Stability Analysis of Delayed Tumor-Antigen-Activated Immune Response in combined BCG and IL-2 Immunotherapy of Bladder Cancer

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Abstract

We use a system biology approach to translate the interaction of Bacillus Calmette-Gurin (BCG) + interleukin 2 (IL-2) for the treatment of bladder cancer into a mathematical model. The model is presented as a system of differential equations with the following variables: number of tumor cells, bacterial cells, immune cells, and cytokines involved in the tumor-immune response. This work investigates the delay effect induced by the proliferation of tumor antigen-specific effector cells after the immune system destroys BCG-infected urothelium cells following BCG and IL-2 immunotherapy in the treatment of bladder cancer. For the proposed model, three equilibrium states are found analytically. The stability of all equilibria is analyzed using the method of Lyapunov functionals construction and the method of linear matrix inequalities (LMIs).

Key words: cancer modeling, combined treatment model; discrete time delay; stability conditions; Lyapunov functionals; linear matrix inequalities (LMIs).

1 Introduction

Bladder cancer (BC) is the fourth most common cancer in males after prostate, lung, and colorectal cancers, accounting for 6.6% of all cancer cases [1,2] and the 11th most common cancer in women [1]. The global prevalence of BC is estimated at more than one million and is steadily increasing [2].

The risks of BC appear to vary across world regions, correlating with smoking and occupational exposures to carcinogens in developed countries [3], and with chronic bladder urothelial irritation from Schistosoma hematobium infection in Africa and the Middle East [4]. This disease places an enormous economic burden on the U.S. health care system due to its requirements of surgical resection, repeated intravesical therapies, and lifelong medical follow-up. Transurethral resection of BC (TURBT) is the standard primary treatment for Ta and T1 stages; however, recurrence rates for TURBT alone can be as high as 70% with up to 30% progressing to muscle-invasive disease requiring cystectomy [3]. The high rates of recurrence and significant risk of progression in higher-grade tumors mandate additional therapy with intravesical agents. To date, intravesical therapy has been used as an adjuvant treatment after TURBT to prevent recurrence and progression of the disease.

Chemotherapeutic agents such as mitomycin C, doxorubicin, and epirubicin have long been used as intravesical therapies for BC [3,4]. Immunotherapy, BCG, a live attenuated strain of Mycobacterium bovis widely used as a vaccine against tuberculosis, was first introduced as an intravesical therapy for BC in 1976 year by Morales and associates [5]. Since then, BCG has been extensively evaluated and demonstrated to be superior to any other single chemotherapeutic agent for reducing recurrence and preventing the progression of the disease [3,6]. To date, BCG has become the mainstay of therapy for BC and remains the most effective treatment [3,6]. However, despite its favorable

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effects, a significant proportion of patients do not respond to BCG or tolerate treatment. Besides, recurrence and side effects are common. Therefore, research has been pursued and efforts made to improve BCG therapy. During the past decades, cytokine-based therapies have been developed [7]. To date, multiple cytokines, such as IFN-α, IL-2 and IL-12, have been evaluated, alone, or in combination with BCG for the treatment of BC. In addition, pre-clinical research continues, aiming to identify new BCG therapeutic modalities.

This research is based on the model of BC immunotherapy [35], focusing on the clinical use of BCG and IL-2, considering the in second phase of the immune response after BCG instillations. Delays in biological systems can be used to model events for which it is impossible to accurately observe the underlying dynamics or to provide an abstraction of some system behavior, which leads to more compact models [8,34]. The historically deterministic modeling of biological systems with delays is based on differential equations with delay, an extension of the usual ones, where the derivative of an unknown function depends on the past states of the system [5,6].

The purpose of the current research is to analyze the stability of BCG model in Delay Differential Equations. The stability of equilibria is analyzed using the classical Lyapunov-Krasovskii functionals method together with Kolmanovskii-Shaikhet general method of Lyapunov functionals construction [9,10] and the method of linear matrix inequalities (LMIs) [11–14].

The considered BCG-model is described by a system of nonlinear differential equations with delays and an order of nonlinearity higher than one. A stability investigation of systems of this type can be reduced to stability investigation of the linear part of a nonlinear system. The obtained sufficient conditions for asymptotic stability of the zero solution of an auxiliary linear system, at the same time, are sufficient conditions for the local stability of the corresponding equilibrium of the initial nonlinear system. Here standard definitions of stability are used (see, for instance [15]).

2 Description of the model

Our model describes the effects of combining BCG and IL-2 as immunotherapy for BC treatment. Based in part upon previous study [16,35,36], we further optimized the model to account for the delayed immune response that occurs due to the effector cell proliferation to specific to the tumor antigen (Ag) after the immune system eradicates BCG infected urothelium cells. The equations of our model are as follows:

$$
\begin{aligned}
\dot{A}(t) =&\gamma - (p_1 - \eta)A(t)B(t) - \mu_A A(t) - \theta p_3 E_B(t)T_i(t)A(t-\tau(t)),\\
\dot{B}(t) =&b - p_1 A(t)B(t) - p_2 B(t)T_u(t) - \mu_B B(t),\\
\dot{A}_B(t) =&p_1 A(t)B(t) - (\beta + \mu_{A_1})A_B(t),\\
\dot{A}_T(t) =&\theta p_3 E_B(t)T_i(t)A(t-\tau(t)) - \lambda A_T(t-\tau(t))T_u(t)\left(\frac{I_2(t)}{I_2(t)+g_I}\right) - (\beta+\mu_{A_1})A_T(t),\\
\dot{E}_B(t) =&\frac{\beta_B A_B(t)I_2(t)}{A_B(t)+g} - p_3 T_i(t)E_B(t) - \mu_E E_B(t),\\
\dot{E}_T(t) =&\frac{\beta_T A_T(t-\tau(t))I_2(t)}{A_T(t-\tau(t))+g} - p_3 T_u(t)E_T(t-\tau(t)) - \mu_E E_T(t),\\
\dot{I}_2(t) =&(A_B(t)+A_T(t)+E_B(t)+E_T(t))\left(q_1 - \frac{q_2 I_2(t)}{I_2(t)+g_I}\right) + i_2 - \mu_{I_2} I_2(t),\\
\dot{T}_i(t) =&p_2 B(t)T_u(t) - p_4 E_B(t)T_i(t),\\
\dot{T}_u(t) =&rT_u(t)\left(1 - \frac{T_u(t)}{K}\right) - p_2 B(t)T_u(t) - \left(\lambda A_T(t-\tau(t))T_u(t)\right.\\
&\left.+ \alpha E_T(t-\tau(t))T_u(t)\frac{\alpha_{T,\beta}F_\beta(t)+e_{T,\beta}}{F_\beta(t)+e_{T,\beta}}\right)\left(\frac{I_2(t)}{I_2(t)+g_I}\right)\left(\frac{g_T}{T_u(t)+g_T}\right),\\
\dot{F}_\beta(t) =&\alpha_{\beta,T}T_u(t) - \mu_\beta F_\beta(t).
\end{aligned}
\tag{2.1}
$$

Here it is supposed that the delay $\tau(t)$ is given by the equality $\tau(t) = \nu_0 + \nu_1 e^{-\nu_2 t}$, $\nu_i \geq 0$, $i = 0, 1, 2$. So, the delay is decreasing and $\tau(0) = \nu_0 + \nu_1$, $\tau(\infty) = \nu_0$. $\tau(t)$ is a time-varying function, representing the delay in immune

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response following treatment, and expressing the number of effector cells in the cancer region. The delay is measured in reference to the beginning of BCG treatment (t = 0), with a maximum delay of approximately 10 days. The influence of BCG tends towards zero over time.

Equations (2.1) describe rates of change in concentrations of molecules or cell populations using the following notations:
-BCG bacteria within the bladder as B;
-APCs (dendritic cells (DCs) and macrophages) as A;
-activated/matured APCs after BCG internalization and processing as A_B;
-activated/matured APCs specific to tumor Ag as A_T ;
-effector T lymphocytes consisting mostly of CTLs that react to BCG as E_B;
-effector T lymphocytes consisting mostly of CTLs that react to tumor Ags as E_T;
-IL-2 units injected inside the bladder as I_2;
-tumor cells infected with BCG as T_i;
-tumor cells not infected by BCG as T_u;
-transforming growth factor-beta (TGF-β) denotes as F_β.

