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USE OF QUASI-NORMAL FORM TO EXAMINE STABILITY OF TUMOR-FREE EQUILIBRIUM IN A MATHEMATICAL MODEL OF BCG TREATMENT OF BLADDER CANCER

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Abstract. Understanding the dynamics of human hosts and tumors is of critical importance. A mathematical model was developed by Bunimovich-Mendrazitsky et al. ([10]), who explored the immune response in bladder cancer as an effect of BCG treatment. This treatment exploits the host's own immune system to boost a response that will enable the host to rid itself of the tumor. Although this model was extensively studied using numerical simulation, no analytical results on global tumor dynamics were originally presented. In this work, we analyze stability in a mathematical model for BCG treatment of bladder cancer based on the use of quasi-normal form and stability theory. These tools are employed in the critical cases, especially when analysis of the linearized system is insufficient. Our goal is to gain a deeper insight into the BCG treatment of bladder cancer, which is based on a mathematical model and biological considerations, and thereby to bring us one step closer to the design of a relevant clinical protocol.

1. **Introduction.** Bladder cancer (BC) is characterized by the growth of malignant cells within the urinary bladder. BC is the fourth most common cancer among men and the eighth most common cancer among women, accounting for approximately 200,000 new cases worldwide annually ([21]). Bladder cancer is an aggressive disease with lethal outcome. If untreated, it slowly grows, first into the bladder wall and then out into the abdomen and nearby organs, such as the prostate, vagina, uterus and rectum. A typical treatment of bladder cancer consists of chemotherapy followed by immunotherapy for eradication of any residual cancer cells.

Intravesical administration of Bacillus Calmette-Gurin (BCG) is a type of immunotherapy used to treat superficial bladder cancer. BCG is an attenuated nonpathogenic strain of Mycobacterium bovis that was originally used as a vaccine against tuberculosis. In this treatment bacterial instillations are introduced into the bladder via catheter inserted through the urethra. BCG is internalized and processed by both antigen-presenting cells (APC) and uninfected tumor cells. BCG antigens stimulate a strong immune response characterized by a surge in cytokine levels in the infected areas and in the urine. The cytokine cascade stemming from

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the APCs activates cytotoxic T cells (CTL) and natural killer cells (NK) ([8]), which ultimately destroy the BCG-infected tumor cells ([26]). This targeting of infected tumor cells can lead to elimination of the entire tumor.

Bunimovich-Mendrazitsky et al. ([10] and [11]) studied the role of BCG immunotherapy in bladder cancer dynamics. The model proposed there deals with four populations: BCG cells; activated cells of the immune system (commonly called the effector cells), such as cytotoxic T-cells, macrophages and natural killer cells that are cytotoxic to the tumor cells; the uninfected tumor cells; and finally, tumor cells infected by BCG.

The model developed by Bunimovich-Mendrazitsky et al. ([10]) exhibits multiple steady states that depend on biological parameters and initial conditions. The most important parameters in that study are the treatment term that represents the rate of administration of BCG cells (b), the tumor growth rate (r), the rate of tumor cell infection by BCG (p_2), and the rate of immune system activation (p_4).
A significant clinically relevant feature of the model is the non-trivial dependence of the tumor dynamics on the treatment rate b:

1. For a non-treatment case (b = 0) with exponential tumor growth, the model, naturally, lacks any stable equilibrium.
2. The effect of BCG immunotherapy (b > 0) can yield three distinct types of equilibrium:
3. For low treatment rates: persistence of the tumor which indicates the failure of the BCG treatment for low treatment rates (tumor equilibrium);
4. For intermediate treatment rates: the tumor is eradicated, with only transient side effects (tumor-free equilibrium);
5. For high treatment rates: the tumor is eradicated but a persistent immune response is elicited (side-effects equilibrium).

The analysis of equilibria in [10] was based on studying a linear approximation to a nonlinear system only. It was shown that the tumor-free equilibrium is stable at certain criterion on dose BCG. From the medical point of view, this result shows that with the application of immunotherapy, the tumor will shrink at a rate that can be controlled by the intensity of BCG treatment. However, analysis of equilibrium based on linear approximation is valid only in the case where the matrix, J, associated with the linear approximation has no critical eigenvalues, because the behavior of a nonlinear system in the critical case may differ from that of a linear system. As a reminder, critical cases of stability are those cases where some of the eigenvalues of matrix J are zero or have zero real parts, while all the remaining eigenvalues have negative real parts ([24]). Because our present system falls into a critical case, it is necessary to study stability in this critical case. To do so, we use the theory of normal forms theory, as discussed in this article.

Normal forms are the most important tool for the local analysis and classification of point equilibrium. The theory of normal forms was initiated by Poincare ([28]) and Liapunov ([24]), and later extended by Birkhoff ([7]) to Hamiltonian vector fields. Contemporary accounts of normal forms and their applications can be found in Bibikov ([6]), Arnold ([2]), Bruno ([9]), Chow & Hale ([13]), Guckenheimer & Holmes ([19]), Iooss & Adelmeyer ([20]), and Arnold et al. ([4]). Normal forms are obtained through an appropriate change of variables to transform a system of nonlinear differential equation into a form that exhibits more clearly the interaction between the linear and nonlinear terms. The purpose of normal forms is to facilitate the analysis of the local dynamics. There are various types of normal forms in use,

depending on the specific problem at hand ([14], [1], [12]). The normal form leads to the maximum simplification of the nonlinear part of the system assuming that the linear part is reduced to a Jordan form ([19]).

In this study, we used a variation of the normal form introduced by Bibikov ([6]), applicable to the critical case, and called the quasi–normal form. The rationale for conversion of a system to a quasi-normal form is similar to that for the normal form. Using a quasi-normal form allows us to simplify preliminary calculations in the critical case and apply the results on stability obtained by Liapunov ([24]) and Malkin ([25]) to the nonlinear model of BCG treatment of bladder cancer.

In this article, we describe our BCG model, analyze its spectrum, describe the normalization procedure and relevant quasi-normal forms, and finally apply this theory to the study of stability of the tumor-free equilibrium in the BCG model.

2. **Model.**

2.1. **Description.** The model proposed in ([10]) was the first mathematical model to describe tumor-immune interactions in the bladder as a result of continuous BCG therapy. A full explanation is given in [10]; here we summarize it briefly as follows. We assume that BCG is introduced into the bladder at a constant rate b. The free BCG binds to tumor cells, infecting them at a rate p_2. We denote by μ_1 the natural death rate for BCG.

