption

$$a\frac{b}{\omega} < rT_1\Big(1-\frac{T_1}{T_K}\Big) - dT_1, \tag{H4}$$

where T_1 is the positive root of (2.5) (under the assumption (H3)). We summarise the above estimates in the following

Proposition 2.6. *Suppose that the assumptions* (H2), (H3), (H4) *are satisfied and f satisfies* ($\mathrm{H1}_f$). *Then the system* (2.3) *has a solution* $(T_1, T_1^*, V_1, Y_1, A_1)$ *(the stationary solution of the system) with the unique T_1 satisfying* (2.7). *All the coordinates are positive, T_1 is the positive root of* (2.5), (2.7) *and the coordinates satisfy*

$$T_1^* = \frac{b}{\omega}, \quad V_1 = \frac{b'}{g}, \quad A_1 = \frac{aNbg - k\omega b'}{q\omega b'}, \tag{2.8}$$

$$Y_1 = (\varrho T_1^*\mathrm{e}^{a\tau_1})^{-1}\Big(\Big(rT_1(1-\frac{T_1}{T_K}\Big) - dT_1\Big) - aT_1^*\mathrm{e}^{a\tau_1},$$

$$aNT_1^* = (k+qA_1)V_1, \quad rT_1\Big(1-\frac{T_1}{T_K}\Big) - dT_1 = f(T_1, V_1),$$

$$\mathrm{e}^{a\tau_1}(a+\varrho Y_1)T_1^* = f(T_1, V_1).$$

We use these equations connecting the coordinates of the stationary solution in the study of stability.

3. Stability properties

Consider the following (non-negative) Volterra function $v(x) = x - 1 - \ln(x)\colon (0,\infty) \to \mathbb{R}_+$, which plays an important role in the construction of the Lyapunov function for the system. An important property is (see, e.g., [23])

$$\frac{(x-1)^2}{2(1+\delta)} \leqslant v(x) \leqslant \frac{(x-1)^2}{2(1-\delta)} \quad \forall\,\delta \in (0,1),\ \forall\, x \in (1-\delta, 1+\delta). \tag{3.1}$$

As before, we denote by $u(t) = (T(t), T^*(t), V(t), Y(t), A(t))$ and $\varphi^* = (T_1, T_1^*, V_1, Y_1, A_1)$ the stationary solution of the system, described in Proposition 2.6.

We also assume that f satisfies the inequality

$$\Big(\frac{V}{V_1} - \frac{f(T,V)}{f(T,V_1)}\Big)\Big(\frac{f(T,V_1)}{f(T,V)} - 1\Big) < 0 \tag{H2$_f$}$$

in some neighbourhood $U_\mu(T_1, V_1)$ of (T_1, V_1) for all $(T, V) \in U_\mu(T_1, V_1)$.

The following assumptions (proposed in [22]) on the state-dependent functionals η and α are based on the properties ($\mathrm{H}^\eta_{\mathrm{ign}}$) and ($\mathrm{H}^\alpha_{\mathrm{ign}}$). For η we consider an arbitrary $\varphi \in C$ and its arbitrary extension $\varphi^{\mathrm{ext}}(s)$, $s \in [-h, \eta_{\mathrm{ign}}]$, with a constant $\eta_{\mathrm{ign}} > 0$ defined in ($\mathrm{H}^\eta_{\mathrm{ign}}$). Due to the property ($\mathrm{H}^\eta_{\mathrm{ign}}$) we could define an auxiliary function $\eta^\varphi(t) \equiv \eta(\varphi^{\mathrm{ext}}_t)$, $t \in [0, \eta_{\mathrm{ign}}]$. Since both η and φ are continuous we see that $\eta^\varphi \in C[0, \eta_{\mathrm{ign}}]$. We are interested in the (right) derivative of η^φ at zero and its properties. Now we are ready to formulate our next local assumption on η, which was proposed in [22].

($\mathrm{H2}_\eta$) There is a μ-neighborhood of the stationary point φ^{st} such that (for any $\varphi \in C$ satisfying $\|\varphi - \varphi^{\mathrm{st}}\|_C < \mu$) the following two properties hold:
  (a) exists $\eta'_+(\varphi) = \lim\limits_{\tau\to 0+} \tau^{-1}(\eta(\varphi^{\mathrm{ext}}_\tau) - \eta(\varphi)) = \lim\limits_{\tau\to 0+} \tau^{-1}(\eta^\varphi(\tau) - \eta(\varphi)) \in \mathbb{R}$;
  (b) $\eta'_+(\cdot)$ is continuous at φ^{st}.

Remark 3.1. Since $\eta'_+(\varphi^{\mathrm{st}}) = 0$, then (b) means that $|\eta'_+(\varphi)| \leqslant \delta_\varepsilon$ with $\delta_\varepsilon \to 0$ as $\varepsilon \to 0$ for $\|\varphi - \varphi^{\mathrm{st}}\|_C < \varepsilon$.

We assume that the similar property ($\mathrm{H2}_\alpha$) holds for the delay α.

Our main stability result follows.

Theorem 3.2. *Suppose that the assumptions* (H2), (H3) *and* (H4) *are satisfied. Assume that the nonlinearity f satisfies* ($\mathrm{H1}_f$) *and* ($\mathrm{H2}_f$). *Suppose that the state-dependent delay $\eta\colon C \to [0,h]$ satisfies* ($\mathrm{H}^\eta_{\mathrm{ign}}$) *and* ($\mathrm{H2}_\eta$) *and $\alpha\colon C \to [0,h]$ satisfies* ($\mathrm{H}^\alpha_{\mathrm{ign}}$) *and* ($\mathrm{H2}_\alpha$).

Then the stationary solution $\varphi^* = (T_1, T_1^*, V_1, Y_1, A_1)$ of the system is locally asymptotically stable.

P r o o f of Theorem 3.2. We introduce the following Lyapunov function with two state-dependent delays along a solution of the system (1.6), (1.7),

$$\begin{aligned}
U^{\rm sdd}(t) &= \mathrm{e}^{-a\tau_1}\Big(T(t) - T_1 - \int_{T_1}^{T(t)} \frac{f(T_1,V_1)}{f(\theta,V_1)}\,\mathrm{d}\theta\Big) + T_1^* v\Big(\frac{T^*(t)}{T_1^*}\Big) \\
&\quad + \frac{a+\varrho Y_1}{aN} V_1 v\Big(\frac{V(t)}{V_1}\Big) + \frac{\varrho}{\omega} Y_1 g\Big(\frac{Y(t)}{Y_1}\Big) + \frac{q}{gN}\Big(1 + \frac{\varrho Y_1}{a}\Big) A_1 g\Big(\frac{A(t)}{A_1}\Big) \\
&\quad + (a+\varrho Y_1) T_1^* \int_{t-\eta(u_t)}^{t} v\Big(\frac{f(T(\theta),V(\theta))}{f(T_1,V_1)}\Big)\,\mathrm{d}\theta \\
&\quad + (a+\varrho Y_1) T_1^* \int_{t-\alpha(u_t)}^{t} v\Big(\frac{T^*(\theta)}{T_1^*}\Big)\,\mathrm{d}\theta.
\end{aligned}$$