Mathematical and biological interpretation of equations (2.1) are examined below:

$\frac{dA}{dt}$ is the dynamic of non-activated APCs, as described in Bunimovich-Mendrazitsky et al. [16], it is governed by two positive terms and three negative terms. The first positive term describes the normal influx of APCs to the tumor at a constant rate γ. The second positive term describes the recruitment of APCs due to bacterial infection at a rate coefficient η. The first negative term describes the activation of APCs by BCG at the rate coefficient p_1. The second negative term is natural cell death at the rate coefficient μ_A. The last negative term accounts for the two-stage elimination of tumor cells, according to recent knowledge, first by effector CTL activity upon BCG -infected tumor cells, which leads to lysis of these cells and flooding of the tumor micro-environment with tumor antigens. Activation of APC cells with tumor-specific antigens occurs with a delay of $\tau(t)$ after the destruction of infected tumor cells. The localized inflammatory response then attracts APCs, such as macrophages, which in turn eliminate uninfected tumor cells, according to the rate θp_3.

$\frac{dB}{dt}$ is the dynamical rate of BCG level changes with time. It is comprised of a positive term corresponding to BCG instillations, and of negative terms corresponding to the elimination of BCG by antigen-presenting cells (APCs) according to the rate coefficient p_1, BCG tumor cell infection at a rate coefficient p_2, and bacteria cell death with rate coefficient μ_B. A quantity b of BCG is instilled into the bladder via a catheter inserted through the urethra once in a week during 6-8 weeks. In this study, we have chosen to simplify the problem by assuming that BCG is introduced into the bladder at a constant rate b.

$\frac{dA_B}{dt}$ is the dynamic of BCG-activated APCs. It is described by one positive term and two negative terms. The positive term is proportional to the numbers of non-activated APCs as well as BCG bacteria, with rate coefficient p_1 (as in $\frac{dA}{dt}$). The first negative term is the migration of the infected, activated APCs to the draining lymphoid tissues, at a rate of coefficient β_1. The second negative term is the death of activated APCs at a rate of coefficient μ_{A_1}.

$\frac{dA_T}{dt}$ is the tumor-Ag-activated APC (TAA-APC) dynamic. It is comprised of one positive term and three negative terms. The positive term describes the APCs which were activated by tumor antigen after eradication of infected tumor cells with the same $\tau(t)$ delay function. The first negative term represents the tumor-Ag-activated APCs cells which destroy the uninfected tumor cells, with a rate coefficient λ after (t) delay. This term is multiplied by an IL-2-dependent parameter with a saturation constant g_I, to propose that in the absence of IL-2, A_T production ceases, while in the presence of external IL-2, the production term is close to 1. The second negative term describes the migration of TAA-APC to the draining lymphoid tissues at a rate of coefficient β_1. The third negative term denotes the natural death of TAA-APC at a rate coefficient μ_{A_1}.

$\frac{dE_B}{dt}$ is the dynamic of effector CTLs that react to BCG infection. It is comprised of their migration rate, determined by their creation in the lymph node and subsequent migration to the bladder, inactivation rate, and their death rate.

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The migration element is proportional to A_B and IL-2, with a maximal rate of coefficient β_B. This rate is brought to saturation by large numbers of A_B, using a Michaelis-Menten saturation function, with Michaelis parameter g. The first negative term is inactivation of effector CTLs via their encounter with infected tumor cells (T_i) at a success rate coefficient p_3. The second negative term corresponds to the BCG-effector CTL (E_B) cells' natural death rate μ_E.

$\frac{dE_T}{dt}$ is the dynamic of effector cells reacting to tumor Ag after delay $\tau(t)$ time due to the eradication of infected tumor cells. It is comprised of their migration rate, inactivation rate, and death rate. The migration element is proportional to A_T and IL-2 with a maximal rate coefficient β_T. This rate is brought to saturation by large numbers of A_T using a Michaelis-Menten saturation function, with Michaelis parameter g (as in $\frac{dE_B}{dt}$). The first negative term describes the inactivation of effector CTLs via their encounter with uninfected tumor cells (T_u), at success rate coefficient p_3. The second negative term describes the E_T natural death rate, with a rate coefficient μ_E.

$\frac{dI_2}{dt}$ is the IL-2 dynamic. It is driven by a natural source, an external source, as well as sink and degradation courses. The first two processes are positive and the last two are negative. They assume equal expression at the constant rate coefficient q_1. They reflect the IL-2 external source i_2, which is injected into the bladder every τ time units. I_2 is consumed by APCs and CTLs. They assume that the rate of consumption is similar for both types of cells and denote its coefficient by q_2. The consumption depends on I_2 and is limited in a Michaelis-Menten fashion, with the Michaelis constant g_I. They also introduce μ_{I_2}, the I_2 degradation rate coefficient.

$\frac{dT_i}{dt}$ is the dynamic of infected tumor cells depend on two mechanisms. The first corresponds only to the rate of bacterial infection of uninfected tumor cells, (T_u), according to rate coefficient p_2. The second mechanism is the elimination of infected tumor cells (T_i) by their interaction with BCG-CTL effector cells (represented by E_B), at rate coefficient p_4.

$\frac{dT_u}{dt}$ is the dynamic of uninfected tumor cells. It is comprised of three processes: one positive term, corresponding to natural tumor growth, and two negative terms, corresponding to tumor infection by bacteria and tumor elimination by immune cells. The natural tumor growth is characterized by a maximal growth rate coefficient, r, which is limited by the maximal tumor cell number, K. The first negative term, due to bacterial infection, is characterized by a coefficient rate of p_2. The second negative term is attributed both to the capture and elimination of T_u cells by APCs cells, which were activated by tumor-Ag at rate coefficient λ, and to the activity of TAA-CTL effectors, (E_T), which destroy uninfected tumor cells, (T_u), at a rate coefficient α. Two These two processes take place after delay $\tau(t)$. The dependence in the equation of T_u on F_β is decreasing from 1 to $a_{T,\beta}$ with Michaelis constant $e_{T,\beta}$ [17]. And then there is a multiplication of those terms by an I_2-dependent Michaelis-Menten term, with Michaelis parameter g_I, to propose that in the absence of I_2, T_u cellular death does not occur. Since the tumor produces a variety of mechanisms in the biological settings that curtail the success of effector cell activity, they multiply $I_2/(I_2+g_I)$ by $g_T/(T_u+g_T)$, to denote the inversely proportional reduction in effector cell activity rate, such that when $T_u=0$ the term is equal to 1 and when $\lim_{T_u\to\infty} g_T/(T_u+g_T)=0$. Note that although this factor can, in principle, nullify the efficacy of CTLs, this is not observed in cases of interest because $T_u \le K$ [16].

$\frac{dF_\beta}{dt}$ is the dynamic of a TGF-β, as proportional to the tumor cell population, T_u, with $a_{\beta,T}$ as a proportion coefficient and is destroyed at a rate of μ_β proportional to F_β.

The real values of the system (2.1) parameters are presented in Table 1.

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Table 1
List of all parameters

