This is a pre-copy editing, author-produced PDF of an article accepted for publication in *Mathematical Biosciences and Engineering* following peer review. The definitive publisher-authenticated version [1] is available at:
https://aimsciences.org/journals/displayArticlesnew.jsp?paperID=11308

References

[1] Sheller, B. D'Alessandro, D. Analysis of a Cancer Dormancy Model and Control of Immuno-Therapy. Mathematical Biosciences and Engineering, Vol. 12, no. 5. October 2015.

MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **12**, Number **5**, October **2015**

doi:10.3934/mbe.2015.12.xx

pp. **X–XX**

ANALYSIS OF A CANCER DORMANCY MODEL AND CONTROL OF IMMUNO-THERAPY

Ben Sheller and Domenico D'Alessandro

Department of Mathematics
Iowa State University
Ames, IA 50011, USA

(Communicated by Urszula Ledzewicz)

Abstract. The goal of this paper is to analyze a model of cancer-immune system interactions from [16], and to show how the introduction of control in this model can dramatically improve the hypothetical patient response and in effect prevent the cancer from growing. We examine all the equilibrium points of the model and classify them according to their stability properties. We identify an equilibrium point corresponding to a survivable amount of cancer cells which are exactly balanced by the immune response. This situation corresponds to *cancer dormancy*. By using Lyapunov stability theory we estimate the region of attraction of this equilibrium and propose two control laws which are able to stabilize the system effectively, improving the results of [16]. Ultimately, the analysis presented in this paper reveals that a slower, continuous introduction of antibodies over a short time scale, as opposed to mere inoculation, may lead to more efficient and safer treatments.

1. **Introduction.** Antibody therapy (immunotherapy) for cancer is a novel and promising approach to treat the disease. There are currently methods of propagating antibodies outside of the body, then returning them in order to boost the immune system [20]. The delivery of antibodies to the patient has to take into consideration two competing factors. On one hand, a large amount of antibodies tends to keep the concentration of proliferating cancer cells low and facilitate their transition into the quiescent state. On the other hand, the addition of too high a concentration of antibodies may induce metastasis of tumors by initially shrinking the tumor, resulting in potentially rapid angiogenesis, which may lead to metastasis of the remaining tumor [1], [5]. The addition of antibodies may also cause other adverse side effects, such as hypophysitis, enterocolitis, and hepatitis (see, e.g. the side effects of some of the subjects in [17]). Therefore, it is important to administer any additional antibodies very carefully. It is in fact advisable to resort, as much as possible, to the natural response of the body.

Given a dynamical model of cancer cell-antibody interaction, a stable and non-lethal situation for the patient corresponds to a perfect balancing of active tumor cells, antibodies and quiescent tumor cells, with active tumor cells remaining at a

2010 *Mathematics Subject Classification.* Primary: 92C50, 93C10; Secondary: 93D05.

Key words and phrases. Modeling of immuno-therapy, application of control theory to cancer therapy, Lyapunov stability.

D. D'Alessandro research was partially supported by ARO MURI under Grant W911NF-11-1-0268.

survivable level. This is often referred to as "cancer dormancy". Mathematically it corresponds to an *equilibrium point* of the model.[1] Given that this point is stable, the body is predicted to have a natural way to return to this equilibrium, after a small perturbation. In system theoretic terms, the perturbation does not move the state of the system away from a *region of attraction* of the equilibrium point, and the state will converge to the equilibrium naturally, as time progresses. The pathological situation occurs when the perturbation is so large that the state exits the region of attraction of the dormancy equilibrium point. In this case, if the cancer is left untreated, the population of cancerous cells will grow to the point of becoming lethal. In the spirit of this analysis, our approach is to use a small dose of antibodies in order to control the state of the system back into the region of attraction and then discontinue the administration of antibody therapy. Moreover, we allow for the possibility of, in principle, *continuous* administration of antibodies, perhaps through a controlled intravenous drip, as opposed to studies that analyze the evolution of the system given an *initial* concentration.

Remark 1. Such an approach requires on one hand a *mathematical model* of the progression of the disease and the effect of antibody therapy. On the other hand, it requires an *analysis of its equilibrium points*, their stability properties as well as physical significance, and the *determination of an estimate of the region of attraction*. Finally, it requires the design of an appropriate and physically realizable control strategy (i.e., antibody therapy) to drive the state of the system to the region of attraction.