We calculate the time derivative (along a solution) of the last two integrals

$$\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}\int_{t-\eta(u_t)}^{t} v\Big(\frac{f(T(\theta),V(\theta))}{f(T_1,V_1)}\Big)\,\mathrm{d}\theta \\
&\qquad = v\Big(\frac{f(T(t),V(t))}{f(T_1,V_1)}\Big) - v\Big(\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T_1,V_1)}\Big)\Big(1 - \frac{\mathrm{d}}{\mathrm{d}t}\eta(u_t)\Big), \\
&\frac{\mathrm{d}}{\mathrm{d}t}\int_{t-\alpha(u_t)}^{t} v\Big(\frac{T^*(\theta)}{T_1^*}\Big)\,\mathrm{d}\theta = v\Big(\frac{T^*(t)}{T_1^*}\Big) - v\Big(\frac{T^*(t-\alpha(u_t))}{T_1^*}\Big)\Big(1 - \frac{\mathrm{d}}{\mathrm{d}t}\alpha(u_t)\Big).
\end{aligned}$$

Comparing this to the derivative of the Lyapunov function for the system with no state-dependent delays, we can see a difference in the appearance of two terms:

$$\begin{aligned}
S^{\rm sdd}(t) &= -v\Big(\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T_1,V_1)}\Big)\frac{\mathrm{d}}{\mathrm{d}t}\eta(u_t), \\
S^{\rm sddd}(t) &= -v\Big(\frac{T^*(t-\alpha(u_t))}{T_1^*}\Big)\frac{\mathrm{d}}{\mathrm{d}t}\alpha(u_t).
\end{aligned}$$

For the form of the above terms $S^{\rm sdd}$ and $S^{\rm sddd}$, see Remark 3.3 below.

Note that the class of non-linear functions f is wider than the type of DeAngelis-Beddington. It is

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}U^{\rm sdd}(t) &= \mathrm{e}^{-a\tau_1}\Big(1 - \frac{f(T_1,V_1)}{f(T(t),V_1)}\Big)\Big(rT(t)\Big(1 - \frac{T(t)}{T_K}\Big) - dT(t) - f(T(t),V(t))\Big) \\
&\quad + \Big(1 - \frac{T_1^*}{T^*(t)}\Big)(\mathrm{e}^{-a\tau_1} f(T(t-\eta(u_t)),V(t-\eta(u_t))) \\
&\qquad\qquad - aT^*(t) - \varrho Y(t) T^*(t))
\end{aligned}$$

$$
\begin{aligned}
&+ \frac{a+\varrho Y_1}{aN}\Big(1-\frac{V_1}{V(t)}\Big)(aNT^*(t-\alpha(u_t)) - kV(t) - qA(t)V(t)) \\
&+ \frac{\varrho}{\omega}\Big(1-\frac{Y_1}{Y(t)}\Big)(\omega T^*(t)Y(t) - bY(t)) \\
&+ \frac{q}{gN}\Big(1+\frac{\varrho Y_1}{a}\Big)\Big(1-\frac{A_1}{A(t)}\Big)(gA(t)V(t) - b'A(t)) \\
&+ \mathrm{e}^{-a\tau_1}(f(T(t),V(t)) - f(T(t-\eta(u_t)),V(t-\eta(u_t)))) \\
&+ (a+\varrho Y_1)T_1^* \ln\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T(t),V(t))} \\
&+ (a+\varrho Y_1)T_1^*\Big(\frac{T^*(t)}{T_1^*} - \frac{T^*(t-\alpha(u_t))}{T_1^*} + \ln\frac{T^*(t-\alpha(u_t))}{T^*(t)}\Big) \\
&+ (a+\varrho Y_1)T_1^*(S^{\mathrm{sdd}}(t) + S^{\mathrm{sddd}}(t)).
\end{aligned}
$$

Substitute the following terms into the expression above

$$
rT_1\left(1-\frac{T_1}{T_K}\right) - dT_1 = f(T_1,V_1); \quad aNT_1^* = (k+qA_1)V_1; \quad T_1^* = \frac{b}{\omega};
$$
$$
V_1 = \frac{b'}{g}; \quad A_1 = \frac{aNbg - \omega k b'}{q\omega b'}.
$$

We have

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}U^{\mathrm{sdd}}(t) = {}& \mathrm{e}^{-a\tau_1}\Big(1-\frac{f(T_1,V_1)}{f(T(t),V_1)}\Big)\Big(rT(t)\Big(1-\frac{T(t)}{T_K}\Big) - dT(t) - rT_1\Big(1-\frac{T_1}{T_K}\Big) \\
&+ dT_1 + f(T_1,V_1) - f(T(t),V(t))\Big) + \Big(1-\frac{T_1^*}{T^*(t)}\Big) \\
&\times (\mathrm{e}^{-a\tau_1} f(T(t-\eta(u_t)),V(t-\eta(u_t))) - aT^*(t) - \varrho Y(t)T^*(t)) \\
&+ \frac{a+\varrho Y_1}{aN}\Big(1-\frac{V_1}{V(t)}\Big)(aNT^*(t-\alpha(u_t)) - kV(t) - qA(t)V(t)) \\
&+ \frac{\varrho}{\omega}\Big(1-\frac{Y_1}{Y(t)}\Big)(\omega T^*(t)Y(t) - bY(t)) \\
&+ \frac{q}{gN}\Big(1+\frac{\varrho Y_1}{a}\Big)\Big(1-\frac{A_1}{A(t)}\Big)(gA(t)V(t) - b'A(t)) \\
&+ \mathrm{e}^{-a\tau_1}(f(T(t),V(t)) - f(T(t-\eta(u_t)),V(t-\eta(u_t)))) \\
&+ (a+\varrho Y_1)T_1^* \ln\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T(t),V(t))} \\
&+ (a+\varrho Y_1)T_1^*\Big(\frac{T^*(t)}{T_1^*} - \frac{\alpha(u_t)}{T_1^*} + \ln\frac{T^*(t-\alpha(u_t))}{T^*(t)}\Big) \\
&+ (a+\varrho Y_1)T_1^*(S^{\mathrm{sdd}}(t) + S^{\mathrm{sddd}}(t)).
\end{aligned}
$$

By simplifying, we get

$$
\begin{aligned}
rT(t)\Big(1-\frac{T(t)}{T_K}\Big) - dT(t) - rT_1\Big(1-\frac{T_1}{T_K}\Big) + dT_1 + f(T_1,V_1) - f(T(t),V(t))& \\
= (r-d)(T(t)-T_1) - \frac{r}{T_K}(T(t)-T_1)(T(t)+T_1) + f(T_1,V_1) - f(T(t),V(t))& \\
= (T(t)-T_1)\Big(r-d-\frac{r}{T_K}(T(t)+T_1)\Big) + f(T_1,V_1) - f(T(t),V(t)).&
\end{aligned}
$$