Tumor cells are tracked by a continuous variable as their number is large and tumor population is generally homogeneous. In our model, tumor cells are divided into two subpopulations: those that have been infected (T_i) with BCG (B) and those that are still uninfected (T_u). Immune cells are also large in number, including those cells that have been stimulated and are ready to respond. To simplify the model, we grouped the immune cells (APC, CTL, NK) into a single population of cells, which we term effector cells (E). They target and destroy infected tumor cells (T_i) at a rate p_3 and take up BCG at a rate p_1. Activation of the immune response is a result of the encounter between immune cells and BCG, and it is controlled by parameter p_4. Infected tumor cells stimulate recruitment of cytotoxic effector cells from the bone marrow ([5]) at the total rate αT_i. The rate of inactivation of E cells via encounter with T_i is given by $p_5 E T_i$. Finally, we denote by μ_2 the natural death rate of effector cells.

The equations that describe the interactions of these four variables are given in the following system, assuming exponential tumor growth:

$$\begin{aligned}
\frac{dB}{dt} &= -\mu_1 B - p_1 EB - p_2 BT_u + b \\
\frac{dE}{dt} &= -\mu_2 E + \alpha T_i + p_4 EB - p_5 ET_i \\
\frac{dT_i}{dt} &= -p_3 ET_i + p_2 BT_u \\
\frac{dT_i}{dt} &= -p_3 ET_i + p_2 BT_u
\end{aligned} \quad . \tag{1}$$

We examine equations (1) with the following initial conditions: $B(0) > 0$; $E(0) = T_i(0) = 0$; $T_u(0) > 0$.

To further clarify the dependence of system (1) on parameters and to improve the performance of calculations, we non-dimensionalize the system and reduce the number of system parameters. Introduce the following dimensionless state variables:

$$B^{'} = \frac{B}{B_0}, \qquad E^{'} = p_1\frac{E}{E_0}, \qquad T_i^{'} = \frac{T_i p_3}{T_{i_0} p_1}, \qquad T_u^{'} = \frac{T_u}{T_{u_0}}, \qquad t^{'} = \mu_1 t$$

and the corresponding parameters:

$$b^{'} = \frac{b}{\mu_1 B_0}, \qquad r^{'} = \frac{r}{\mu_1}, \qquad \mu = \frac{\mu_2}{\mu_1}, \qquad p_1^{'} = \frac{p_1}{\mu_1}E_0, \qquad p_2^{'} = \frac{p_2}{\mu_1}T_{u_0},$$

$$p_3^{'} = \frac{p_3}{\mu_1}E_0, \qquad \alpha^{'} = \frac{\alpha(p_1^{'})^2}{\mu_1 p_3^{'}}, \qquad p_4^{'} = \frac{p_4}{\mu_1}B_0, \qquad p_5^{'} = \frac{p_5 p_1^{'}}{\mu_1 p_3^{'}}T_{i_0}, \qquad p_6 = \frac{p_1^{'}p_2^{'}}{p_3^{'}}.$$

In practice, there is a trade-off between reducing the number of parameters and retaining parameters that have operational meaning. For these reasons, we chose the scaling $B_0 = E_0 = T_{i_0} = T_{u_0} = 10^6$ cells ([23]), which allows us to deal with smaller values of state variables. Leaving the other parameters unchanged and dropping the primes for notational clarity, the non-dimensional system is now given by:

$$\begin{aligned}
\frac{dB}{dt} &= -B - EB - p_2 T_u B + b \\
\frac{dE}{dt} &= E(-\mu + p_4 B - p_5 T_i) + \alpha T_i \\
\frac{dT_i}{dt} &= -ET_i + p_6 B T_u \\
\frac{dT_u}{dt} &= T_u(-p_2 B + r)
\end{aligned} \qquad . \tag{2}$$

Those model parameters that can be estimated from biological data are summarized in Appendix B. The estimates are based on the values reported in [10]. We emphasize that dimensionless units are used throughout the model analysis that follows unless stated otherwise.

2.2. **The spectrum of system (2).** Qualitative research of the system (2) includes studying its local and global properties. On the first stage, we will limit ourselves to the local study of fixed points, which is a necessary component of the study of global dynamics. In the [10] study, fixed points were studied for the linearized system. Here, we continue this study for the nonlinear system (2).

We separate the linear and nonlinear parts in the nonlinear equation (2):

$$\frac{dX}{dt} = JX + f(X) + \beta\,, \tag{3}$$

where $X = (B, E, T_i, T_u)$, $\beta = (b, 0, 0, 0)$ and entries of matrix J are represented by the coefficients for linear terms of (2). Denote $X^* = (B^*, E^*, T_i^*, T_u^*)$ as equilibrium (or fixed) point of the system. Introduce the vector $\Xi = (\xi_1, \xi_2, \xi_3, \xi_4)$ as

$$\Xi = X - X^*\,. \tag{4}$$

The purpose of the linear transformation (4) is to move the fixed point to the origin. After transformation (4) system (3) becomes homogeneous and takes on the

form:

$$\frac{d\Xi}{dt} = J\Xi + g(\Xi)\ , \tag{5}$$

where J is the linear part and g is the nonlinear part of the system (5):

$$J = \begin{bmatrix} -(1+E^*+p_2T_u^*) & -B^* & 0 & -p_2B^* \\ p_4E^* & -\mu+p_4B^*-p_5T_i^* & -p_5E^*+\alpha & 0 \\ p_6T_u^* & -T_i^* & -E^* & p_6B^* \\ -p_2T_u^* & 0 & 0 & -p_2B^*+r \end{bmatrix},$$

$$g(\Xi) = \begin{bmatrix} -\xi_1\xi_2 - p_2\xi_1\xi_4 \\ p_4\xi_1\xi_2 - p_5\xi_2\xi_3 \\ -\xi_2\xi_3 + p_6\xi_1\xi_4 \\ p_2\xi_1\xi_2 \end{bmatrix}.$$

In the current study, we examine the most biologically interesting equilibrium called "tumor-free" equilibrium. If this fixed point is stable then treatment will result in cancer elimination and there will no be side effects. "Tumor free" equilibrium is given by:

$$B^* = b, \qquad E^* = T_i^* = T_u^* = 0,$$

or, in the new variables,

$$\xi_i : \quad \xi_1 = \xi_2 = \xi_3 = \xi_4 = 0\ . \tag{6}$$

Analysis of the spectrum of this equilibrium ([10]) leads us to consider a critical case in which the characteristic equation of matrix J has one zero eigenvalue while other eigenvalues are negative. The spectrum of matrix J has the form: $\Lambda = [-1;\ -\mu+p_4b\ ;\ 0;\ -p_2b+r]$. Thus if

$$\frac{r}{p_2} < b < \frac{\mu}{p_4}\ , \tag{7}$$

then all eigenvalues except one ($\lambda_3 = 0$) will be negative. It should be noted that parameters p_2 and p_4 in (7) were obtained by numerical simulations ([10]) and have not been previously estimated in medical or biologic literature. Note that the values of parameters considered in this work (see Appendix B) satisfy conditions (7).