Remark 2. While there are currently a number of different models describing cancer dormancy from a mathematical perspective (see [24] for an excellent review), we choose a particular model from [16] for its simplicity in order to demonstrate how continuous administration of antibodies may be more effectively applied to manipulate the system dynamics, as opposed to simple inoculation, as discussed in [16], and because it seems to be the most realistic model presented there. This particular choice of model additionally allows us to demonstrate a non-standard control technique, by recognizing the form of the differential equation, solving it, and using this solution to dictate our control scheme. This will, in effect, allow us to choose a profile for the way the active tumor cells behave, at least for a short time scale.

In this paper we demonstrate a system theoretic analysis of a mathematical model of cancer dormancy and antibody therapy presented in [16], and propose control laws (which have the meaning of therapeutic strategies) to modify the progression of the disease to a dormant state. We shall see from analysis and simulations that we are able to obtain a better performance than in [16]. In particular, even when compared with the most favorable situation presented in [16], the maximum density of cancer cells is lower with our protocols, which, on the other hand, also use a lower concentration of antibodies. Our mathematical tools come from Lyapunov stability theory (see, e.g., [7]) while we also take advantage of the specific form of the equations of the model which are a combination of bilinear and Riccati type.

The paper is organized as follows. In section 2, we recall the model presented in [16], to which we add a *control function* which represents our ability to increase the concentration of antibodies as compared to the natural body response. In

[1] or in some models to a limit cycle, see, e.g., [24]

section 3, we find all the equilibrium points of this model and determine their stability properties. We single out one equilibrium point which corresponds to the situation of a dormant balance between active tumor cells, quiescent tumor cells and antibodies. We prove that this equilibrium point is stable. In section 4, we find an estimate of the region of attraction for such an equilibrium point. In section 5, combining analysis and simulations, we propose control laws for this model and give a comparison with the performance of the therapeutic approach described in [16]. This shows a significant improvement in terms of the dynamics proposed here both in terms of a lower maximum density of proliferating cancer cells and in terms of a lesser use of antibodies. A discussion is presented in section 6.

2. **The model.** The cancer dormancy model we consider is given by

$$\dot{x} = \alpha_1 zy - \alpha_3 zx - \lambda x + my, \tag{1}$$

$$\dot{y} = ry(1 - y/K) - \alpha_1 zy - \alpha_2 zy - my = ry(1 - \frac{y}{K}) - \alpha zy - my \tag{2}$$

$$\dot{z} = \varepsilon z(\gamma(x + y) - b) + u(t) \tag{3}$$

This is the model presented in [16],[2] with an extra 'control' term $u = u(t)$ which represents our ability to influence the concentration of antibodies. The density of proliferating cancer cells is denoted by y and the density of quiescent cancer cells is denoted by x, while the concentration of antibodies is denoted by z. Moreover α_1 is the rate of initiation of cell cycle arrest; α_2 and α_3 are the rates of apoptosis induced by the antibodies; $\alpha = \alpha_1 + \alpha_2$. The parameter r is the replication rate of the proliferating cancer cells minus the antibody-independent natural death rate; λ is the natural death rate of the quiescent cells; m is the rate of the initiation of cell cycle arrest without antibodies; γ is the rate of production of antibodies induced by the presence of cancer cells; b is the decay rate of the antibodies; K is the carrying capacity of the proliferating cancer cells; ε is a time constant which describes how quickly antibodies are created. Since we can only increase the rate of production of antibodies we must assume $u(t) \geq 0$.

A mathematical analysis of the model starts with determining and classifying the equilibrium points. In [16] the authors do not discuss *all* of the equilibrium points, and give few mathematical details about their stability analysis. They observe that a high initial concentration of antibody results in clearance of the cancer. However, our dynamical analysis indicates that the situation is more subtle. While a very high initial concentration of antibodies may increase the death rate of active tumor cells to begin with, it will not kill them all off. As a result of the sudden initial decrease in active tumor cells, the presence of antibodies will drastically decrease, allowing the surviving active tumor cells to proliferate to a potentially lethal level before the necessary antibodies can be reproduced. This situation is depicted in the simulation in Figure 1.

2.1. **Parameters used.** In the following, we shall compare the results of our analysis with the results of [16] (cf. in particular Figure 7 of that paper). Therefore for convenience, we provide the model parameters used in [16].

$$\gamma = \alpha_2 = b = \alpha_3 = 1.0, \quad m = \lambda = .01, \quad r = \alpha_1 = 0.1, \quad \varepsilon = .001 \quad K = 10.0. \tag{4}$$

We shall refer to these values in our analysis and simulations. The authors of [16] stress that these values are for illustration purposes only and do not specifically refer

[2] The authors also present other models but this is the one deemed to be the most realistic.