Parameters	Physical Interpretation (units)	Estimated value	Reference
μ_A	APC half life $[days^{-1}]$	0.038	[18]
μ_{A_1}	Activated APC half life $[days^{-1}]$	0.138	[19]
μ_{E_1}	Effector cells mortality rate w/o IL-2 $[days^{-1}]$	0.19	[17] and calculated
μ_{E_2}	Effector cells mortality rate with IL-2 $[days^{-1}]$	0.034	[20]
μ_B	BCG half life $[days^{-1}]$	0.1	[21]
p_1	The rate of BCG binding with APC $[cells^{-1}][days^{-1}]$	1.25×10^{-4}	[22] adjusted for liters
p_2	Infection rate of tumor cells by BCG $[cells^{-1}][days^{-1}]$	0.028×10^{-6}	From model simulation
p_3	Rate of E deactivation after binding with infected tumor cells $[cells^{-1}][days^{-1}]$	1.03×10^{-10}	[23]
p_4	Rate of destruction of infected tumor cells by effector cells $[cells^{-1}][days^{-1}]$	1.1×10^{-6}	[23]
λ	Production rate of TAA-APC $[days^{-1}]$	10^{-8}	[24]
β_B	Recruitment rate of effector cells in response to signals released by BCG-infected and activated APC $[cells^{-1}][days^{-1}][I_2^{-1}]$	1.45×10^{8}	[25]
β_T	Recruitment rate of effector cells in response to signals released by TAA-infected and activated APC $[cells^{-1}][days^{-1}][I_2^{-1}]$	1.514×10^{6}	[26]
γ	Initial APC cell numbers $[cells^{-1}][days^{-1}]$	4700	[19]
η	Rate of recruited additional resting APCs $[cells^{-1}][days^{-1}]$	2.8×10^{-6}	[18]
r	Tumor growth rate $[days^{-1}]$	$0.0048 - 0.0085$	[27]
b	Bio-effective dose of BCG [c.f.u./week]	2.2×10^{8}	From clinical data provided by Dr. Sarel Halachmi
β	Migration rate of TAA-APC and bacteria activated APC to the lymph node $[cells^{-1}][days^{-1}]$	0.034	[18]
α	Efficacy of an effector cell on tumor cell $[cells^{-1}][days^{-1}]$	3.7×10^{-6}	[28]
g	Michaelis-Menten constant for BCG activated CTLs and for TAA-CTLs[cells]	10^{13}	From model simulation
g_T	Michaelis-Menten constant for tumor cells[cells]	5200	[16]
K	Maximal tumor cell population [cells]	10^{11}	[29]
q_1	Rate of IL-2 production IU $[cells^{-1}][days^{-1}]$	0.007	[30] and simulations
q_2	The proportion of IL-2 used for differentiation of effector cells IU $[cells^{-1}][days^{-1}]$	1.2×10^{-3}	[26]
μ_{I_2}	Degradation rate $[days^{-1}]$	11.5	[26,31]
θ	Recruitment rate of Tumor-Ag-activated APC cells in response to signals released after binding effector cells, that react to BCG infection, with infected tumor cells $[1/cell^{-1}]$	0.01	From model simulation
$\alpha_{\beta,T}$	The release term per tumor cell $[pg/cell^{-1} * d^{-1}]$	1.38×10^{-4}	[17]
$\alpha_{T,\beta}$	Michaelis-Menten saturation dynamics. The dependence on F_β is decreasing from 0 to $\alpha_{T,\beta}$ $[none]$	0.69	[17]
$e_{T,\beta}$	Michaelis constant $[pg]$	10000	[17]
μ_β	The constant rate, accounts for degradation of F_β $[d^{-1}]$	166.32	[17]
g_I	Michaelis-Menten constant for IL-2 [cells]	10000	From model calculations
i_2	Rate of external source [units per treatment]	$8{\times}10^5{-}7.7{\times}10^6$	[32]

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3 Equilibria

Equilibria of the model (2.1) are defined by the system of the algebraic equations

$$
\begin{aligned}
&(1')\ \ \gamma = [(p_1-\eta)B + \mu_A + \theta p_3 E_B T_i]A,\\
&(2')\ \ b = (p_1 A + p_2 T_u + \mu_B)B,\\
&(3')\ \ p_1 AB = (\beta + \mu_{A_1})A_B,\\
&(4')\ \ \theta p_3 E_B T_i A = \lambda A_T T_u\left(\frac{I_2}{I_2+g_I}\right) + (\beta+\mu_{A_1})A_T,\\
&(5')\ \ \frac{\beta_B A_B I_2}{A_B+g} = (p_3 T_i + \mu_E)E_B,\\
&(6')\ \ \frac{\beta_T A_T I_2}{A_T+g} = (p_3 T_u + \mu_E)E_T,\\
&(7')\ \ (A_B + A_T + E_B + E_T)\left(q_1 - \frac{q_2 I_2}{I_2+g_I}\right) + i_2 = \mu_{I_2} I_2,\\
&(8')\ \ p_2 B T_u = p_4 E_B T_i,\\
&(9')\ \ rT_u\left(1-\frac{T_u}{K}\right) = p_2 B T_u + T_u\left(\lambda A_T + \alpha E_T \frac{\alpha_{T,\beta}F_\beta + e_{T,\beta}}{F_\beta + e_{T,\beta}}\right)\left(\frac{I_2}{I_2+g_I}\right)\left(\frac{g_T}{T_u+g_T}\right),\\
&(10')\ \ \alpha_{\beta,T} T_u = \mu_\beta F_\beta,
\end{aligned}
\tag{3.1}
$$

that follows from (2.1) by the assumption that $A(t), B(t), A_B(t), A_T(t), E_B(t), E_T(t), I_2(t), T_i(t), T_u(t), F_\beta(t)$ are constants.

Note that the solution of the system (3.1) can be not unique. Let us get some solutions of the system (3.1) in two different situations: $b > 0$ and $b = 0$.

3.1 Equilibrium with $b > 0$, $i_2 \geq 0$

Consider the following way to get a solution of the system (3.1), i.e., an equilibrium of the system (2.1) for the "'tumor-free" case:
1) From (9') it follows that one of the possible T_u is $T_u = 0$.
2) From (10') it follows $F_\beta = 0$ (via $T_u = 0$).
3) From (8') it follows $E_B T_i = 0$ (via $T_u = 0$).
4) From (4') it follows $A_T = 0$ (via $T_u = 0$ and $E_B T_i = 0$).
5) From (6') it follows $E_T = 0$ (via $T_u = 0$ and $A_T = 0$).
6) From (1'), (2') the system for A, B it follows (via $E_B T_i = 0$ and $T_u = 0$)

$$
\begin{aligned}
&(p_1 A + \mu_B)B = b,\\
&[(p_1-\eta)B + \mu_A]A = \gamma,
\end{aligned}
\tag{3.2}
$$

with the solution (see Appendix 7.1)

$$
\begin{aligned}
&A^* = \frac{\sqrt{a_1^2 + 4a_0 a_2} - a_1}{2a_0}, \quad B^* = \frac{b}{p_1 A^* + \mu_B},\\
&a_0 = p_1\mu_A, \quad a_1 = b(p_1-\eta) + \mu_A\mu_B - \gamma p_1, \quad a_2 = \gamma\mu_B.
\end{aligned}
$$

7) From (3') it follows $A_B^* = \dfrac{p_1}{\beta+\mu_{A_1}} A^* B^*$ (via A^*, B^*).
8) From (5') it follows that if $E_B = 0$ then $I_2 = 0$ but via (7') it is impossible. So, from $E_B T_i = 0$ it follows $T_i = 0$.
9) From (5') and (7') the system for E_B^*, I_2^* it follows (via $A_T = E_T = T_i = 0$)

$$
\frac{\beta_B A_B^* I_2}{A_B^* + g} = \mu_E E_B, \quad (A_B^* + E_B)\left(q_1 - \frac{q_2 I_2}{I_2+g_I}\right) + i_2 = \mu_{I_2} I_2,
\tag{3.3}
$$

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with the solution (see Appendix 7.2)

$$I_2^* = \frac{\sqrt{c_1^2 + 4c_0c_2} - c_1}{2c_0}, \quad E_B^* = \nu I_2^*,$$
$$c_0 = \mu_{I_2} - \nu(q_1 - q_2), \quad c_1 = (\mu_{I_2} - \nu q_1)g_I - i_2 - A_B^*(q_1 - q_2),$$
$$c_2 = (i_2 + A_B^* q_1)g_I, \quad \nu = \frac{\beta_B A^*}{\mu_E(A_B^* + g)}.$$

As a result we obtain a tumor-free equilibrium

$$\begin{aligned} E_1 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& (A^*, B^*, A_B^*, 0, E_B^*, 0, I_2^*, 0, 0, 0). \end{aligned} \tag{3.4}$$

3.2 Equilibria with $b = 0$, $i_2 \geq 0$

Consider another way to get equilibria of the system (2.1):
1) From (2') it follows $B = 0$.
2) From (3') it follows $A_B = 0$ (via $B = 0$).
3) From (5') it follows $E_B = 0$ (via $A_B = 0$).
4) From (4') it follows $A_T = 0$ (via $E_B = 0$).
5) From (6') it follows $E_T = 0$ (via $A_T = 0$).
6) From (1') it follows $A = \frac{\gamma}{\mu_A}$ (via $B = E_B = 0$).
7) From (7') it follows $I_2 = \frac{i_2}{\mu_{I_2}}$ (via $A_B = A_T = E_B = E_T = 0$).
8) From (9') it follows $T_u = 0$ or $T_u = K$ (via $B = A_T = E_T = 0$).
9) From (10') it follows $F_\beta = 0$ or $F_\beta = \frac{\alpha_{\beta,T}}{\mu_\beta} K$ (via $T_u = 0$ or $T_u = K$).
10) From (8') it follows $T_i = C = const$ (via $B = E_B = 0$).