Due to the assumption (H3), we have $T_1 > \frac{1}{2}T_K(1-dr^{-1})$. Under the conditions of Theorem 3.2, we see that the function $(T-T_1)(r-d-rT_K^{-1}(T+T_1))$ vanishes when $T=T_1$ and changes the sign from positive to negative (when increasing in T). Also the function $\mathrm{e}^{-a\tau_1}(1-f(T_1,V_1)/f(T,V_1))$ changes the sign from positive to negative. That means that the product of these terms is non-positive, actually equals zero, when $T=T_1$ only. We denote this non-positive term by $D_1 \leqslant 0$. Hence

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}U^{\mathrm{sdd}}(t) = D_1 &+ \mathrm{e}^{-a\tau_1}\Big(1-\frac{f(T_1,V_1)}{f(T(t),V_1)}\Big)(f(T_1,V_1)-f(T(t),V(t))) \\
&+ \mathrm{e}^{-a\tau_1}\Big(1-\frac{f(T_1,V_1)}{f(T(t),V_1)}\Big)(\mathrm{e}^{a\tau_1}(a+\varrho Y_1)T_1^* - f(T(t),V(t))) \\
&+ \mathrm{e}^{-a\tau_1}f(T(t-\eta(u_t)),V(t-\eta(u_t))) - aT^*(t) - \varrho Y(t)T^*(t) \\
&- \frac{T_1^*}{T^*(t)}(\mathrm{e}^{-a\tau_1}f(T(t-\eta(u_t)),V(t-\eta(u_t))) - aT^*(t) - \varrho Y(t)T^*(t)) \\
&+ (a+\varrho Y_1)T^*(t-\alpha(u_t)) - \frac{k(a+\varrho Y_1)}{aN}V(t) - \frac{q(a+\varrho Y_1)}{aN}A(t)V(t) \\
&- \frac{V_1}{V(t)}\Big((a+\varrho Y_1)T^*(t-\alpha(u_t)) - \frac{k(a+\varrho Y_1)}{aN}V(t) \\
&\qquad\qquad - \frac{q(a+\varrho Y_1)}{aN}A(t)V(t)\Big) \\
&+ \varrho T^*(t)Y(t) - \frac{\varrho b}{\omega}Y(t) - \frac{Y_1}{Y(t)}\Big(\varrho T^*(t)Y(t) - \frac{\varrho b}{\omega}Y(t)\Big) \\
&+ \frac{q}{aN}(a+\varrho Y_1)A(t)V(t) - \frac{q}{gN}\Big(1+\frac{\varrho Y_1}{a}\Big)b'A(t) \\
&- \frac{q}{gN}\Big(1+\frac{\varrho Y_1}{a}\Big)gV(t)A_1 + \frac{q}{gN}\Big(1+\frac{\varrho Y_1}{a}\Big)b'A_1 \\
&+ \mathrm{e}^{-a\tau_1}f(T(t),V(t)) - \mathrm{e}^{-a\tau_1}f(T(t-\eta(u_t)),V(t-\eta(u_t))) \\
&+ (a+\varrho Y_1)T_1^*\ln\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T(t),V(t))} \\
&+ (a+\varrho Y_1)T_1^*\Big(\frac{T^*(t)}{T_1^*} - \frac{T^*(t-\alpha(u_t))}{T_1^*} + \ln\frac{T^*(t-\alpha(u_t))}{T^*(t)}\Big) \\
&+ (a+\varrho Y_1)T_1^*(S^{\mathrm{sdd}}(t) + S^{\mathrm{sddd}}(t)).
\end{aligned}
$$

So, one has

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}U^{\mathrm{sdd}}(t) &= D_1 + \mathrm{e}^{-a\tau_1}\Big(1 - \frac{f(T_1,V_1)}{f(T(t),V_1)}\Big)(f(T_1,V_1) - f(T(t),V(t))) \\
&\quad + (a+\varrho Y_1)T_1^* - \frac{f(T_1,V_1)}{f(T(t),V_1)}(a+\varrho Y_1)T_1^* - \mathrm{e}^{-a\tau_1} f(T(t),V(t)) \\
&\quad + \mathrm{e}^{-a\tau_1}\frac{f(T_1,V_1)}{f(T(t),V_1)} f(T(t),V(t)) - aT^*(t) \\
&\quad - (a+\varrho Y_1)T_1^*\frac{T_1^*}{T^*(t)}\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T_1,V_1)} \\
&\quad + aT_1^* + \varrho Y(t)T_1^* + (a+\varrho Y_1)T^*(t-\alpha(u_t)) - \frac{k(a+\varrho Y_1)}{aN}V(t) \\
&\quad - \frac{V_1}{V(t)}(a+\varrho Y_1)T^*(t-\alpha(u_t)) + \frac{k(a+\varrho Y_1)}{aN}V_1 + \frac{q(a+\varrho Y_1)}{aN}A(t)V_1 \\
&\quad - \frac{\varrho b}{\omega}Y(t) - \varrho T^*(t)Y_1 + \frac{\varrho b}{\omega}Y_1 - \frac{q}{gN}\Big(1 + \frac{\varrho Y_1}{a}\Big)b' A(t) \\
&\quad - \frac{q}{gN}\Big(1 + \frac{\varrho Y_1}{a}\Big)gV(t)A_1 + \frac{q}{gN}\Big(1 + \frac{\varrho Y_1}{a}\Big)b' A_1 + \mathrm{e}^{-a\tau_1} f(T(t),V(t)) \\
&\quad + (a+\varrho Y_1)T_1^* \ln\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T(t),V(t))} \\
&\quad + (a+\varrho Y_1)T_1^*\Big(\frac{T^*(t)}{T_1^*} - \frac{T^*(t-\alpha(u_t))}{T_1^*} + \ln\frac{T^*(t-\alpha(u_t))}{T^*(t)}\Big) \\
&\quad + (a+\varrho Y_1)T_1^*(S^{\mathrm{sdd}}(t) + S^{\mathrm{sddd}}(t)).
\end{aligned}$$

We see that

$$\begin{aligned}
\mathrm{e}^{-a\tau_1}\frac{f(T_1,V_1)f(T(t),V(t))}{f(T(t),V_1)} &= (a+\varrho Y_1)T_1^*\frac{f(T(t),V(t))}{f(T(t),V_1)}, \\
\frac{k(a+\varrho Y_1)}{aN}V_1 = \frac{aNT_1^* - qA_1V_1}{aN}(a+\varrho Y_1) &= (a+\varrho Y_1)T_1^* - \frac{q}{aN}(a+\varrho Y_1)A_1V_1, \\
aT_1^* = \frac{k+qA_1}{N}V_1 &= \frac{k}{N}V_1 + \frac{q}{N}A_1V_1.
\end{aligned}$$