The "tumor-free" equilibrium has zero eigenvalue ($\lambda_3 = 0$) regardless of the particular values of model parameters. Hence the study of this fixed point does not require bifurcation analysis. The existence of zero eigenvalue refers to the neutrality of the linear approximation to a system of non-linear ODE. In other words, for all relevant values of model parameters, analysis of the linear approximation cannot solve the problem of stability for the non linear system. Similar systems, but for another critical cases, were studied in the papers of Goltser ([15], [16], [17], [18]). Should all eigenvalues have negative real parts, the local equilibrium would be asymptotically stable.

In what follows (if condition (7) is true) we study stability of tumor-free equilibrium of the nonlinear system in question in the critical case of one zero eigenvalue and assuming that condition (7) is satisfied. In section 3, we reduce the nonlinear system to a quasi-normal form. In section 4, we use the results from section 3 and the reduction principle to perform stability analysis of the "tumor-free" equilibrium.

3. **Critical case investigation: One zero eigenvalue.** The normalization process for system (5) will be carried out in accordance with the general scheme outlined in Appendix A.

In this section we perform quasinormalization procedure in a critical case of one zero eigenvalue and realize procedure of stability research (Theorems 3.1 & 3.3, Lemma 3.2), using normal form and reduction principle.

Consider a system (5) of nonlinear ODE that has the trivial solution $\Xi = 0$. We divide the equations in (5) into two groups: one critical equation, corresponding to the zero eigenvalue and three non critical equations, containing three non- critical eigenvalues:

$$\begin{cases} \dfrac{dy}{dt} = F(y, Z) \\ \dfrac{dZ}{dt} = yR + QZ + G(y, Z) \end{cases}, \tag{8}$$

where $Z = [z_1, z_2, z_3]; F(y, Z)$, $G(y, Z)$ are nonlinear vector-functions; Q is the matrix $Q_{[3x3]}$ for non critical eigenvalues. The equation for y corresponds to the zero eigenvalue of matrix J.

The linear part of system (8) is

$$J = \begin{vmatrix} 0 & O \\ R & Q \end{vmatrix}, \tag{9}$$

where: element $j_{11} = 0; O_{[1\times3]}$ is the zero matrix; $R_{[3\times1]}$ is the column matrix with elements r_{s0}, s= 1, 2, 3; and $Q_{[3\times3]}$ is a matrix with coefficients $r_{si\,[1x3]}$, s, i = 1, 2, 3.

The transformations required for the system normalization procedure performed in two stages. On the first stage, we make a linear substitution (10) to reduce the linear part of (8) in a block-diagonal form:

$$\begin{cases} Y = \theta \\ Z = \tau + S\theta \end{cases}, \tag{10}$$

where $S_{[3\times1]}$-transform matrix that will convert (9) to block-diagonal form as $K = \begin{vmatrix} 0 & 0 \\ 0 & T \end{vmatrix}$, where in block-matrix $T_{[3\times3]}$ all eigenvalues have negative real parts. Matrix S is calculated so that in the new system (11) linear approximation is depended on non-critical variables only. (All necessary calculations for a matrix S are executed for the BCG system in section 4).

After substitution (10) system (8) becomes

$$\begin{cases} \dfrac{d\theta}{dt} = \displaystyle\sum_{j=2}^{\infty} h^{(j)}(\theta, \tau) = H(\theta, \tau) \\ \dfrac{d\tau}{dt} = T\tau + \displaystyle\sum_{j=2}^{\infty} p^{(j)}(\theta, \tau) = T\tau + P(\theta, \tau) \end{cases}, \tag{11}$$

where $h^{(j)}(\theta, \tau)$, $p^{(j)}(\theta, \tau)$ are j-th order nonlinear terms in the power series expansion of vector-functions $H(\theta, \tau)$, $P(\theta, \tau)$ in the neighborhood of the origin ($\tau_1 = \tau_2 = \tau_3 = \theta = 0$), respectively.

Transformation from (8) to (11) with (10) is always possible, because (10) is inverse linear transformation, hence (8) and (11) are equivalent. In particular, the zero solution of both systems is stable or unstable simultaneously.

The stability of system (11) is depends on the structure of nonlinear terms. We assume that these nonlinear terms are computed and their coefficients are known (as a minimum) up to order k. In the second stage, we transform nonlinear terms of system (11) using the following substitution:

$$\begin{cases} \theta = u + \sum_{j=2}^{k} \Phi^{(j)}(u, V) \\ \tau_s = v_s + \sum_{j=2}^{k} \Psi_s^{(j)}(u, V); \quad (s = 1, 2, 3) \end{cases}, \tag{12}$$

where $\Phi^{(j)}$, $\Psi_s^{(j)}$are forms (i.e. a homogeneous polynomial) of order j. Using substitution (12) we convert system (11) into the quasi-normal form up to order k:

$$\begin{cases} \frac{du}{dt} = \sum_{j=2}^{k} g_j u^j + O^{(k+1)}(u, 0) \\ \frac{dv_s}{dt} = \sum_{m=1}^{3} t_{sm} v_m + \sum_{j=2}^{k} v_s^{(j)}(u, V) + O^{(k+1)}(u, V) \end{cases}. \tag{13}$$

In the first equation of (13) contains resonant terms, which are explained in detail in Appendix A. According to the reduction principle (Appendix A), setting $V = 0$ in (13) and selecting the critical equation from the system, we obtain:

$$\frac{du}{dt} = \sum_{j=2}^{k} g_j u^j + O^{k+1}(u, 0) \, . \tag{14}$$

As shown in Malkin([25]), Pliss ([27]) and Kelley ([22]), stability of system (13) reduces to that of equation (14). The number k in this equation should be chosen according to the following rule: k is the number such that $g_2 = g_3 = ... = g_{k-1} = 0$ and $g_k-$is the first non-zero resonance coefficient (see Appendix A). If such k exists then the critical case is called an algebraic case, otherwise it is called a transcendental case. According to the well-known results ([24], [25], [6]) the following theorem holds:

Theorem 3.1. *In an algebraic case, fixed point of system (8) is asymptotically stable if and only if $g_k < 0$ and k is an odd number. Otherwise, the fixed point is unstable.*

From a theoretical point of view, the coefficient of primary interest is g_2. The coefficient g_2 from system (13) essentially depends on the coefficients of the $h^{(2)}(\theta, \tau)$in the system (11), and, as will be shown below, the coefficient g of the term $h^{(2)}(\theta, 0) = g\theta^2$.

This coefficient is closely related to a factor g, which is known prior to the normalization process and is defined from system (11): $h^{(2)}(\theta, 0) = g\theta^2$. Our goal here is to find a relationship between coefficients g and g_2.