As a result we obtain two following equilibria:
1) tumor-free ($T_u^* = 0$)

$$\begin{aligned} E_2 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& \left(\frac{\gamma}{\mu_A}, 0, 0, 0, 0, 0, \frac{i_2}{\mu_{I_2}}, C, 0, 0\right), \end{aligned} \tag{3.5}$$

2) not tumor-free ($T_u^* \neq 0$)

$$\begin{aligned} E_3 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& \left(\frac{\gamma}{\mu_A}, 0, 0, 0, 0, 0, \frac{i_2}{\mu_{I_2}}, C, K, \frac{\alpha_{\beta,T}}{\mu_\beta} K\right). \end{aligned} \tag{3.6}$$

Remark 1 *Suppose that $E_B = E_T = 0$. Then from the equations (5') and (6') of the system (3.1) it follows that $A_B = A_T = 0$. From (7') it follows that $I_2 = i_2/\mu_{I_2}$. From (3') it follows that $AB = 0$. From (1') it follows that A cannot be zero by $\gamma > 0$ and from (2') it follows that B is zero by $b = 0$. So, we obtain again the equilibria E_2, E_3.*

4 Centralization and linearization

Let $(A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*)$ be a solution of the system (3.1), i.e., one of the possible equilibria of the system (2.1). Using the new variables $y_1 = A - A^*$, $y_2 = B - B^*$, $y_3 = A_B - A_B^*$, $y_4 = A_T - A_T^*$, $y_5 = E_B - E_B^*$, $y_6 = E_T - E_T^*$, $y_7 = I_2 - I_2^*$, $y_8 = T_i - T_i^*$, $y_9 = T_u - T_u^*$, $y_{10} = F_\beta - F_\beta^*$, we centralize the system (2.1) around the considered equilibrium (see Appendix 7.3):

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$$
\begin{aligned}
\dot{y}_1(t) =& -[(p_1-\eta)B^*+\mu_A]y_1(t)-(p_1-\eta)A^*y_2(t)-\theta p_3A^*T_i^*y_5(t)\\
&-\theta p_3A^*E_B^*y_8(t)+\theta p_3E_B^*T_i^*y_1(t-\tau(t))+N_1(y),\\
\dot{y}_2(t) =& -p_1B^*y_1(t)-(p_1A^*+p_2T_u^*+\mu_B)y_2(t)-p_2B^*y_9(t)+N_2(y),\\
\dot{y}_3(t) =& p_1B^*y_1(t)+p_1A^*y_2(t)-(\beta+\mu_{A_1})y_3(t)+N_3(y),\\
\dot{y}_4(t) =& -(\beta+\mu_{A_1})y_4(t)+\theta p_3A^*T_i^*y_5(t)-\frac{\lambda A_T^*T_u^*g_I}{(I_2^*+g_I)^2}y_7(t)+\theta p_3A^*E_B^*y_8(t)\\
&-\frac{\lambda A_T^*I_2^*}{I_2^*+g_I}y_9(t)+\theta p_3E_B^*T_i^*y_1(t-\tau(t))-\frac{\lambda T_u^*I_2^*}{I_2^*+g_I}y_4(t-\tau(t))+N_4(y),\\
\dot{y}_5(t) =& \frac{\beta_BI_2^*g}{(A_B^*+g)^2}y_3(t)-(p_3T_i^*+\mu_E)y_5(t)+\frac{\beta_BA_B^*}{A_B^*+g}y_7(t)-p_3E_B^*y_8(t)+N_5(y),\\
\dot{y}_6(t) =& -\mu_Ey_6(t)+\frac{\beta_TA_T^*}{A_T^*+g}y_7(t)-p_3E_Ty_9(t)+\frac{\beta_TgI_2^*}{(A_T+g)^2}y_4(t-\tau(t))-p_3E_T^*y_6(t-\tau(t))+N_6(y),\\
\dot{y}_7(t) =& Q_7y_3(t)+Q_7y_4(t)+Q_7y_5(t)+Q_7y_6(t)-\left[\mu_{I_2}+q_2g_I\frac{A_B^*+A_T^*+E_B^*+E_T^*}{(I_2^*+g_I)^2}\right]y_7(t)+N_7(y),\\
\dot{y}_8(t) =& p_2T_u^*y_2(t)-p_4T_i^*y_5(t)-p_4E_B^*y_8(t)+p_2B^*y_9(t)+N_8(y),\\
\dot{y}_9(t) =& -p_2T_u^*y_2(t)-\frac{Q_9T_u^*}{I_2^*+g_I}y_7(t)-\left(p_2B^*+\frac{Q_9g_T}{T_u^*+g_T}+r\left(\frac{2T_u^*}{K}-1\right)\right)y_9(t)\\
&+\alpha E_T^*R_9\frac{(1-\alpha_{T,\beta})e_{T,\beta}}{(F_\beta^*+e_{T,\beta})^2}y_{10}(t)+\lambda R_9y_4(t-\tau(t))+\alpha R_9\frac{\alpha_{T,\beta}F_\beta^*+e_{T,\beta}}{F_\beta^*+e_{T,\beta}}y_6(t-\tau(t))+N_9(y),\\
\dot{y}_{10}(t) =& \alpha_{\beta,T}y_9(t)-\mu_\beta y_{10}(t).
\end{aligned}
\tag{4.1}
$$

Here

$$
\begin{aligned}
Q_7 =& q_1-q_2\frac{I_2^*}{I_2^*+g_I},\quad R_9=T_u^*\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right),\\
Q_9 =& \left(\lambda A_T^*+\alpha E_T^*\frac{\alpha_{T,\beta}F_\beta^*+e_{T,\beta}}{F_\beta^*+e_{T,\beta}}\right)\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right),
\end{aligned}
\tag{4.2}
$$

via $N_i(y)$ in the differential equation for $y_i(t)$, $i=1,...,9$, all nonlinear terms of the variables $y=\{y_1,...,y_{10}\}$ are denoted, $N_i(0)=0$.

It is clear that stability of the zero solution of the system (4.1) is equivalent to stability of the equilibrium of the system (2.1). For the local stability in the first approximation it is enough to consider the linear part of the nonlinear system (4.1). Thus, removing from (4.1) the nonlinear terms $N_i(y)$, represent the linear part of this system in the matrix form

$$
\dot{z}(t)=Hz(t)+Dz(t-\tau(t)),
\tag{4.3}
$$

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where $z = \{z_1, ..., z_{10}\}'$, H and D are the matrices of the dimension 10×10,

$$H = \begin{bmatrix} a_{11} & a_{12} & 0 & 0 & a_{15} & 0 & 0 & a_{18} & 0 & 0 \\ a_{21} & a_{22} & 0 & 0 & 0 & 0 & 0 & 0 & a_{29} & 0 \\ a_{31} & a_{32} & a_{33} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & a_{44} & a_{45} & 0 & a_{47} & a_{48} & a_{49} & 0 \\ 0 & 0 & a_{53} & 0 & a_{55} & 0 & a_{57} & a_{58} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & a_{66} & a_{67} & 0 & a_{69} & 0 \\ 0 & 0 & a_{73} & a_{74} & a_{75} & a_{76} & a_{77} & 0 & 0 & 0 \\ 0 & a_{82} & 0 & 0 & a_{85} & 0 & 0 & a_{88} & a_{89} & 0 \\ 0 & a_{92} & 0 & 0 & 0 & 0 & a_{97} & 0 & a_{99} & a_{9,10} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{10,9} & a_{10,10} \end{bmatrix}, \quad D = \begin{bmatrix} d_{11} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ d_{41} & 0 & 0 & d_{44} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & d_{64} & 0 & d_{66} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & d_{94} & 0 & d_{96} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \tag{4.4}$$