Hence

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}U^{\mathrm{sdd}}(t) &= D_1 + (a+\varrho Y_1)T_1^* - \frac{f(T_1,V_1)}{f(T(t),V_1)}(a+\varrho Y_1)T_1^* \\
&\quad + (a+\varrho Y_1)T_1^*\frac{f(T(t),V(t))}{f(T(t),V_1)} \\
&\quad - (a+\varrho Y_1)T_1^*\frac{T_1^*}{T^*(t)}\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T_1,V_1)} \\
&\quad + \frac{k}{N}V_1 + \frac{q}{N}A_1V_1 - \frac{k(a+\varrho Y_1)}{aN}V(t)
\end{aligned}$$

$$
\begin{aligned}
&- (a+\varrho Y_1)T_1^*\Big(\frac{T^*(t-\alpha(u_t))}{T_1^*}\frac{V_1}{V(t)}\Big) + (a+\varrho Y_1)T_1^*\\
&- \frac{q}{N}A_1V_1 - \frac{q\varrho}{aN}Y_1A_1V_1 + \frac{q(a+\varrho Y_1)}{aN}A(t)V_1 + \frac{\varrho b}{\omega}Y_1\\
&- \frac{qb'}{gN}A(t) - \frac{q\varrho b'}{gNa}Y_1A(t) - \frac{q}{N}V(t)A_1 - \frac{q\varrho}{Na}V(t)Y_1A_1\\
&+ \frac{qb'}{gN}A_1 + \frac{q\varrho b'}{gNa}Y_1A_1 + (a+\varrho Y_1)T_1^*\ln\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T(t),V(t))}\\
&+ (a+\varrho Y_1)T^*(t-\alpha(u_t)) - aT^*(t) - \varrho T^*(t)Y_1\\
&+ (a+\varrho Y_1)T_1^*\Big(\frac{T^*(t)}{T_1^*} - \frac{T^*(t-\alpha(u_t))}{T_1^*} + \ln\frac{T^*(t-\alpha(u_t))}{T^*(t)}\Big)\\
&+ (a+\varrho Y_1)T_1^*(S^{\mathrm{sdd}}(t) + S^{\mathrm{sddd}}(t)).
\end{aligned}
$$

It is easy to show that

$$
\begin{aligned}
&\frac{k}{N}V_1 - \frac{k}{aN}(a+\varrho Y_1)V(t) + \frac{q}{aN}(a+\varrho Y_1)A(t)V_1 + \frac{\varrho}{\omega}Y_1b - \frac{qb'}{gN}A(t)\\
&\quad - \frac{q\varrho b'}{gNa}Y_1A(t) - \frac{q}{N}V(t)A_1 - \frac{q\varrho}{Na}V(t)Y_1A_1 + \frac{qb'}{gN}A_1\\
&= (a+\varrho Y_1)T_1^*\Big(1-\frac{V(t)}{V_1}\Big),\\
\frac{\mathrm{d}}{\mathrm{d}t}U^{\mathrm{sdd}}(t) &= D_1 - (a+\varrho Y_1)T_1^*\Big[\frac{f(T_1,V_1)}{f(T(t),V_1)} - \frac{f(T(t),V(t))}{f(T(t),V_1)}\\
&\quad + \frac{T_1^*}{T^*(t)}\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T_1,V_1)}\frac{T^*(t-\alpha(u_t))}{T_1^*}\frac{V_1}{V(t)} + \frac{V(t)}{V_1} - 3\Big]\\
&\quad - \ln\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))T^*(t-\alpha(u_t))}{f(T(t),V(t))T^*(t)}\\
&\quad + (a+\varrho Y_1)T_1^*(S^{\mathrm{sdd}}(t) + S^{\mathrm{sddd}}(t)).
\end{aligned}
$$

We add and subtract the expression $1-V(t)f(T(t),V_1)/(V_1f(T(t),V(t)))$ into the square brackets above,

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}U^{\mathrm{sdd}}(t) = D_1 - (a+\varrho Y_1)T_1^*\Big(&\frac{f(T_1,V_1)}{f(T(t),V_1)} + \frac{T^*(t-\alpha(u_t))}{T_1^*}\frac{V_1}{V(t)}\\
&+ \frac{V(t)f(T(t),V_1)}{V_1f(T(t),V(t))} + \frac{T_1^*}{T^*(t)}\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T_1,V_1)}\\
&- 4 - \ln\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))T^*(t-\alpha(u_t))}{f(T(t),V(t))T^*(t)}\\
&+ \frac{V(t)}{V_1} - \frac{f(T(t),V(t))}{f(T(t),V_1)} + 1 - \frac{V(t)f(T(t),V_1)}{V_1f(T(t),V(t))}\Big)\\
&+ (a+\varrho Y_1)T_1^*(S^{\mathrm{sdd}}(t) + S^{\mathrm{sddd}}(t)).
\end{aligned}
$$

By $R^1(t)$, we denote the following terms in the equality above,

$$R^1(t) \equiv \frac{V(t)}{V_1} - \frac{f(T(t),V(t))}{f(T(t),V_1)} + 1 - \frac{V(t)f(T(t),V_1)}{V_1 f(T(t),V(t))}. \tag{3.2}$$

We have

$$\begin{aligned} R^1(t) &= \frac{V(t)}{V_1} - \frac{f(T(t),V(t))}{f(T(t),V_1)} + \frac{f(T(t),V(t))f(T(t),V_1)}{f(T(t),V_1)f(T(t),V(t))} - \frac{V(t)f(T(t),V_1)}{V_1 f(T(t),V(t))} \\ &= \frac{V(t)}{V_1}\Big(1 - \frac{f(T(t),V_1)}{f(T(t),V(t))}\Big) - \frac{f(T(t),V(t))}{f(T(t),V_1)}\Big(1 - \frac{f(T(t),V_1)}{f(T(t),V(t))}\Big) \\ &= \Big(\frac{V(t)}{V_1} - \frac{f(T(t),V(t))}{f(T(t),V_1)}\Big)\Big(1 - \frac{f(T(t),V_1)}{f(T(t),V(t))}\Big). \end{aligned}$$

The assumption (H2$_f$) guarantees that $R^1(t) \geqslant 0$ in a neighbourhood of the stationary solution. We split the logarithm as

$$\begin{aligned} &\ln \frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))T^*(t-\alpha(u_t))}{f(T(t),V(t))T^*(t)} \\ &\quad = \ln \frac{f(T_1,V_1)}{f(T(t),V_1)} + \ln \frac{T^*(t-\alpha(u_t))V_1}{T_1^* V(t)} \\ &\qquad + \ln \frac{T_1^* f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{T^*(t)f(T_1,V_1)} + \ln \frac{V(t)f(T(t),V_1)}{V_1 f(T(t),V(t))}. \end{aligned}$$