Lemma 3.2. *After the transformation of system (11) to system (13) by means of transformation (12), the resonant coefficient g_2 in (14) will be defined by equality $g_2 = g$.*

Proof. We compare systems (11) and (13). The normalization process is defined by forms $\theta^{(2)}, \tau_k^{(2)}$, $\Phi^{(2)}$, $\Psi_j^{(2)}$. Differentiating transformation (12) in t (where is k=2),

using (11) and (13), we obtain:

$$\frac{d\theta}{dt} = \underbrace{h^{(2)}\left(u+\Phi^{(2)}(u,V), V+\Psi^{(2)}(u,V)\right)+O\left(\|u,V\|^3\right)}_{I} =$$

$$= \frac{du}{dt}+\frac{\partial\Phi^{(2)}}{\partial u}\frac{du}{dt}+\sum_{s=1}^{3}\frac{\partial\Phi^{(2)}}{\partial v_s}\frac{dv_s}{dt} \equiv$$

$$\equiv \underbrace{g_2u^2+O(\|u,V\|^3)+\frac{\partial\Phi^{(2)}}{\partial u}\left[(g_2u^2+O(\|u,V\|^3)\right]+}_{II} \qquad (15)$$

$$\underbrace{+\sum_{s=1}^{3}\left[\frac{\partial\Phi^{(2)}}{\partial v_s}(\sum_{m=1}^{3}t_{sm}v_m+O(\|u,V\|^2)\right]}_{II}$$

Comparison of second order terms in both parts of this identity (I and II) in (15), we get the following equation:

$$h^{(2)}(u,V) = g_2u^2+\sum_{s=1}^{3}\left[\frac{\partial\Phi^{(2)}}{\partial v_s}\sum_{m=1}^{3}t_{sm}v_m\right]. \qquad (16)$$

By the definition of coefficient g_2 in the normal form, we substitute $v_1 = v_2 = v_3 = 0$ in (16) and considering that $h^{(2)}(\theta,0) = g\theta^2$, we obtain $g_2\,u^2 = h^{(2)}(u,0)$, whence $g_2 = g$. Lemma is proved. □

Remark 1. Theorem 3.1 and Lemma 3.2 show that establishing stability in the case where $g \neq 0$ does not require to compute g_3: the resonant coefficient g_2 coincides with g, which is calculated at the second step. Only in a case where $g_2 = g = 0$ is it necessary to do the next step and compute g_3 by normalizing the terms of the third order. More generally, the normalization process continues on until the first non-zero term g_k is found, after which one applies Theorem 3.1.

From Theorem 3.1 and Lemma 3.2 the following result for the studied system (11) is obtained:

Theorem 3.3. *If $g \neq 0$ in the system (11), then the fixed point of system (13), and hence also system (11), is not unstable.*

In the next section, we analyze stability of the "tumor-free" equilibrium in the BCG system. We perform the calculations necessary for obtaining coefficient g. It is important to note that if $g \neq 0$ then there is no need to calculate all coefficients of the quasi-normal form in the 2nd order approximation.

4. **Application of the quasi-normal form to the analysis of tumor-free equilibrium in the BCG model.** We examine stability of the "tumor-free" equilibrium (6) of system (5) using the quasi-normal form obtained in the previous section.

The calculations necessary for the stability analysis are performed as follows.
Step 1: Separation of the critical part from the system

$$\frac{d\xi_j}{dt} = p_{j1}\xi_1+p_{j2}\xi_2+p_{j3}\xi_3+p_{j4}\xi_4+\Xi_j(\xi,\xi_1,\xi_2,\xi_3), \quad (j=1,2,3,4)\,. \qquad (17)$$

As we have shown, the linear part of system (17) has a single zero eigenvalue while the other three eigenvalues have negative real parts.

For the purpose of separation to identify the equation corresponding to zero eigenvalue, we introduce a new variable y:

$$y = a_1\xi_1 + a_2\xi_2 + a_3\xi_3 + a_4\xi_4 \ .$$

The constant coefficients $a_j\,(j = 1, 2, 3, 4)$ are calculated so that:

$$\frac{dy}{dt} = \sum_1^4 a_j \frac{d\xi_j}{dt} = 0 \ .$$

We obtain:

$$a_1 = 0, \qquad a_2 = 0, \qquad a_3 = \frac{p_2}{p_3} - \frac{r}{bp_3}, \qquad a_4 = 1. \tag{18}$$

By substituting (18) in (5), we obtain the following transformation:

$$\begin{cases} y = (\frac{p_2}{p_3} - \frac{r}{bp_3})\xi_3 + \xi_4 \\ z_j = \xi_j (j = \overline{1,3}) \end{cases}$$

After this substitution, the system takes on the form:

$$\begin{cases} \dfrac{dy}{dt} = -z_2z_3 + p_3yz_1 - \left(\dfrac{p_2}{p_3} - \dfrac{r}{bp_3}\right) z_1z_3 \\ \dfrac{dz_1}{dt} = -z_1 - bz_2 - bp_2\left[y - \left(\dfrac{p_2}{p_3} - \dfrac{r}{bp_3}\right) z_3\right] - \\ -z_1z_2 - p_2z_1\left[y - \left(\dfrac{p_2}{p_3} - \dfrac{r}{bp_3}\right) z_3\right] \\ \dfrac{dz_2}{dt} = z_2(-\mu + p_4b) + \alpha z_3 + p_4z_1z_2 - p_5^{'}z_2z_3 \\ \dfrac{dz_3}{dt} = bp_3\left[y - \left(\dfrac{p_2}{p_3} - \dfrac{r}{bp_3}\right) z_3\right] - z_2z_3 + p_3z_1\left[y - \left(\dfrac{p_2}{p_3} - \dfrac{r}{bp_3}\right) z_3\right] \end{cases} \tag{19}$$

The matrix J for system (19) is

$$\left(\begin{array}{c|ccc} 0 & 0 & 0 & 0 \\ \hline -bp_2 & -1 & -b & \frac{p_2}{p_3}(bp_2 - r) \\ 0 & 0 & -\mu + p_4b & \alpha \\ bp_3 & 0 & 0 & bp_2 - r \end{array}\right) \ .$$

$\underbrace{\qquad}_{R}$ $\underbrace{\qquad\qquad\qquad}_{Q}$

Step 2: Block-diagonalization of matrix J

Matrix J represents the linear part of system (19). To obtain its quasi-normal form, it is necessary to convert J into a new block-diagonal matrix K, so that $K = \left|\begin{array}{cc} 0 & 0 \\ 0 & T \end{array}\right|$, where $T_{[3\times3]}$ is a matrix.