the nonzero elements a_{ij} and d_{ij} of these matrices respectively are

$$\begin{aligned}
a_{11} =& -[(p_1 - \eta)B^* + \mu_A], \quad a_{12} = -(p_1 - \eta)A^*, \quad a_{15} = -\theta p_3 A^* T_i^*, \quad a_{18} = -\theta p_3 A^* E_B^*, \\
a_{21} =& -p_1 B^*, \quad a_{22} = -(p_1 A^* + p_2 T_u^* + \mu_B), \quad a_{29} = -p_2 B^*, \\
a_{31} =& p_1 B^*, \quad a_{32} = p_1 A^*, \quad a_{33} = -(\beta + \mu_{A_1}), \\
a_{44} =& -(\beta + \mu_{A_1}), \quad a_{45} = \theta p_3 A^* T_i^*, \quad a_{47} = -\frac{\lambda g_I A_T^* T_u^*}{(I_2^* + g_I)^2}, \quad a_{48} = \theta p_3 A^* E_B^*, \quad a_{49} = -\frac{\lambda A_T^* I_2^*}{I_2^* + g_I}, \\
a_{53} =& \frac{\beta_B g I_2^*}{(A_B^* + g)^2}, \quad a_{55} = -(p_3 T_i^* + \mu_E), \quad a_{57} = \frac{\beta_B A_B^*}{A_B^* + g}, \quad a_{58} = -p_3 E_B^*, \\
a_{66} =& -\mu_E, \quad a_{67} = \frac{\beta_T A_T^*}{A_T^* + g}, \quad a_{69} = -p_3 E_T^*, \\
a_{73} =& Q_7, \quad a_{74} = Q_7, \quad a_{75} = Q_7, \quad a_{76} = Q_7, \quad a_{77} = -\left(\mu_{I_2} + q_2 g_I \frac{A_B^* + A_T^* + E_B^* + E_T^*}{(I_2^* + g_I)^2}\right), \\
a_{82} =& p_2 T_u^*, \quad a_{85} = -p_4 T_i^*, \quad a_{88} = -p_4 E_B^*, \quad a_{89} = p_2 B^*, \\
a_{92} =& -p_2 T_u^*, \quad a_{97} = -\frac{Q_9 T_u^*}{I_2^* + g_I}, \quad a_{99} = -\left(p_2 B^* + \frac{Q_9 T_u^*}{T_u^* + g_T} + r\left(\frac{2T_u^*}{K} - 1\right)\right), \\
a_{9,10} =& \alpha E_T^* R_9 \frac{(1 - \alpha_{T,\beta}) e_{T,\beta}}{(F_\beta^* + e_{T,\beta})^2}, \quad a_{10,9} = \alpha_{\beta,T}, \quad a_{10,10} = -\mu_\beta,
\end{aligned} \tag{4.5}$$

and

$$\begin{aligned}
d_{11} =& \theta p_3 E_B^* T_i^*, \quad d_{41} = \theta p_3 E_B^* T_i^*, \quad d_{44} = -\frac{\lambda g T_u^* I_2^*}{I_2^* + g_I}, \\
d_{64} =& \frac{\beta_T g I_2^*}{(A_T^* + g)^2}, \quad d_{66} = -p_3 E_T^*, \quad d_{94} = \lambda R_9, \quad d_{96} = \alpha R_9 \frac{\alpha_{T,\beta} F_\beta^* + e_{T,\beta}}{F_\beta^* + e_{T,\beta}}.
\end{aligned} \tag{4.6}$$

5 Stability

In [10] stability conditions for the equation (4.3) are obtained in the form of nonlinear matrix Riccati equations. Via Schur complement (see Appendix 7.4) similarly to [13,14] these conditions can be reformulated in the form of LMIs:

Lemma 1 *Put $\Phi_0(P) = H'P + PH$. If $\dot{\tau}(t) \le 0$ and for some positive definite matrices P and R at least one of the LMIs*

$$\begin{bmatrix} \Phi_0(P) + R & PD \\ D'P & -R \end{bmatrix} < 0, \qquad \begin{bmatrix} \Phi_0(P) + R & D'P \\ PD & -R \end{bmatrix} < 0, \qquad \begin{bmatrix} \Phi_0(P) + D'RD & P \\ P & -R \end{bmatrix} < 0, \tag{5.1}$$

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holds then the zero solution of the equation (4.3) *is asymptotically stable.*

Corollary 1 *If at least one of the LMIs* (5.1) *holds then the appropriate equilibrium of the system* (2.1) *is locally asymptotically stable.*

Remark 2 *For LMIs* (5.1) *the matrix* H *has to be the Hurwitz matrix.*

Example 1 *Let be* $r = 0.0048$, $i_2 = 5 \times 10^6$, $\mu_E = 0.034$ *and all other parameters are given in Table 1. Via the LMIs* (5.1) *and MATLAB it is shown that the equilibrium* E_1 *is locally asymptotically stable for* $b \in B_1 = [2.2 \times 10^4, 58.9 \times 10^9]$. *In particular, the equilibria*

$$\begin{aligned} b =& 2.2 \times 10^4, \\ E_1 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& (223.2, 1.72 \times 10^5, 2.790 \times 10^4, 0, 4.14 \times 10^4, 0, 4.348 \times 10^5, 0, 0, 0) \end{aligned}$$

and

$$\begin{aligned} b =& 6 \times 10^6, \\ E_1 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& (0.6415, 5.995 \times 10^7, 2.795 \times 10^4, 0, 118.96, 0, 4.348 \times 10^5, 0, 0, 0) \end{aligned}$$

are locally asymptotically stable. For $b \leq 2.1 \times 10^4$ *and* $b \geq 59 \times 10^9$ *the equilibrium* E_1 *is unstable.*

Example 2 *Let be again* $r = 0.0048$ *but* $i_2 = 0$, $\mu_E = 0.19$ *and all other parameters are given in Table 1. Similarly to Example 1 it is shown that the equilibrium* E_1 *is locally asymptotically stable in the same interval* $b \in B_1 = [2.2 \times 10^4, 58.9 \times 10^9]$. *In particular, the equilibria*

$$\begin{aligned} b =& 2.2 \times 10^4, \\ E_1 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& (223.2, 1.72 \times 10^5, 2.790 \times 10^4, 0, 0.289, 0, 16.98, 0, 0, 0) \end{aligned}$$

and

$$\begin{aligned} b =& 6 \times 10^6, \\ E_1 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& (0.6415, 5.995 \times 10^7, 2.795 \times 10^4, 0, 8.328 \times 10^{-4}, 0, 17.01, 0, 0, 0) \end{aligned}$$

are locally asymptotically stable.

Example 3 *Let be* $r = 0.0085$ *and all other parameters as in Example 1. In this case, the equilibrium* E_1 *is locally asymptotically stable for* $b \in B_2 = [3.6 \times 10^4, 53.9 \times 10^9]$. *In particular, the equilibria*

$$\begin{aligned} b =& 3.6 \times 10^4, \\ E_1 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& (123.16, 3.12 \times 10^5, 2.792 \times 10^4, 0, 2.284 \times 10^4, 0, 4.348 \times 10^5, 0, 0, 0) \end{aligned}$$

and

$$\begin{aligned} b =& 6 \times 10^6, \\ E_1 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& (0.6415, 5.995 \times 10^7, 2.795 \times 10^4, 0, 118.96, 0, 4.348 \times 10^5, 0, 0, 0). \end{aligned}$$

are locally asymptotically stable. For $b \leq 3.5 \times 10^4$ *and* $b \geq 54 \times 10^9$ *the equilibrium* E_1 *is unstable.*

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Example 4 *Let be again* $r = 0.0085$ *but but* $i_2 = 0$, $\mu_E = 0.19$ *and all other parameters as in Example 3. In this case the equilibrium* E_1 *is locally asymptotically stable for* $b \in B_2 = [3.6 \times 10^4, 53.9 \times 10^9]$. *In particular, the equilibria*

$$\begin{aligned} b =& 3.6 \times 10^4, \\ E_1 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& (123.16, 3.12 \times 10^5, 2.792 \times 10^4, 0, 0.1597, 0, 16.99, 0, 0, 0) \end{aligned}$$

and

$$\begin{aligned} b =& 6 \times 10^6, \\ E_1 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& (0.6415, 5.995 \times 10^7, 2.795 \times 10^4, 0, 8.328 \times 10^{-4}, 0, 17.01, 0, 0, 0) \end{aligned}$$

are locally asymptotically stable.