One has

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t}U^{\mathrm{sdd}}(t) &\\ = D_1 &- (a+\varrho Y_1)T_1^* R^1(t) \\ &- (a+\varrho Y_1)T_1^*\Big(v\Big(\frac{f(T_1,V_1)}{f(T(t),V_1)}\Big) + v\Big(\frac{T^*(t-\alpha(u_t))}{T_1^*}\frac{V_1}{V(t)}\Big) \\ &+ v\Big(\frac{V(t)f(T(t),V_1)}{V_1 f(T(t),V(t))}\Big) + v\Big(\frac{T_1^*}{T^*(t)}\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T_1,V_1)}\Big)\Big) \\ &+ (a+\varrho Y_1)T_1^*(S^{\mathrm{sdd}}(t) + S^{\mathrm{sddd}}(t)). \end{aligned} \tag{3.3}$$

Note that $D_1 \leqslant 0$. Then

$$\frac{\mathrm{d}}{\mathrm{d}t}U^{\mathrm{sdd}}(t) = -D^{\mathrm{sdd}}(t) + (a+\varrho Y_1)T_1^* \cdot S^{\mathrm{sdd}}(t) + (a+\varrho Y_1)T_1^* \cdot S^{\mathrm{sddd}}(t), \tag{3.4}$$

where

$$\begin{aligned} D^{\mathrm{sdd}}(t) = &-D_1 + (a+\varrho Y_1)T_1^* R^1(t) + (a+\varrho Y_1)T_1^*\Big(v\Big(\frac{f(T_1,V_1)}{f(T(t),V_1)}\Big) \\ &+ v\Big(\frac{T^*(t-\alpha(u_t))}{T_1^*}\frac{V_1}{V(t)}\Big) + v\Big(\frac{V(t)f(T(t),V_1)}{V_1 f(T(t),V(t))}\Big) \\ &+ v\Big(\frac{T_1^*}{T^*(t)}\frac{f(T(t-\eta(u_t)),V(t-\eta(u_t)))}{f(T_1,V_1)}\Big)\Big). \end{aligned} \tag{3.5}$$

Our goal is to prove that there exists a neighbourhood of $u^* \in C$ in which $\frac{\mathrm{d}}{\mathrm{d}t}U^{\mathrm{sdd}}(t) < 0$ except for the point u^*. Note that $D^{\mathrm{sdd}}(t) \geqslant 0$ at the same time when the signs of $S^{\mathrm{sdd}}(t)$ and $S^{\mathrm{sddd}}(t)$ are not defined (may change). We show that a neighbourhood of the stationary point, where $|S^{\mathrm{sdd}}(t) + S^{\mathrm{sddd}}(t)| < D^{\mathrm{sdd}}(t)$ exists. We consider the auxiliary functionals $D^6(x), S^{61}(x)$ and $S^{62}(x)$, which are defined on $\mathbb{R}^6$. We simplify the notation, i.e.

$$x^{(1)} = T, \quad x^{(2)} = T^*(t-\alpha), \quad x^{(3)} = T^*, \quad x^{(4)} = V,$$
$$x^{(5)} = T(t-\eta), \quad x^{(6)} = V(t-\eta),$$

$$\begin{aligned} D^6(x) = {}&\Big(\frac{f(T_1,V_1)}{f(x^{(1)},V_1)} - 1\Big)^2 + \Big(\frac{x^{(2)}V_1}{T_1^* x^{(4)}} - 1\Big)^2 \\ &+ \Big(\frac{x^{(4)} f(x^{(1)},V_1)}{V_1 f(x^{(1)},x^{(4)})} - 1\Big)^2 + \Big(\frac{T_1^* f(x^{(5)},x^{(6)})}{x^{(3)} f(T_1,V_1)} - 1\Big)^2 \\ &+ c^{(1)}(x^{(1)} - T_1)^2 + c^{(2)}(x^{(4)} - V_1)^2, \quad c^{(i)} \in \mathbb{R}, \end{aligned} \tag{3.6}$$

$$S^{61}(x) = \alpha v\Big(\frac{f(x^{(5)},x^{(6)})}{f(T_1,V_1)}\Big), \quad S^{62}(x) = \beta v\Big(\frac{x^{(2)}}{T_1^*}\Big), \quad \alpha,\beta \geqslant 0. \tag{3.7}$$

Note that $D^6(x) = 0$ if and only if $x = (T_1, T_1^*, T_1^*, V_1, T_1, V_1)$.

Let us verify that $D^6(x)$ gives the factor r^2 in front of the sum, i.e.

$$D^6(x) = r^2 \cdot \Phi(r, \xi_1, \ldots, \xi_5).$$

We start by considering examples and using spherical coordinates

$$\begin{aligned} x^{(1)} &= T_1 + r\cos\xi_5\cos\xi_4\cos\xi_3\cos\xi_2\cos\xi_1; \\ x^{(2)} &= T_1^* + r\cos\xi_5\cos\xi_4\cos\xi_3\cos\xi_2\sin\xi_1; \\ x^{(3)} &= T_1^* + r\cos\xi_5\cos\xi_4\cos\xi_3\sin\xi_2; \\ x^{(4)} &= V_1 + r\cos\xi_5\cos\xi_4\sin\xi_3; \\ x^{(5)} &= T_1 + r\cos\xi_5\sin\xi_4; \\ x^{(6)} &= V_1 + r\sin\xi_5; \quad r \geqslant 0,\ \xi_1 \in [0; 2\pi),\ \xi_i \in [-\tfrac{1}{2}\pi; \tfrac{1}{2}\pi],\ i = 2,\ldots,5. \end{aligned}$$

It is interesting to see how the spherical coordinates show an important property in particular case of the DeAngelis-Beddington functional response f. The corresponding calculations are presented in Remark 3.4 below.

In general case we apply the Taylor formula

$$\tilde f(x^{(1)}, x^{(2)}, \ldots, x^{(6)}) = \sum_{k=0}^{2} \frac{\mathrm{d}^k \tilde f(\hat x_1, \hat x_2, \ldots, \hat x_6)}{k!} + R_2(x^{(1)}, x^{(2)}, \ldots, x^{(6)}), \tag{3.8}$$
$$R_2(x) = \overline{o}(\varrho^2),$$

with $\varrho = \Big(\sum\limits_{i=1}^{6}(x^{(i)} - \hat{x}_i)^2\Big)^{1/2}$ to the function $\tilde{f}(x^{(1)}, x^{(2)}, \dots, x^{(6)}) = D^6(x)$ (see (3.6)) of six variables at the point $\hat{x} = (\hat{x}_1, \hat{x}_2, \hat{x}_3, \hat{x}_4, \hat{x}_5, \hat{x}_6)$ with coordinates

$$\hat{x}_1 = T_1, \quad \hat{x}_2 = T_1^*, \quad \hat{x}_3 = T_1^*, \quad \hat{x}_4 = V_1, \quad \hat{x}_5 = T_1, \quad \hat{x}_6 = V_1.$$