Introduce vector $\eta = (y, z_1, z_2, z_3)$, so that the linear part of the system (19) is given by:

$$\overset{\bullet}{\eta} = J\eta = \begin{pmatrix} 0 & 0 \\ R & Q \end{pmatrix} \begin{pmatrix} y \\ z_1 \\ z_2 \\ z_3 \end{pmatrix} \ .$$

We represent vector η in the form:

$$\eta = CW \ , \tag{20}$$

where

$$W = \begin{bmatrix} u \\ v_1 \\ v_2 \\ v_3 \end{bmatrix}, \qquad C = \begin{pmatrix} B_{11} & B_{12} \\ S & B_{22}^{'} \end{pmatrix} .$$

B_{11} is a scalar and $B_{12\ [1\times3]}$, $S\ _{[3x1]}$ and $B_{22\ [3x3]}$ are some matrices. The equation for W then becomes:

$$\dot{W} = C^{-1}JCW \equiv KW ,$$

where $K = C^{-1}JC$. Solving for C we obtain the desired transformation matrix

$$C = \begin{pmatrix} B_{11} & B_{12} \\ S & B_{22} \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 & 0 \\ -\dfrac{b^2\alpha p_3}{(-\mu+p_4b)(bp_2-r)} & 1 & 0 & 0 \\ -\dfrac{b\alpha p_3}{(-\mu+p_4b)(-bp_2+r)} & 0 & 1 & 0 \\ -\dfrac{bp_3}{(bp_2-r)} & 0 & 0 & 1 \end{pmatrix} .$$

Applying the linear transformations (20) to the nonlinear system (19), we obtain a new nonlinear system:

$$\begin{cases} \dfrac{d\theta}{dt} = -\left(\dfrac{\alpha bp_3}{(-\mu+p_4b)(bp_2-r)}\theta+\tau_2\right)\left(-\dfrac{bp_3}{(bp_2-r)}\theta+\tau_3\right)+ \\ +p_3^{'}\theta\left(-\dfrac{b^2\alpha p_3}{(-\mu+p_4\,b)(bp_2-r)}\theta+\tau_1\right)-\left(\dfrac{p_2}{p_3}-\dfrac{r}{bp_3}\right)\times \\ \times\left(-\dfrac{b^2\alpha p_3}{(-\mu+p_4b)(bp_2-r)}\theta+\tau_1\right)\left(-\dfrac{bp_3}{(bp_2-r)}\theta+\tau_3\right) \\ \dfrac{d\tau_1}{dt} = -\tau_1-b\tau_2-bp_2\left[\theta-(\dfrac{p_2}{p_3}-\dfrac{r}{bp_3})\tau_3\right]- \\ -\left(-\dfrac{b^2\alpha p_3}{(-\mu+p_4b)(bp_2-r)}\theta+\tau_1\right)\times\left(\dfrac{\alpha bp_3}{(-\mu+p_4b)(bp_2-r)}\theta+\tau_2\right)- \\ -p_2\left(-\dfrac{b^2\alpha p_3}{(-\mu+p_4b)(bp_2-r)}\theta+\tau_1\right)\times \\ \times\left[\theta-\left(\dfrac{p_2}{p_3}-\dfrac{r}{bp_3}\right)\left(-\dfrac{bp_3}{(bp_2-r)}\theta+\tau_3\right)\right] \\ \dfrac{d\tau_2}{dt} = \tau_2(-\mu+p_4b)+\alpha\tau_3+p_4\left(-\dfrac{b^2\alpha p_3}{(-\mu+p_4b)(bp_2-r)}\theta+\tau_1\right)\times \\ \times\left(\dfrac{\alpha bp_3}{(-\mu+p_4b)(bp_2-r)}\theta+\tau_2\right)-p_5\left(\dfrac{\alpha bp_3}{(-\mu+p_4b)(bp_2-r)}\theta+\tau_2\right)\times \\ \times\left(-\dfrac{bp_3}{(bp_2-r)}\theta+\tau_3\right) \\ \dfrac{d\tau_3}{dt} = bp_3\left[\theta-(\dfrac{p_2}{p_3}-\dfrac{r}{bp_3})\tau_3\right]-\left(\dfrac{\alpha bp_3}{(-\mu+p_4b)(bp_2-r)}\theta+\tau_2\right) \\ \left(-\dfrac{bp_3}{(bp_2-r)}\theta+\tau_3\right)+p_3\left(-\dfrac{b^2\alpha p_3}{(-\mu+p_4b)(bp_2-r)}\theta+\tau_1\right)\times \\ \times\left[\theta-\left(\dfrac{p_2}{p_3}-\dfrac{r}{bp_3}\right)\left(-\dfrac{bp_3}{(bp_2-r)}\theta+\tau_3\right)\right] \end{cases} . \quad (21)$$

To compute coefficient g_2, we choose the first equation from (21) and calculate the coefficients for θ^2 (see Section 3). First, denote

$$\alpha_1 = -\frac{b^2\alpha p_3}{(-\mu + p_4 b)(bp_2 - r)}; \quad \alpha_2 = \frac{\alpha b p_3}{(-\mu + p_4 b)(bp_2 - r)}; \quad \alpha_3 = -\frac{bp_3}{(bp_2 - r)}.$$

Next, we rewrite the first equation as follows:

$$\begin{aligned}
&\frac{d\theta}{dt} = -(\alpha_2\theta + \tau_2)(\alpha_3\theta + \tau_3) + p_3\theta(\alpha_1\theta + \tau_1) - \\
&- \left(\frac{p_2}{p_3} - \frac{r}{bp_3}\right)(\alpha_1\theta + \tau_1)(\alpha_3\theta + \tau_3) = \\
&= \theta^2\left[p_3\alpha_1 - \alpha_2\alpha_3 - \left(\frac{p_2}{p_3} - \frac{r}{bp_3}\right)\alpha_1\alpha_3\right] - \theta\tau_3\left[\alpha_2 + \left(\frac{p_2}{p_3} - \frac{r}{bp_3}\right)\alpha_1\right] + \\
&+\theta\tau_1\left[p_3 - \left(\frac{p_2}{p_3} - \frac{r}{bp_3}\right)\alpha_3\right] - \alpha_3\theta\tau_2 - \tau_2\tau_3 - \left(\frac{p_2}{p_3} - \frac{r}{bp_3}\right)\tau_1\tau_3
\end{aligned}.$$

Therefore, the coefficient for θ^2 can be rewritten in the following form:

$$g = p_3\alpha_1 - \alpha_2\alpha_3 - \left(\frac{p_2}{p_3} - \frac{r}{bp_3}\right)\alpha_1\alpha_3 = \frac{p_3 b^2\alpha(p_3 bp_2 - p_3 r - p_3 + bp_2 - r)}{(\mu - p_4 b)(bp_2 - r)^2}. \quad (22)$$

We are interesting to find out the set of parameters for which the coefficient g becomes zero. Taking the fixed set of parameters (see Appendix B) for the applicable interval of b ($.238 = r/p_2 < b < \mu/p_4 = 3.41$, see Table 2), we obtain that the coefficient g has the largest value on the boundary of the interval, decreasing to the middle of the interval, and equal to zero when $b \approx 1.477$. The coefficient g estimation summary is presented in the Table 1.

b	g
Min=.238	-308637
0.7	-17.7
1.1	-6.232
1.47749	$.43 \times 10^{-8}$
2.15	18.2
Max=3.41	9080

TABLE 1. Summary of the calculations of the values of g given by the formula (22), with varying intensities of treatment b (other parameters are constant as in Table 2: μ= 0.41; p_3 =1.1; α =0.52; p_4 =0.12; p_2 =0.285; r =0.068). Equating the numerator (22) to zero, we obtain the function for b when $g = 0$ for all other fixed parameters of the BCG model: $b = \frac{p_3(\alpha+r)+\alpha r}{p_2(p_3+\alpha)} \approx 1.47749$.