Remark 3 *Note that in the equilibrium* E_1 *we have* $A_T^* = E_T^* = T_i^* = T_u^* = F_\beta^* = 0$. *From* (4.6), (4.2) *it follows that* $d_{11} = d_{14} = d_{44} = d_{66} = d_{94} = d_{96} = 0$. *If* $i_2 = 5 \times 10^6$ *then* $d_{64} = 0.0658$ *for both* $r = 0.0048$ *and* $r = 0.0085$. *If* $i_2 = 0$ *then* $d_{64} = 2.575 \times 10^{-6}$ *for* $r = 0.0085$ *and* $d_{64} = 0$ *for* $r = 0.0048$. *So, one can see that dependence on delay is low enough.*

Example 5 *By* $b = 0$, $i_2 = 5 \times 10^6$, $\mu_T = 0.034$ *and the same values of all other parameters the following two equilibria are unstable:*

$$\begin{aligned} E_2 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& (123680, 0, 0, 0, 0, 0, 434783, 0, 0, 0), \\ E_3 =& (A^*, B^*, A_B^*, A_T^*, E_B^*, E_T^*, I_2^*, T_i^*, T_u^*, F_\beta^*) \\ =& (123680, 0, 0, 0, 0, 0, 434783, 0, 10^{11}, 82973). \end{aligned} \tag{5.2}$$

Remark 4 *If the matrix* H *is the Hurwitz matrix then* $\det(H) > 0$. *For the equilibria* E_2 *and* E_3 *we have* $E_B = 0$. *From* (4.5) *it follows that* $a_{18} = a_{48} = a_{58} = a_{88} = 0$, *i.e., all elements of the eighth column of the matrix* H *are zeros and therefore* $\det(H) = 0$. *It means that the matrix* H *is not the Hurwitz matrix and the equilibrium* E_2 *and* E_3 *are unstable for all values of the parameters.*

6 Conclusions

In this work we present the improved model of combined therapy BCG+IL-2 immunotherapy in superficial BC with constant instillations of BCG and IL-2. The current manuscript describes the outcome of analytical methods used to derive the equilibria points and especially the tumor-free equilibrium point, at which cancer cells are effectively eliminated. The model demonstrates several equilibria which depend on biologically related parameters and initial conditions.

Adding BCG to the tumor-immune interaction may increase the immune response, which will be enhanced by the addition of effector cells specific for tumor Ag. These effector cells appear only after a time delay caused by their proliferation and maturation, and capture tumor cells containing this Ag. The entire reaction can only take place with the presence of BCG. It is shown that the considered system has three equilibria describing the different states of the patient. The stability of these states is investigated using the method of Lyapunov functionals and the method of linear matrix inequalities (LMIs). Only in the E_1 and E_2 equilibria do get cancer cell eradication ($T_u = 0$), meaning successful treatment. Stability analysis of the system (2.1) shows the equilibrium E_1 is stable if the for BCG dose is reflected in the condition depend on the growth of cancer cells (as indicated in Examples 1-4). In equilibrium E_1 we obtain a strong immune response because $A_B = 10^5$ and $I_2 = 10^5$ that help to arrive at a tumor-free fixed point.

The delay does not influence to the stability of the first equilibrium that is shown in the Remark 3. The system does not stable in the equilibria E_2 and E_3 with IL-2 therapy only (see Example 5, Remark 4).

By registering the basic parameters of BCG, maximum tumor size, tumor growth rate, and immune response parameters, we found the BCG dose where E_1 will be stable (Example 1-4). The ability to plan and predict by calculating

a modulated dose of treatment may benefit patients who are unable to receive conventional treatment because of its serious side effects, and as for patients who were previously considered refractory.

We would like to raise awareness in the community of urological-oncological doctors about the possibilities of mathematical modeling and receive quantitative data to improve this model. The ability to plan and predict by calculating a modulated dose of treatment can benefit patients who are unable to take routine treatment because of its serious side effects, as well as to patients who were previously not considered treatable.

It is necessary to note also that three equilibria that are investigated in this work are equilibria obtained from the system (3.1) in an analytical way. So, there is a possibility of continuing stability investigation of the considered model via getting additional equilibria by numerical methods and using additional results of stability theory [10]. So, it will be the interest of experts in this direction to the obtained here results, and it is supposed to continue this research.

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7 Appendix

7.1 Solution of (3.2)

From the second equation (3.2) we have $B = \dfrac{b}{p_1 A + \mu_B}$. Substituting it into the first equation (3.2), we obtain

$$
\begin{aligned}
&\gamma = A\left[\frac{b(p_1-\eta)}{p_1 A+\mu_B}+\mu_A\right],\\
&\gamma p_1 A+\mu_B\gamma = Ab(p_1-\eta)+p_1\mu_A A^2+\mu_A\mu_B A,\\
&a_0A^2+a_1A-a_2=0, \quad a_0=p_1\mu_A,\\
&a_1=b(p_1-\eta)+\mu_A\mu_B-\gamma p_1, \quad a_2=\gamma\mu_B,\\
&A^*=\frac{\sqrt{a_1^2+4a_0a_2}-a_1}{2a_0}, \quad B^*=\frac{b}{p_1A^*+\mu_B}.
\end{aligned}
$$

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7.2 *Solution of* (3.3)

From the first equation (3.3) we have $E_B = \nu I_2$, $\nu = \dfrac{\beta_B A^*}{\mu_E(A_B^* + g)}$. Substituting E_B into the second equation (3.3), we obtain the equation for I_2:

$$
\begin{aligned}
&(A_B^* + \nu I_2)\left(q_1 - \frac{q_2 I_2}{I_2 + g_I}\right) = \mu_{I_2} I_2 - i_2,\\
&(A_B^* + \nu I_2)((q_1 - q_2)I_2 + q_1 g_I) = (\mu_{I_2} I_2 - i_2)(I_2 + g_I),\\
&c_0 I_2^2 + c_1 I_2 - c_2 = 0, \quad c_0 = \mu_{I_2} - \nu(q_1 - q_2),\\
&c_1 = (\mu_{I_2} - \nu q_1)g_I - i_2 - A_B^*(q_1 - q_2), \quad c_2 = (i_2 + A_B^* q_1)g_I,\\
&I_2^* = \frac{\sqrt{c_1^2 + 4c_0 c_2} - c_1}{2c_0}, \quad E_B^* = \nu I_2^*.
\end{aligned}
$$

7.3 *Centralization of the system* (2.1)

For the first equation of the system (2.1) using (3.1) we have

$$
\begin{aligned}
\dot{y}_1(t) =& \gamma - (p_1 - \eta)(y_1(t) + A^*)(y_2(t) + B^*) - \mu_A(y_1(t) + A^*)\\
&- \theta p_3(y_1(t - \tau(t)) + A^*)(y_5(t) + E_B^*)(y_8(t) + T_i^*)\\
=& -[(p_1 - \eta)B^* + \mu_A]y_1(t) - (p_1 - \eta)A^* y_2(t) - \theta p_3 A^* T_i^* y_5(t)\\
&- \theta p_3 A^* E_B^* y_8(t) + \theta p_3 E_B^* T_i^* y_1(t - \tau(t)) + N_1(y).
\end{aligned}
$$

Similarly for the second and the third equations of (2.1) using (3.1) we have

$$
\begin{aligned}
\dot{y}_2(t) =& b - (p_1(y_1(t) + A^*) + p_2(y_9(t) + T_u^*) + \mu_B)(y_2(t) + B^*)\\
=& - p_1 B^* y_1(t) - (p_1 A^* + p_2 T_u^* + \mu_B)y_2(t) - p_2 B^* y_9(t) + N_2(y),
\end{aligned}
$$

$$
\begin{aligned}
\dot{y}_3(t) =& p_1(y_1(t) + A^*)(y_2(t) + B^*) - (\beta + \mu_{A_1})(y_3(t) + A_B^*)\\
=& p_1 B^* y_1(t) + p_1 A^* y_2(t) - (\beta + \mu_{A_1})y_3(t) + N_3(y).
\end{aligned}
$$

For the fourth equation of (2.1) we obtain

$$
\begin{aligned}
\dot{y}_4(t) =& \theta p_3(y_1(t - \tau(t)) + A^*)(y_5(t) + E_B^*)(y_8(t) + T_i^*)\\
&- \lambda(y_4(t - \tau(t)) + A_T^*)(y_9(t) + T_u^*)\frac{y_7(t) + I_2^*}{y_7(t) + I_2^* + g_I} - (\beta + \mu_{A_1})(y_4(t) + A_T^*)\\
=& -(\beta + \mu_{A_1})y_4(t) + \theta p_3 A^* T_i^* y_5(t) + \theta p_3 A^* E_B^* y_8(t) + \theta p_3 E_B^* T_i^* y_1(t - \tau(t)) - \lambda G_4 + N_4(y),
\end{aligned}
$$

where

$$
G_4 = (y_4(t - \tau(t)) + A_T^*)(y_9(t) + T_u^*)\frac{y_7(t) + I_2^*}{y_7(t) + I_2^* + g_I} - \frac{A_T^* T_u^* I_2^*}{I_2^* + g_I}.
$$