Let us put $\tilde{f}_0 = \tilde{f}(\hat{x}_1, \hat{x}_2, \dots, \hat{x}_6)$, so we have (3.8) with

$$\begin{aligned}
\tilde{f}_0 &= 0,\\
\mathrm{d}\tilde{f}_0 &= (x^{(1)} - \hat{x}_1)\frac{\partial \tilde{f}_0}{\partial x^{(1)}} + (x^{(2)} - \hat{x}_2)\frac{\partial \tilde{f}_0}{\partial x^{(2)}} + \dots + (x^{(6)} - \hat{x}_6)\frac{\partial \tilde{f}_0}{\partial x^{(6)}},\\
\frac{\mathrm{d}^2 \tilde{f}_0}{2} &= \frac{1}{2}(x^{(1)} - \hat{x}_1)^2\frac{\partial^2 \tilde{f}_0}{\partial x^{(1)2}} + \frac{1}{2}(x^{(2)} - \hat{x}_2)^2\frac{\partial^2 \tilde{f}_0}{\partial x^{(2)2}} + \dots + \frac{1}{2}(x^{(6)} - \hat{x}_6)^2\frac{\partial^2 \tilde{f}_0}{\partial x^{(6)2}}\\
&\quad + (x^{(1)} - \hat{x}_1)(x^{(2)} - \hat{x}_2)\frac{\partial^2 \tilde{f}_0}{\partial x^{(1)}x^{(2)}} + \dots + (x^{(5)} - \hat{x}_5)(x^{(6)} - \hat{x}_6)\frac{\partial^2 \tilde{f}_0}{\partial x^{(5)}x^{(6)}}.
\end{aligned}$$

It is easy to see that $\mathrm{d}\tilde{f}_0$ equals zero at the point $\hat{x} = (\hat{x}_1, \hat{x}_2, \hat{x}_3, \hat{x}_4, \hat{x}_5, \hat{x}_6)$, so starting with $\frac{1}{2}\mathrm{d}^2\tilde{f}_0$ one has r^2 as a multiplier. More precisely, we substitute the spherical coordinates in $\mathbb{R}^6$ to show that $D^6(x) = r^2 \cdot \Phi(r, \xi_1, \dots, \xi_5)$, where $\Phi(r, \xi_1, \dots, \xi_5)$ is continuous and $\Phi(r, \xi_1, \dots, \xi_5) \neq 0$ if $r \neq 0$ (otherwise exists $r^0 \neq 0$: $\Phi(r^0, \xi_1, \dots, \xi_5) = 0$, which contradicts (3.1)). Hence, by the Bolzano-Weierstrass theorem, the continuous function Φ in a closed neighbourhood of the stationary point φ^{st} has a minimum $\Phi_{\min} > 0$. Hence, $D^6(x) \geqslant r^2 \cdot \Phi_{\min}$.

Now we estimate from above the absolute values of $S^{61}(x)$, $S^{62}(x)$.

For this, we use the inequality $v(x) \leqslant \frac{1}{2}(x-1)^2/(1-\delta)$ (see (3.1)) to get

$$\begin{aligned}
|S^{61}(x)| &= \alpha\Big|v\Big(\frac{f(x^{(5)}, x^{(6)})}{f(T_1, V_1)}\Big)\Big| \leqslant \alpha\Big|\frac{1}{2(1-\delta)}\Big(\frac{f(x^{(5)}, x^{(6)})}{f(T_1, V_1)} - 1\Big)^2\Big|\\
&= \alpha\Big|\frac{1}{2(1-\delta)}\Big(\frac{\beta x^{(5)}x^{(6)}(1 + \mu T_1 + \gamma V_1) - \beta T_1 V_1(1 + \mu x^{(5)} + \gamma x^{(6)})}{f(T_1, V_1)(1 + \mu T_1 + \gamma V_1)(1 + \mu x^{(5)} + \gamma x^{(6)})}\Big)^2\Big|.
\end{aligned}$$

Substituting the spherical coordinates implies $|S^{61}(x)| \leqslant \alpha_\varepsilon \cdot r^2$, where $\alpha_\varepsilon \to 0$ for $\varepsilon \to 0$. Here $\varepsilon \leqslant \delta$. Similarly

$$\begin{aligned}
|S^{62}(x)| &= \Big|\beta v\Big(\frac{x^{(2)}}{T_1^*}\Big)\Big| \leqslant \beta\Big|\frac{1}{2(1-\delta)}\Big(\frac{x^{(2)}}{T_1^*} - 1\Big)^2\Big|\\
&= \beta\Big|\Big(\frac{T_1^* + r\cos\xi_5\cos\xi_4\cos\xi_3\cos\xi_2\sin\xi_1 - T_1^*}{T_1^* 2(1-\delta)}\Big)^2\Big|.
\end{aligned}$$

We arrive at $|S^{62}(x)| \leqslant \omega_\varepsilon \cdot r^2$, where $\omega_\varepsilon \to 0$ for $\varepsilon \to 0$. As a result, we have

$$\frac{\mathrm{d}}{\mathrm{d}t}U^{\mathrm{sdd}}(t) \leqslant -cr^2 \cdot (\Phi_{\min} - \alpha_\varepsilon - \omega_\varepsilon) < 0.$$

The proof of Theorem 3.2 is complete. □

R e m a r k 3.3 (cf. [22]). Note that for any $u \in C^1([-r;b);\mathbb{R}^5)$ we have $\frac{\mathrm{d}}{\mathrm{d}t}\eta(u_t) = [(D\eta)(u_t)](\dot{u_t})$, $\frac{\mathrm{d}}{\mathrm{d}t}\alpha(u_t) = [(D\alpha)(u_t)](\dot{u_t})$ for $t \in [0;b)$, where $[(D\eta)(u_t)](\dot{u_t})$ is the Fréchet derivative of η at the point u_t, $[(D\alpha)(u_t)](\dot{u_t})$ is the Fréchet derivative of α at the point u_t. Therefore, for a solution in the μ-neighborhood of the stationary solution φ, the estimate $|\frac{\mathrm{d}}{\mathrm{d}t}\eta(u_t)| \leqslant \|(D\eta)(u_t)\|_{L(C;R)} \cdot \|\dot{u_t}\|_C \leqslant \mu\|(D\eta)(u_t)\|_{L(C;R)}$ guarantees the property $|\frac{\mathrm{d}}{\mathrm{d}t}\eta(u_t)| \leqslant \alpha_\mu$ with $\alpha_\mu \to 0$ for $\mu \to 0$ because of the boundedness of $\|(D\eta)(\psi)\|_{L(C;R)}$ for $\mu \to 0$ (from $\|\psi - \varphi\|_C < \mu$). Similarly, $|\frac{\mathrm{d}}{\mathrm{d}t}\alpha(u_t)| \leqslant \|(D\alpha)(u_t)\|_{L(C;R)} \cdot \|\dot{u_t}\|_C \leqslant \mu\|(D\alpha)(u_t)\|_{L(C;R)}$ guarantees the property $|\frac{\mathrm{d}}{\mathrm{d}t}\alpha(u_t)| \leqslant \sigma_\mu$ with $\sigma_\mu \to 0$ for $\mu \to 0$ due to the boundedness of $\|(D\alpha)(\psi)\|_{L(C;R)}$ with $\mu \to 0$ (from $\|\psi - \varphi\|_C < \mu$).