Applying Theorem 3.3 we conclude that the system (1) is unstable in all parameter space except the point where $b \approx 1.477$ ($g = 0$). For this specific case the additional stability investigation should be done in such a way that the first $g_n \neq 0$ will be found.

To confirm this result, we solved the system of equations (1) numerically using a fourth order Runge-Kutta scheme. Fig. 1 (a&b) shows a typical simulation for a treatment protocol in which BCG instillations at respective rates a) $b = 0.9$; b) $b = 1.477$ (critical value of b because $g_2 = 0$). Because our goal was to examine local stability of the tumor-free fixed point, we chose initial conditions close to the value of this fixed point: B(0) = 0 (BCG is not present at the beginning of the treatment), E(0) = 0.01; $T_i(0) = 0$ (no infected tumor cells at the beginning of treatment); $T_u(0) = 0.35$.

The presence of zero eigenvalue means that the fixed point is unstable (in the sense of Lyapunov stability) in the most of the cases. As a result of the simulation (Fig. 1 a&b), the integral curves for B, E, T_i are increased in the power low [these sites are marked in the figure by the letter U] and hence this fixed point is not locally stable. Based on Fig. 1 (a&b), we can confirm that the solutions are unstable for all values of b with sufficient accuracy.

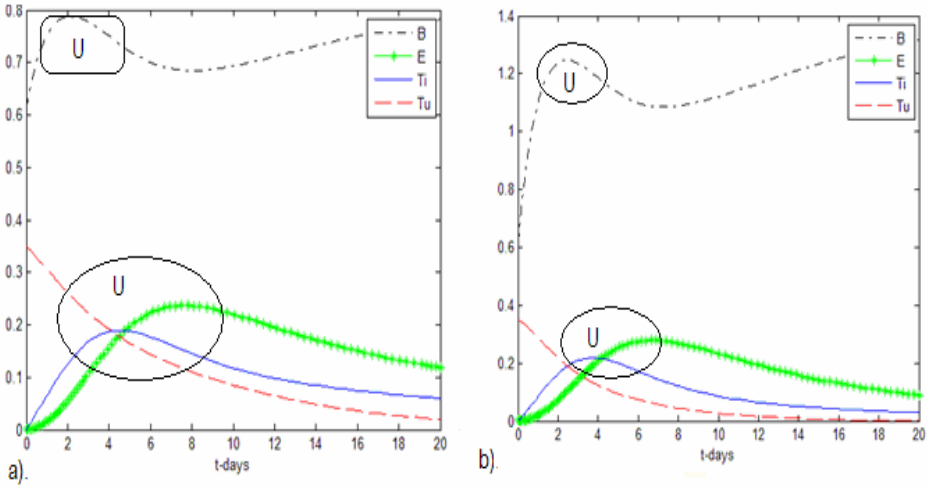

FIGURE 1. Numerical simulation of system (1) for two different therapy regimens. In each case, we plotted the time-series of uninfected tumor cells (dashed line), effector cells (solid heavy line), tumor cells infected with BCG (solid line) and BCG (dash-dotted line). BCG instillation rates are: a)$b = 0.9$; b)$b = 1.4$. Parameter values are as in Table 2 with the initial tumor size before treatment $T_u(0)$=0.35.

Fig. 1 & 2 are fully consistent with the definition of instability by Lyapunov.
In each case, we plotted the time-series of uninfected tumor cells (dashed line), effector cells (solid heavy line), tumor cells infected with BCG (solid line) and BCG (dash-dotted line).

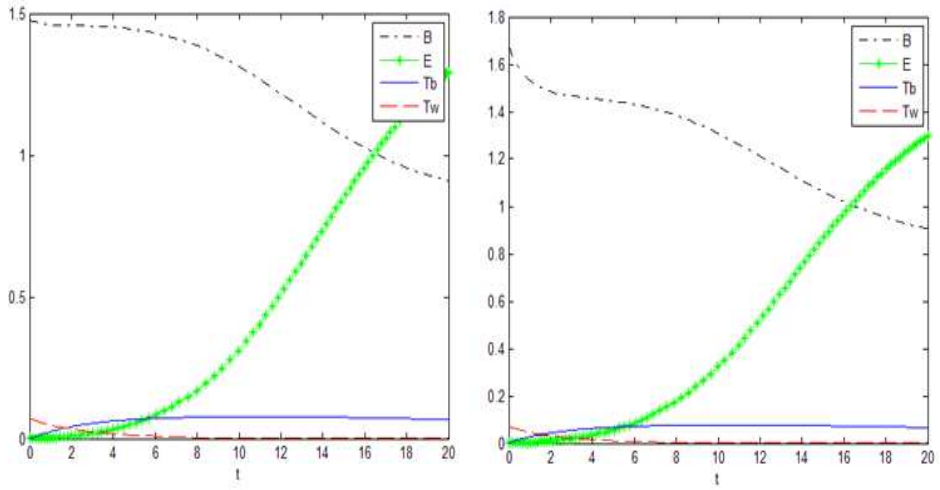

FIGURE 2. Numerical simulation of system (1) for two different initial conditions: a). b is close to the critical value: $b = 1.488$. b). b is a far from critical value: $b = 1.65$.

5. **Discussion.** The aim of this work was to study BCG model in the case of zero eigenvalue, because this issue has not been studied previously. Why is this important? Intravesical BCG therapy has been proven to be effective in the prophylaxis and treatment of superficial bladder cancer but no prognostic indicator of treatment success has ever been formulated. In addition, several complications occurring after BCG immunotherapy have been reported in 80% of patients. These complications were classified as minor side effects and major side effects. In our model, we examined tumor-free equilibrium without side effects or with only minor side effects and tumor-free equilibrium with major side-effects. Bladder cancer is rarely cured without side effects resulting from BCG immunotherapy. In the case that treatment is successful, it is still difficult to determine what factors brought about this result. Therefore, by analyzing the mathematical model we are trying to find the answer to this question.