Using Taylor's expansion in the form $f(y) = f(0) + f'(0)y + o(y)$, we have

$$
\frac{1}{a + y} = \frac{1}{a} - \frac{y}{a^2} + o(y), \quad \lim_{y \to 0} \frac{o(y)}{y} = 0. \tag{7.1}
$$

Thus,

$$
\begin{aligned}
G_4 =& (y_4(t - \tau(t)) + A_T^*)(y_7(t) + I_2^*)(y_9(t) + T_u^*)\left(\frac{1}{I_2^* + g_I} - \frac{y_7(t)}{(I_2^* + g_I)^2} + o(y_7)\right) - \frac{A_T^* T_u^* I_2^*}{I_2^* + g_I}\\
=& \frac{A_T^* T_u^* g_I}{(I_2^* + g_I)^2} y_7(t) + \frac{A_T^* I_2^*}{I_2^* + g_I} y_9(t) + \frac{T_u^* I_2^*}{I_2^* + g_I} y_4(t - \tau(t)) + N_4(y).
\end{aligned}
$$

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As a result

$$\begin{aligned}\dot{y}_4(t) =& -(\beta+\mu_{A_1})y_4(t)+\theta p_3 A^* T_i^* y_5(t)-\frac{\lambda A_T^* T_u^* g_I}{(I_2^*+g_I)^2}y_7(t)+\theta p_3 A^* E_B^* y_8(t)-\frac{\lambda A_T^* I_2^*}{I_2^*+g_I}y_9(t)\\ &+\theta p_3 E_B^* T_i^* y_1(t-\tau(t))-\frac{\lambda T_u^* I_2^*}{I_2^*+g_I}y_4(t-\tau(t))+N_4(y).\end{aligned}$$

For the fifth equation of (2.1) via (3.1) we have

$$\begin{aligned}\dot{y}_5(t) =&\frac{\beta_B(y_3(t)+A_B^*)(y_7(t)+I_2^*)}{y_3(t)+A_B^*+g}-p_3(y_8(t)+T_i^*)(y_5(t)+E_B^*)-\mu_E(y_5(t)+E_B^*),\\ =&-(p_3T_i^*+\mu_E)y_5(t)-p_3E_B^*y_8(t)+\beta_B G_5+N_5(y),\end{aligned}$$

where

$$G_5=\frac{(y_3(t)+A_B^*)(y_7(t)+I_2^*)}{y_3(t)+A_B^*+g}-\frac{A_B^*I_2^*}{A_B^*+g}.$$

Using (7.1), we obtain

$$\begin{aligned}G_5=&(y_3(t)+A_B^*)(y_7(t)+I_2^*)\left(\frac{1}{A_B^*+g}-\frac{y_3(t)}{(A_B^*+g)^2}+o(y_3)\right)-\frac{A_B^*I_2^*}{A_B^*+g}\\ =&\frac{I_2^*g}{(A_B^*+g)^2}y_3(t)+\frac{A_B^*}{A_B^*+g}y_7(t)+N_5(y).\end{aligned}$$

As a result

$$\dot{y}_5(t)=\frac{\beta_B I_2^* g}{(A_B^*+g)^2}y_3(t)-(p_3T_i^*+\mu_E)y_5(t)+\frac{\beta_B A_B^*}{A_B^*+g}y_7(t)-p_3E_B^*y_8(t)+N_5(y).$$

For the sixth equation of (2.1) we have

$$\begin{aligned}\dot{y}_6(t) =&\frac{\beta_T(y_4(t-\tau(t))+A_T^*)(y_7(t)+I_2^*)}{y_4(t-\tau(t))+A_T^*+g}-p_3(y_9(t)+T_u^*)(y_6(t-\tau(t))+E_T^*)-\mu_E(y_6(t)+E_T^*),\\ =&-\mu_E y_6(t)-p_3E_T^*y_9(t)-p_3E_T^*y_6(t-\tau(t))+\beta_T G_6+N_6(y),\end{aligned}$$

where

$$G_6=\frac{(y_4(t-\tau(t))+A_T^*)(y_7(t)+I_2^*)}{y_4(t-\tau(t))+A_T^*+g}-\frac{A_T^*I_2^*}{A_T^*+g}$$

and via (7.1)

$$\begin{aligned}G_6=&(y_4(t-\tau(t)+A_T^*)(y_7(t)+I_2^*)\left(\frac{1}{A_T^*+g}-\frac{y_4(t-\tau(t))}{(A_T^*+g)^2}+o(y_4)\right)-\frac{A_T^*I_2^*}{A_T^*+g}\\ =&\frac{A_T^*}{A_T^*+g}y_7(t)+\frac{gI_2^*}{(A_T+g)^2}y_4(t-\tau(t))+N_6(y).\end{aligned}$$

Thus,

$$\dot{y}_6(t)=-\mu_E y_6(t)+\frac{\beta_T A_T^*}{A_T^*+g}y_7(t)-p_3E_T^*y_9(t)+\frac{\beta_T gI_2^*}{(A_T^*+g)^2}y_4(t-\tau(t))-p_3E_T^*y_6(t-\tau(t))+N_6(y).$$

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For the seventh equation of (2.1) we have

$$\begin{aligned}\dot{y}_7(t) =&(y_3(t)+A_B^*+y_4(t)+A_T^*+y_5(t)+E_B^*+y_6(t)+E_T^*)\left(q_1-\frac{q_2(y_7(t)+I_2^*)}{y_7(t)+I_2^*+g_I}\right)\\&+i_2-\mu_{I_2}(y_7(t)+I_2^*).\end{aligned}$$

Putting $Q_7 = q_1 - \dfrac{q_2 I_2^*}{I_2^*+g_I}$, via (7.1) we obtain

$$\begin{aligned}q_1-\frac{q_2(y_7(t)+I_2^*)}{y_7(t)+I_2^*+g_I} =&q_1-\frac{q_2}{I_2^*+g_I}(y_7(t)+I_2^*)+\frac{q_2y_7(t)}{(I_2^*+g_I)^2}(y_7(t)+I_2^*)+o(y_7)\\ =&Q_7-\left(\frac{q_2}{I_2^*+g_I}-\frac{q_2I_2^*}{(I_2^*+g_I)^2}\right)y_7(t)+o(y_7)\\ =&Q_7-\frac{q_2g_I}{(I_2^*+g_I)^2}y_7(t)+o(y_7).\end{aligned}$$

Thus,

$$\begin{aligned}\dot{y}_7(t) =&(y_3(t)+y_4(t)+y_5(t)+y_6(t)+A_B^*+A_T^*+E_B^*+E_T^*)\left(Q_7-\frac{q_2g_I}{(I_2^*+g_I)^2}y_7(t)+o(y_7)\right)\\&+i_2-\mu_{I_2}(y_7(t)+I_2^*)\\ =&Q_7y_3(t)+Q_7y_4(t)+Q_7y_5(t)+Q_7y_6(t)-\left[\mu_{I_2}+q_2g_I\frac{A_B^*+A_T^*+E_B^*+E_T^*}{(I_2^*+g_I)^2}\right]y_7(t)+N_7(y).\end{aligned}$$

For the eighth equation of (2.1)

$$\begin{aligned}\dot{y}_8(t) =&p_2(y_2(t)+B^*)(y_9(t)+T_u^*)-p_4(y_5(t)+E_B^*)(y_8(t)+T_i^*)\\ =&p_2T_u^*y_2(t)-p_4T_i^*y_5(t)-p_4E_B^*y_8(t)+p_2B^*y_9(t)+N_8(t).\end{aligned}$$

For the ninth equation of (2.1) we have

$$\dot{y}_9(t) =(y_9(t)+T_u^*)\left[r\left(1-\frac{y_9(t)+T_u^*}{K}\right)-p_2(y_2(t)+B^*)-G_9\right],$$

where

$$\begin{aligned}G_9 =&\left(\lambda(y_4(t-\tau(t))+A_T^*)+\alpha(y_6(t-\tau(t))+E_T^*)\frac{\alpha_{T,\beta}(y_{10}(t)+F_\beta^*)+e_{T,\beta}}{y_{10}(t)+F_\beta^*+e_{T,\beta}}\right)\\&\times\left(\frac{y_7(t)+I_2^*}{y_7(t)+I_2^*+g_I}\right)\left(\frac{g_T}{y_9(t)+T_u^*+g_T}\right).\end{aligned}$$