R e m a r k 3.4. In Theorem 3.2, in the particular case of the DeAngelis-Beddington functional response f, we use the following six properties:

$$(1)\qquad \Big(\frac{f(T_1,V_1)}{f(x^{(1)},V_1)} - 1\Big)^2 = \Big(\frac{\beta T_1 V_1(1+\mu x^{(1)}+\gamma V_1)}{\beta x^{(1)} V_1(1+\mu T_1+\gamma V_1)} - 1\Big)^2$$
$$= \Big(\frac{T_1(1+\mu x^{(1)}+\gamma V_1) - x^{(1)}(1+\mu T_1+\gamma V_1)}{x^{(1)}(1+\mu T_1+\gamma V_1)}\Big)^2$$
$$= \Big(\frac{(1+\gamma V_1)(T_1 - T_1 - r\cos\xi_5\cos\xi_4\cos\xi_3\cos\xi_2\cos\xi_1)}{x^{(1)}(1+\mu T_1+\gamma V_1)}\Big)^2$$
$$= r^2 \cdot \Phi_1(r,\xi_1,\ldots,\xi_5).$$

$$(2)\quad \Big(\frac{x^{(2)}V_1}{T_1^* x^{(4)}} - 1\Big)^2 = \Big(\frac{x^{(2)}V_1 - T_1^* x^{(4)}}{T_1^* x^{(4)}}\Big)^2$$
$$= \Big(\frac{(T_1^* + r\cos\xi_5\cos\xi_4\cos\xi_3\cos\xi_2\sin\xi_1)V_1 - T_1^*(V_1 + r\cos\xi_5\cos\xi_4\sin\xi_3)}{T_1^* x^{(4)}}\Big)^2$$
$$= r^2 \cdot \Phi_2(r,\xi_1,\ldots,\xi_5).$$

$$(3)\qquad \Big(\frac{x^{(4)}f(x^{(1)},V_1)}{V_1 f(x^{(1)},x^{(4)})} - 1\Big)^2 = \Big(\frac{x^{(4)}f(x^{(1)},V_1) - V_1 f(x^{(1)},x^{(4)})}{V_1 f(x^{(1)},x^{(4)})}\Big)^2$$
$$= \Big(\frac{x^{(4)}\beta x^{(1)}V_1(1+\mu x^{(1)}+\gamma V_1)^{-1} - V_1\beta x^{(1)}x^{(4)}(1+\mu x^{(1)}+\gamma x^{(4)})^{-1}}{V_1 f(x^{(1)},x^{(4)})}\Big)^2$$
$$= \Big(\frac{x^{(4)}\beta x^{(1)}V_1(1+\mu x^{(1)}+\gamma x^{(4)}) - V_1\beta x^{(1)}x^{(4)}(1+\mu x^{(1)}+\gamma V_1)}{V_1 f(x^{(1)},x^{(4)})(1+\mu x^{(1)}+\gamma V_1)(1+\mu x^{(1)}+\gamma x^{(4)})}\Big)^2$$
$$= \Big(\frac{x^{(4)}\beta x^{(1)}V_1(1+\mu x^{(1)}+\gamma x^{(4)} - 1 - \mu x^{(1)} - \gamma V_1)}{V_1 f(x^{(1)},x^{(4)})(1+\mu x^{(1)}+\gamma V_1)(1+\mu x^{(1)}+\gamma x^{(4)})}\Big)^2$$
$$= \Big(\frac{x^{(4)}\beta x^{(1)}V_1\gamma(V_1 + r\cos\xi_5\cos\xi_4\sin\xi_3 - V_1)}{V_1 f(x^{(1)},x^{(4)})(1+\mu x^{(1)}+\gamma V_1)(1+\mu x^{(1)}+\gamma x^{(4)})}\Big)^2$$
$$= r^2 \cdot \Phi_3(r,\xi_1,\ldots,\xi_5).$$

$$
\begin{aligned}
(4)\quad \Big(\frac{T_1^* f(x^{(5)},x^{(6)})}{x^{(3)}f(T_1,V_1)}-1\Big)^2 &= \Big(\frac{T_1^* f(x^{(5)},x^{(6)})-x^{(3)}f(T_1,V_1)}{x^{(3)}f(T_1,V_1)}\Big)^2\\
&= \Big(\frac{T_1^*\beta x^{(5)}x^{(6)}(1+\mu x^{(5)}+\gamma x^{(6)})^{-1}-x^{(3)}\beta T_1V_1(1+\mu T_1+\gamma V_1)^{-1}}{x^{(3)}f(T_1,V_1)}\Big)^2\\
&= \Big(\frac{T_1^*\beta(T_1+r\cos\xi_5\sin\xi_4)(V_1+r\sin\xi_5)(1+\mu T_1+\gamma V_1)}{x^{(3)}f(T_1,V_1)(1+\mu x^{(5)}+\gamma x^{(6)})(1+\mu T_1+\gamma V_1)}\\
&\quad -\frac{(T_1^*+r\cos\xi_5\cos\xi_4\cos\xi_3\sin\xi_2)\beta T_1V_1(1+\mu(T_1+r\cos\xi_5\sin\xi_4))}{x^{(3)}f(T_1,V_1)(1+\mu x^{(5)}+\gamma x^{(6)})(1+\mu T_1+\gamma V_1)}\\
&\quad -\frac{(T_1^*+r\cos\xi_5\cos\xi_4\cos\xi_3\sin\xi_2)\beta T_1V_1\gamma(V_1+r\sin\xi_5)}{x^{(3)}f(T_1,V_1)(1+\mu x^{(5)}+\gamma x^{(6)})(1+\mu T_1+\gamma V_1)}\Big)^2.
\end{aligned}
$$

We see that all the terms above include the factor r^2, so

$$
\Big(\frac{T_1^* f(x^{(5)},x^{(6)})}{x^{(3)}f(T_1,V_1)}-1\Big)^2 = r^2\cdot\Phi_4(r,\xi_2,\dots,\xi_5).
$$

Further:

$$
\begin{aligned}
(5)\qquad c^{(1)}(x^{(1)}-T_1)^2 &= c^{(1)}(T_1+r\cos\xi_5\cos\xi_4\cos\xi_3\cos\xi_2\cos\xi_1-T_1)^2\\
&= r^2\cdot\Phi_5(r,\xi_1,\dots,\xi_5).\\
(6)\qquad c^{(2)}(x^{(4)}-V_1)^2 &= c^{(2)}(V_1+r\cos\xi_5\cos\xi_4\sin\xi_3-V_1)^2\\
&= r^2\cdot\Phi_6(r,\xi_3,\dots,\xi_5).
\end{aligned}
$$

The estimates above show that the factor r^2 is present in $D^6(x)$.