An important aspect of the study of the model of BCG treatment of bladder cancer is investigation of the stability of the tumor-free equilibrium. This fixed point is critical in that one of the eigenvalues of the corresponding linearized system is zero (regardless of the values of biological parameters of the model) while all others are negative (under conditions (7)). For our system, zero eigenvalue is always present; hence degenerate co-dimension one situation cannot occur in our case. In this case, analysis of stability cannot be performed on the basis of the linearized system alone but rather requires analyzing nonlinear terms as well. We showed that stability (or lack thereof) of the tumor-free equilibrium is determined (under condition (7)) by the value of a single combination g of model parameters, see formula (22). As a result, the behavior of the system about this fixed point does not produce bifurcations where stability changes near the singular point. We note also the irrelevance of the transversality condition, since zero eigenvalue does not leave the origin of the plane of eigenvalues for all values of model parameters. The existence of zero eigenvalue in the spectrum is the property of the trajectories of the

system (rate of parameters changing), and do not fully characterize the behavior of the entire system.

We showed that stability of the tumor-free equilibrium is possible only at the intermediate levels of treatment intensity($r/p_2 < b < \mu/p_4$). However, even for intermediate levels of b, if $g \neq 0$ then this equilibrium is unstable. Thus, stability is an exceptionally rare phenomenon. Practically, achieving stability requires a careful selection of the rate b of BCG instillation. From mathematical standpoint, our main result was obtained through computing the quasi-normal form of the system and application of the reduction principle.

From the medical point of view, at intermediate levels of treatment intensity ($r/p_2 < b < \mu/p_4$), the tumor-free equilibrium is unstable and tumor cure is impossible, except the point $b \approx 1.477$, where g=0. The analysis of g_3 requires an additional sophisticated calculations which are not in the scope of this work. However, considering the simulation results, it can be argued that for $b \approx 1.477$, tumor-free equilibrium is not local stable too.

From Theorem 3.1, under the conditions $g_2 = 0,\ g_3 < 0$, the fixed point will be asymptotically stable. However, a question arises as to whether there are biologically significant sets of model parameters for which the above conditions are met. From our study it is clear that stability essentially depends on the estimation of the values of biological parameters: BCG infection rate (p_2), rate of killing of infected tumor cells by effector cells (p_3), rates of recruitment of effector cells (p_4) and their natural mortality rate (μ), natural growth (r) of bladder tumor cells, and the BCG treatment dose (b).

The general results obtained in section 3 can be used to perform stability analysis for the other critical fixed points of system (1). The study by [10] revealed in particular that, in a "side-effect" equilibrium, in which the spectrum contains two zero eigenvalues, depending on the values of model parameters, bifurcation phenomena with degeneracy of co-dimension 2 will manifest themselves. Thus, investigating stability of the system with particular type of nonlinearity should be a matter of future research.

By addition of term of bursting of infected tumor cells or term of tumor infected cells mortality in the T_i equation in the system (1), we can liquidate of zero eigenvalue in spectrum. However, these values will be very small relative to the values of p_3 in system (1), and therefore, we should examine the bifurcation in the zero eigenvalue neighborhood (just as is done in the study of Hopf bifurcation) and this means that this problem is essentially nonlinear and requires using of the normal form theory also. In this regard, we assert that our analysis is important for the study of other models when real eigenvalue is very small.

The analysis of stability presented here was performed under the assumption of the exponential growth of cancer cells in the bladder. From the mathematical and biological points of view, it is clear that a similar analysis can be performed under the assumption that tumor growth can be approximated by any other smooth differentiable function obtained from biological experiments.

In our work, complex biological interactions between tumor, immune system, and BCG were represented by a 4-dimensional system. As the dimension of the system was relatively small, all calculations were performed without the aid of a computer. Additional variables that would provide a more detailed description of the underlying biology can be envisioned; however, this would require more complex

calculations. To perform them, algorithms for the reduction to normal forms of systems of various orders are available ([32]).

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Appendix A. Quasi-normal form and reduction principle.

In this section we examine the notations and basic concepts used in this study and summarize briefly the ideas of the quasi-normal theory, based on Bibikov ([6]).

To consider the general (n+s) nonlinear ODE system, which is similar to (5) and having the trivial solution $\Xi = 0$. Suppose that (n+s) eigenvalues of a matrix J are divided into two groups: a critical part, containing n eigenvalues and a non critical part, containing s no critical eigenvalues with negative real parts.

Without loss of generality we may assume that $J_{[(n+s)x(n+s)]} = \begin{pmatrix} A & 0 \\ R & Q \end{pmatrix}$ where the matrix $A_{[nxn]}$has critical eigenvalue only; the matrix $Q_{[sxs]}$ has no critical eigenvalues. The ODE system corresponding matrix J looks like:

$$\begin{cases} \dfrac{dY}{dt} = AY + F(Y,Z) = AY + \sum_{j=2}^{\infty} F^{(j)}(Y,Z) \\ \dfrac{dZ}{dt} = RY + QZ + G(Y,Z) = RY + QZ + \sum_{j=2}^{\infty} G^{(j)}(Y,Z) \end{cases}, \tag{A.1}$$

where $Y = [y_1, y_2, ..., y_n]$, $Z = [z_1, z_2, ..., z_s]$; $F(Y,Z)$, $G(Y,Z)$ are vector-functions; and $F^{(j)}(Y,Z)$, $G^{(j)}(Y,Z)$ are j-th order nonlinear terms in the power series expansion of functions $F(Y,Z)$, $G(Y,Z)$ in the neighborhood of the origin, respectively.

The system (A.1) is characterized that the equations for the critical variables are being separated from the equations for non critical variables.

In the research of critical cases, an initial position is the assumption that the linear part of the studied system has a certain canonical form. For example, it can be assumed that the matrix of the linear approximation has a Jordan form, and this is used in the normal forms theory of the resonant type. In our work has been used a quasi-normal form, which implies that the canonical form of the matrix of the linear approximation, has a block structure, in which the blocks correspond to the critical and noncritical eigenvalues appropriately. To use a quasi-normal form, there is no requirement that the block corresponding to the noncritical part of the spectrum has Jordan form, and this fact considerably reduces calculations.

In this connection, consider nonlinear transformation in the form of a power series, having introduced new variables U and V as:

$$\begin{cases} Y = U + \sum_{j=2}^{\infty} \Phi^{(j)}(U,V) \\ Z = V + SU + \sum_{j=2}^{\infty} \Psi^{(j)}(U,V) \end{cases}, \tag{A.2}$$

where $S_{[nxs]}$ is the matrix; $\Phi^{(j)}$ and $\Psi^{(j)}$ are vector-forms of the j order. The system (A.1) after the transformation (A.1) looks like as:

$$\begin{cases} \frac{dU}{dt} = AU + h(U,V) = AU + \sum_{j=2}^{\infty} H^{(j)}(U,V) \\ \frac{dV}{dt} = TV + p(U,V) = TV + \sum_{j=2}^{\infty} P^{(j)}(U,V) \end{cases}. \tag{A.3}$$

In nonlinear transformation (A.2) its linear part with block-triangle matrix $\begin{pmatrix} A & 0 \\ R & Q \end{pmatrix}$splits the linear part of the system (A.3), completely separating critical variables from the non critical. Following transformation (A.2), the linear part of the system (A.3) is characterized by a block diagonal matrix: $\begin{pmatrix} A & 0 \\ 0 & T \end{pmatrix}$.