Note that via (7.1)

$$\begin{aligned}\frac{y_7(t)+I_2^*}{y_7(t)+I_2^*+g_I} =&(y_7(t)+I_2^*)\left(\frac{1}{I_2^*+g_I}-\frac{y_7(t)}{(I_2^*+g_I)^2}+o(y_7)\right)\\ =&\frac{I_2^*}{I_2^*+g_I}+\frac{y_7(t)}{I_2^*+g_I}-\frac{I_2^*y_7(t)}{(I_2^*+g_I)^2}+o(y_7)\\ =&\frac{I_2^*}{I_2^*+g_I}+\frac{g_I}{(I_2^*+g_I)^2}y_7(t)+o(y_7),\end{aligned}$$

$$\frac{g_T}{y_9(t)+T_u^*+g_T}=\frac{g_T}{T_u^*+g_T}-\frac{g_T}{(T_u^*+g_T)^2}y_9(t)+o(y_9)$$

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and

$$\begin{aligned}\frac{\alpha_{T,\beta}(y_{10}(t)+F_\beta^*)+e_{T,\beta}}{y_{10}(t)+F_\beta^*+e_{T,\beta}} &= (\alpha_{T,\beta}y_{10}(t)+\alpha_{T,\beta}F_\beta^*+e_{T,\beta})\left(\frac{1}{F_\beta^*+e_{T,\beta}}-\frac{y_{10}(t)}{(F_\beta^*+e_{T,\beta})^2}+o(y_{10})\right)\\ &= \frac{\alpha_{T,\beta}F_\beta^*+e_{T,\beta}}{F_\beta^*+e_{T,\beta}}+\frac{\alpha_{T,\beta}y_{10}(t)}{F_\beta^*+e_{T,\beta}}-\frac{(\alpha_{T,\beta}F_\beta^*+e_{T,\beta})y_{10}(t)}{(F_\beta^*+e_{T,\beta})^2}+o(y_{10})\\ &= \frac{\alpha_{T,\beta}F_\beta^*+e_{T,\beta}}{F_\beta^*+e_{T,\beta}}-\frac{(1-\alpha_{T,\beta})e_{T,\beta}}{(F_\beta^*+e_{T,\beta})^2}y_{10}(t)+o(y_{10}).\end{aligned}$$

Put

$$Q_9=\left(\lambda A_T^*+\alpha E_T^*\frac{\alpha_{T,\beta}F_\beta^*+e_{T,\beta}}{F_\beta^*+e_{T,\beta}}\right)\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right).$$

Then via (3.1) $rT_u^*\left(1-\frac{T_u^*}{K}\right)=T_u^*(p_2B^*+Q_9)$ and

$$\begin{aligned}G_9=&\Bigg(\lambda(y_4(t-\tau(t))+A_T^*)\\ &+\alpha(y_6(t-\tau(t))+E_T^*)\left(\frac{\alpha_{T,\beta}F_\beta^*+e_{T,\beta}}{F_\beta^*+e_{T,\beta}}-\frac{(1-\alpha_{T,\beta})e_{T,\beta}}{(F_\beta^*+e_{T,\beta})^2}y_{10}(t)+o(y_{10})\right)\Bigg)\\ &\times\left(\frac{I_2^*}{I_2^*+g_I}+\frac{g_I}{(I_2^*+g_I)^2}y_7(t)+o(y_7)\right)\left(\frac{g_T}{T_u^*+g_T}-\frac{g_T}{(T_u^*+g_T)^2}y_9(t)+o(y_9)\right)\\ =&\Bigg(\lambda A_T^*+\alpha E_T^*\frac{\alpha_{T,\beta}F_\beta^*+e_{T,\beta}}{F_\beta^*+e_{T,\beta}}-\alpha E_T^*\frac{(1-\alpha_{T,\beta})e_{T,\beta}}{(F_\beta^*+e_{T,\beta})^2}y_{10}(t)\\ &+\lambda y_4(t-\tau(t))+\alpha\frac{\alpha_{T,\beta}F_\beta^*+e_{T,\beta}}{F_\beta^*+e_{T,\beta}}y_6(t-\tau(t))\Bigg)\\ &\times\left(\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)+\left(\frac{g_I}{(I_2^*+g_I)^2}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_7(t)\right.\\ &\left.-\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{(T_u^*+g_T)^2}\right)y_9(t)\right)+N_9(y)\\ =&Q_9+\frac{Q_9}{I_2^*+g_I}y_7(t)-\frac{Q_9}{T_u^*+g_T}y_9(t)-\alpha E_T^*\frac{(1-\alpha_{T,\beta})e_{T,\beta}}{(F_\beta^*+e_{T,\beta})^2}\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_{10}(t)\\ &+\lambda\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_4(t-\tau(t))\\ &+\alpha\frac{\alpha_{T,\beta}F_\beta^*+e_{T,\beta}}{F_\beta^*+e_{T,\beta}}\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_6(t-\tau(t)))+N_9(y).\end{aligned}$$

Thus,

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$$
\begin{aligned}
\dot{y}_9(t) =& T_u^*\Bigg[r\left(1-\frac{T_u^*}{K}\right)-p_2B^*-p_2y_2(t)-\frac{r}{K}y_9(t)-Q_9-\frac{Q_9}{I_2^*+g_I}y_7(t)+\frac{Q_9}{T_u^*+g_T}y_9(t)\\
&+\alpha E_T^*\frac{(1-\alpha_{T,\beta})e_{T,\beta}}{(F_\beta^*+e_{T,\beta})^2}\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_{10}(t)+\lambda\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_4(t-\tau(t))\\
&+\alpha\frac{\alpha_{T,\beta}F_\beta^*+e_{T,\beta}}{F_\beta^*+e_{T,\beta}}\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_6(t-\tau(t)))\Bigg]\\
&+y_9(t)\left[r\left(1-\frac{T_u^*}{K}\right)-p_2B^*-Q_9\right]+N_9(y)\\
=& T_u^*\Bigg[-p_2y_2(t)-\frac{Q_9}{I_2^*+g_I}y_7(t)+\left(\frac{Q_9}{T_u^*+g_T}-\frac{r}{K}\right)y_9(t)\\
&+\alpha E_T^*\frac{(1-\alpha_{T,\beta})e_{T,\beta}}{(F_\beta^*+e_{T,\beta})^2}\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_{10}(t)\Bigg]\\
&+\left[r\left(1-\frac{T_u^*}{K}\right)-p_2B^*-Q_9\right]y_9(t)+\lambda T_u^*\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_4(t-\tau(t))\\
&+\alpha T_u^*\frac{\alpha_{T,\beta}F_\beta^*+e_{T,\beta}}{F_\beta^*+e_{T,\beta}}\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_6(t-\tau(t))+N_9(y)
\end{aligned}
$$

or

$$
\begin{aligned}
\dot{y}_9(t) =& -p_2T_u^*y_2(t)-\frac{Q_9T_u^*}{I_2^*+g_I}y_7(t)-\left(p_2B^*+\frac{Q_9g_T}{T_u^*+g_T}+r\left(\frac{2T_u^*}{K}-1\right)\right)y_9(t)\\
&+\alpha E_T^*T_u^*\frac{(1-\alpha_{T,\beta})e_{T,\beta}}{(F_\beta^*+e_{T,\beta})^2}\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_{10}(t)\\
&+\lambda T_u^*\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_4(t-\tau(t))\\
&+\alpha T_u^*\frac{\alpha_{T,\beta}F_\beta^*+e_{T,\beta}}{F_\beta^*+e_{T,\beta}}\left(\frac{I_2^*}{I_2^*+g_I}\right)\left(\frac{g_T}{T_u^*+g_T}\right)y_6(t-\tau(t))+N_9(y).
\end{aligned}
$$

At last for the last equation of (2.1) via (3.1) we obtain

$$\dot{y}_{10}(t)=\alpha_{\beta,T}y_9(t)-\mu_\beta y_{10}(t).$$

7.4 Schur complement

Schur complement [33]. The symmetric matrix $\begin{bmatrix}A & B\\ B' & C\end{bmatrix}$ is negative definite if and only if C and $A-BC^{-1}B'$ are both negative definite.