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References

[1] *J. R. Beddington*: Mutual interference between parasites or predators and its effect on searching efficiency. J. Animal Ecology *44* (1975), 331–340. doi

[2] *D. L. DeAngelis, R. A. Goldstein, R. V. O'Neill*: A model for trophic interaction. Ecology *56* (1975), 881–892. doi

[3] *O. Diekmann, S. A. van Gils, S. M. Verduyn Lunel, H.-O. Walther*: Delay Equations: Functional-, Complex-, and Nonlinear Analysis. Applied Mathematical Sciences 110. Springer, New York, 1995. zbl MR doi

[4] *R. D. Driver*: A two-body problem of classical electrodynamics: the one-dimensional case. Ann. Phys. *21* (1963), 122–142. zbl MR doi

[5] Global Hepatitis Report 2017. World Health Organization, Geneva, 2017. Available at `http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf`.

[6] *S. A. Gourley, Y. Kuang, J. D. Nagy*: Dynamics of a delay differential equation model of hepatitis B virus infection. J. Biol. Dyn. *2* (2008), 140–153. zbl MR doi

[7] *J. K. Hale*: Theory of Functional Differential Equations. Applied Mathematical Sciences 3. Springer, Berlin, 1977. zbl MR doi

[8] *F. Hartung, T. Krisztin, H.-O. Walther, J. Wu*: Functional differential equations with state-dependent delays: Theory and applications. Handbook of Differential Equations: Ordinary Differential Equations. Vol. 3 (A. Cañada et al., eds.). Elsevier, North Holland, Amsterdam, 2006, pp. 435–545. MR doi

[9] *G. Huang, W. Ma, Y. Takeuchi*: Global properties for virus dynamics model with Beddington-DeAngelis functional response. Appl. Math. Lett. *22* (2009), 1690–1693. zbl MR doi

[10] *G. Huang, W. Ma, Y. Takeuchi*: Global analysis for delay virus dynamics model with Beddington-DeAngelis functional response. Appl. Math. Lett. *24* (2011), 1199–1203. zbl MR doi

[11] *A. Korobeinikov*: Global properties of infectious disease models with nonlinear incidence. Bull. Math. Biol. *69* (2007), 1871–1886. zbl MR doi

[12] *Y. Kuang*: Delay Differential Equations with Applications in Population Dynamics. Mathematics in Science and Engineering 191. Academic Press, Boston, 1993. zbl MR doi

[13] *A. M. Lyapunov*: The General Problem of the Stability of Motion. Charkov Mathematical Society, Charkov, 1892. (In Russian.) zbl

[14] *C. C. McCluskey*: Using Lyapunov functions to construct Lyapunov functionals for delay differential equations. SIAM J. Appl. Dyn. Syst. *14* (2015), 1–24. zbl MR doi

[15] *M. Nowak, C. Bangham*: Population dynamics of immune response to persistent viruses. Science *272* (1996), 74–79. doi

[16] *A. S. Perelson, P. Nelson*: Mathematical analysis of HIV dynamics in vivo. SIAM Rev. *41* (1999), 3–44. zbl MR doi

[17] *A. Perelson, A. Neumann, M. Markowitz, J. Leonard, D. Ho*: HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time. Science *271* (1996), 1582–1586. doi

[18] *A. V. Rezounenko*: Differential equations with discrete state-dependent delay: Uniqueness and well-posedness in the space of continuous functions. Nonlinear Anal., Theory Methods Appl., Ser. A, Theory Methods *70* (2009), 3978–3986. zbl MR doi

[19] *A. V. Rezounenko*: Non-linear partial differential equations with discrete state-dependent delays in a metric space. Nonlinear Anal., Theory Methods Appl., Ser. A, Theory Methods *73* (2010), 1707–1714. zbl MR doi

[20] *A. V. Rezounenko*: A condition on delay for differential equations with discrete state-dependent delay. J. Math. Anal. Appl. *385* (2012), 506–516. zbl MR doi

[21] *A. V. Rezounenko*: Local properties of solutions to non-autonomous parabolic PDEs with state-dependent delays. J. Abstr. Differ. Equ. Appl. *2* (2012), 56–71. zbl MR

[22] *A. V. Rezounenko*: Continuous solutions to a viral infection model with general incidence rate, discrete state-dependent delay, CTL and antibody immune responses. Electron. J. Qual. Theory Differ. Equ. *2016* (2016), 1–15. zbl MR doi

[23] *A. V. Rezounenko*: Stability of a viral infection model with state-dependent delay, CTL and antibody immune responses. Discrete Contin. Dyn. Syst., Ser. B *22* (2017), 1547–1563. zbl MR doi

[24] *A. V. Rezounenko*: Viral infection model with diffusion and state-dependent delay: a case of logistic growth. Proc. Equadiff 2017 Conf., Bratislava, 2017 (K. Mikula et al., eds.). Slovak University of Technology, Spektrum STU Publishing, 2017, pp. 53–60.

[25] *H. L. Smith*: Monotone Dynamical Systems. An Introduction to the Theory of Competitive and Cooperative Systems. Mathematical Surveys and Monographs 41. AMS, Providence, 1995. zbl MR doi

[26] *H.-O. Walther*: The solution manifold and C^1-smoothness for differential equations with state-dependent delay. J. Diff. Equations *195* (2003), 46–65. zbl MR doi

[27] *X. Wang, S. Liu*: A class of delayed viral models with saturation infection rate and immune response. Math. Methods Appl. Sci. *36* (2013), 125–142. zbl MR doi
[28] *J. Wang, J. Pang, T. Kuniya, Y. Enatsu*: Global threshold dynamics in a five-dimensional virus model with cell-mediated, humoral immune responses and distributed delays. Appl. Math. Comput. *241* (2014), 298–316. zbl MR doi
[29] *D. Wodarz*: Hepatitis C virus dynamics and pathology: the role of CTL and antibody responses. J. General Virology *84* (2003), 1743–1750. doi
[30] *D. Wodarz*: Killer Cell Dynamics. Mathematical and Computational Approaches to Immunology. Interdisciplinary Applied Mathematics 32. Springer, New York, 2007. zbl MR doi
[31] *S. Xu*: Global stability of the virus dynamics model with Crowley-Martin functional response. Electron. J. Qual. Theory Differ. Equ. *2012* (2012), Paper No. 9, 10 pages. zbl MR doi
[32] *Y. Yan, W. Wang*: Global stability of a five-dimesional model with immune responses and delay. Discrete Contin. Dyn. Syst., Ser. B *17* (2012), 401–416. zbl MR doi
[33] *N. Yousfi, K. Hattaf, A. Tridane*: Modeling the adaptive immune response in HBV infection. J. Math. Biol. *63* (2011), 933–957. zbl MR doi
[34] *Y. Zhao, Z. Xu*: Global dynamics for a delayed hepatitis C virus infection model. Electron. J. Differ. Equ. *2014* (2014), 1–18. zbl MR
[35] *H. Zhu, X. Zou*: Dynamics of a HIV-1 infection model with cell-mediated immune response and intracellular delay. Discrete Contin. Dyn. Syst., Ser. B *12* (2009), 511–524. zbl MR doi

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