The system (A.3) is called a quasi-normal form of the system (A.1) if the system (A.3) has the following properties:

1) $h(U,V)$ is not dependent on V and contains only resonance terms;

2) $p(U,0) = 0$

For the definition of the resonance term, denote vector $\Omega = [U,V]$, spectrum matrix J as N = [Λ, M], where N = $[\nu_1, \nu_2, ..., \nu_n, \nu_{n+1}, \nu_{n+2}, ..., \nu_{n+s}]$;
$\Lambda = [\lambda_1, \lambda_2, ..., \lambda_n]$ is the critical part of the spectrum and $M = [\mu_1, \mu_2, ..., \mu_s]$ is non critical part of the spectrum. The nonlinear part of the (A.3) is presented as a serious of vector-monomials. A monomial in the j-th equation appears as:$\Omega^L = U^P V^Q$, where multi-index $L = (l_1, l_2, .., l_{n+s})$, $l_j \geq 0$, $l_j \in Z$, i.e. $L = (P,Q)$ where $P = (p_1, p_2, ..., p_n)$, $p_i \geq 0$, $p_i \in Z$ and $Q = (q_1, q_2, ..., q_s)$, $q_j \geq 0$, $q_j \in Z$. The order of the monomial is $|L| = |P| + |Q|$ and $|L| = \sum_{j=1}^{n+s} l_j$

Monomial $\Omega^L$is called the resonance term in the j-th equation ($j = 1, 2, ..., n+s$) of the system (A.1) and (A.3), if $< N, L >= \nu_j$, ($j = 1, 2, ..., n+s$), where $< N, L >$ is scalar product. $< N, L >= 0$ defines resonance term for the case when at least one of them is zero, i.e. in the j-th equation corresponding eigenvalue will beν_j=0. (It is the case of zero eigenvalue, examined in this work.)

We highlight that in our case, when non critical part of the spectrum has eigenvalues with negative real part, monomial $\Omega^L = U^P V^Q$in the critical equation will be resonant only if $Q = 0$, otherwise normal part of the critical equation does not depend on V.

As a rule, all series are formal and, moreover, divergent in a critical case ([9]). For the research of critical case stability, when the problem is solved in a final approach, it is not necessary to use the transformation (A.2) in the series form. It is enough

to perform polynomial transformation only, as follows:

$$\begin{cases} Y = U + \sum_{j=2}^{k} \Phi^{(j)}(U,V) \\ Z = V + SU + \sum_{j=2}^{k} \Psi^{(j)}(U,V) \end{cases} . \tag{A.4}$$

This transformation normalizes system (A.1) until k-order terms are included, i.e. instead of system (A.3) we will obtain the following system:

$$\begin{cases} \frac{dU}{dt} = AU + \sum_{j=2}^{k} H^{(j)}(U) + O^{k+1}(U,V) \\ \frac{dV}{dt} = TV + \sum_{j=2}^{k} P^{(j)}(U,V) + O^{k+1}(U,V) \end{cases} , \tag{A.5}$$

where $H^{(j)}(U)$in the system (A.5) contains resonance terms only;$P^{(j)}(U,0) = 0$, $j = 2,3,..k$; and $O^{k+1}(U,V)$ are not re-normalized terms of a higher order than k. It is important to underline that (A.1) and (A.5) are equivalent systems. In particular, the fixed point (origin point) stability (or instability) is a feature of the system (A.1) and coincides with a similar property of system (A.5). However, how should k be chosen?

For stability research it is necessary to choose k by an optimum procedure since the number of calculations depends on the value of k. The number k actually characterizes the degree of the degeneracy in a critical case. To describe the property of the degeneracy, we examined the critical subsystem such as:

$$\frac{dU}{dt} = AU + \sum_{j=2}^{k} H^{(j)}(U) + O^{k+1}(U,0) . \tag{A.6}$$

Suppose the zero solution of the system (A.6) is asymptotically stable (or stable or not stable) without dependence on terms of a higher order $O^{k+1}(U,0)$.

Considering that the system (A.5) has a quasi-normal form to k-th order (inclusive), it is possible to confirm the following: if the fixed point U=0 of the system (A.6) is asymptotic stable (or stable or not stable) without dependence on terms of a higher k order i.e. $O^{k+1}(U,0)$, then for the system (A.5) we apply the reduction principle, as in [24], [25], [27] and [22]. From this principle it follows that the same property has the fixed point U=0, V=0 of the system (A.6).

From the above it follows that: the number k (Eq. (A.1)) needs to be chosen so that the trivial solution in system (A.6) will be stable or unstable, independent of the terms of the O^{k+1} order.

Appendix B. **Parameter estimation.** Parameter values were estimated in [10] and are summarized in the Table 2.

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Param	Physical Interpretation (units)	Dimensional estimate (Dimensionless estimate)	Reference
μ_1	BCG half life $[days^{-1}]$	0.1(1.00)	[3]
μ_2	Effector cells mortality rate $[days^{-1}]$	0.041(0.41)	[23]
p_1	The rate of BCG killed by APC $[cells^{-1}][days^{-1}]$	1.25×10^{-7}(1.25)	[31]
p_2	Infection rate of tumor cells by BCG $[cells^{-1}][days^{-1}]$	0.285×10^{-6}(0.285)	[10].
p_3	Rate of destruction of infected tumor cells by effector cells $[cells^{-1}][days^{-1}]$	1.1×10^{-7}(1.1)	[23]
p_4	Immune response activation rate $[cells^{-1}][days^{-1}]$	0.12×10^{-7}(0.12)	[10].
p_5	Rate of E deactivation after binding with infected tumor cells; $[cells^{-1}][days^{-1}]$	0.03×10^{-8} (0.0034)	[23]
α	Rate of E stimulation due to infected tumor cells $[days^{-1}]$	0.052(0.52)	[31]
r	Tumor growth rate $[days^{-1}]$	0.0033 (0.033) 0.012 (0.12) 0.0068 (0.068)	[29]; [30]; In all simulations.
b	bio-effective concentration of BCG [c.f.u./day]	$[3 \times 10^5 : 1 \times 10^6]$ ([3 : 10], Range used[0:10])	[12]

TABLE 2. List of all parameters. Note that dimensionless estimates were obtained from source values using the transformations stated in section 2.1.