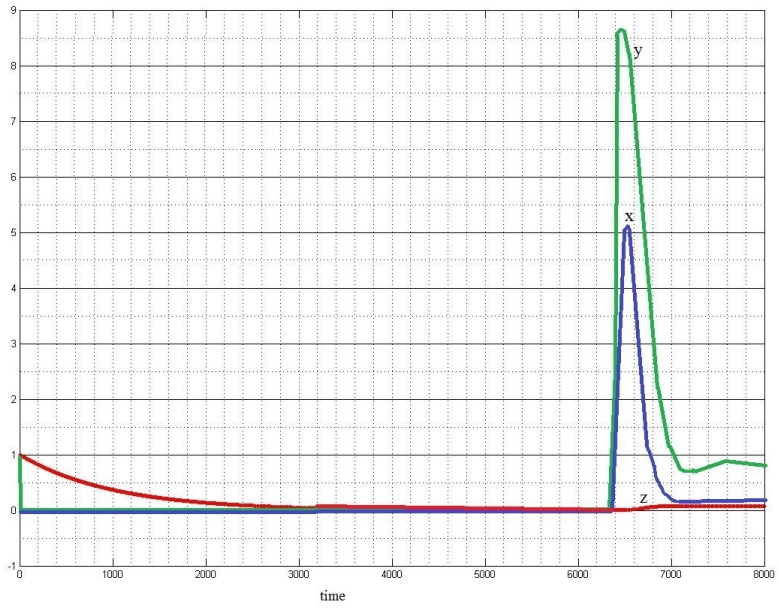

FIGURE 1. Using the parameter values given in (4), and initial values of $x_0 = 0$, $y_0 = 1$, and $z_0 = 1$, this simulation corresponds to a situation where too high a concentration of antibodies has been given in the inoculation, so that while the density of active cancer cells (y) initially decreases and stays low for a long period of time, it eventually increases drastically to the point of presumed lethality (i.e. $y \geq 1.8$). The horizontal axis corresponds to time, and the vertical axis to antibody concentration, density of active tumor cells, and density of quiescent tumor cells. $x(t)$ is blue, $y(t)$ is green, $z(t)$ is red.

to any clinical and/or experimental situation. Therefore they are not meant to be in any particular units. The authors of [16] do however describe in their appendix a methodology to estimate the parameters of the model in *experiments with mice*. Some work in this respect has been done by V.A. Kuznetsov and co-authors who estimated the cancer cell division rate for mice models (approximately $0.2\mathtt{days}^{-1}$) which gives an idea of the orders of magnitude involved.

The quantities x and y represent densities measured in number of cells per volume, under the assumption that spatial effects are unimportant, while z represents the concentration of antibodies in the immediate environment surrounding the tumor. As a consequence of equation (3) the parameters γ and b have the dimensions of $[volume] \times [time]^{-1}$. The dimensions of the other parameters in equations (1) and (2) are determined similarly. The parameter ϵ is an adimensional parameter which is assumed to be small compared to the other parameters, meaning that the dynamics of the antibodies (without the control) are *slow* as compared to the rate of proliferation of cancer cells and the rate of transition of the cancer cells from proliferating to quiescent. Choosing the parameter $b = 1$ in (4) means that we chose

a unit of time so that the decay rate of antibodies is $\epsilon b = 0.001$, while $\frac{b}{\gamma}$ has the meaning of the concentration of cancer cells $x + y$ at the (dormancy) equilibrium (this is obtained by setting $\dot{z} = 0$ in equation (3)). Setting $\gamma = 1$ therefore means that we have set the units of volume so that such a density is equal to 1. Having set the units and quantities this way, the interpretation of the other values, λ, m, r, K, α_1, α_2, α_3, follows. For example, $m = 0.01$ means that the rate of initiation of cell arrest for proliferating cancer cells is 10 times faster than the rate of decay of antibodies, while $K = 10$ means that the maximum (plateau) value of proliferating cancer cells is ten times the density of cancer cells at dormancy.[3]

As for the implementation of our results (as well as the results of [16]) into clinical practice this requires the estimation of parameters in vivo for humans. As observed in [24] this is one of the most important issues facing mathematical modeling of cancer-immune systems in the future. From the mathematical point of view, we believe that system theoretic techniques of parameter identification and adaptive control (see, e.g., [19]) can be very helpful. However, the problem is not only mathematical since technological and medical tools have to be available in order to measure, in vivo, the quantities under consideration, x, y, z, or some other quantity directly related to them. We believe that the theoretical predictions for the model with parameters (4) are representative of models for different values of the parameters. For instance, we will see in the next section that many properties concerning the existence and stability of equilibrium points are valid for a large set of values of the parameters.

3. **Equilibrium points.** We denote by x_{eq}, y_{eq}, and z_{eq} the x, y and z coordinates, respectively, of the equilibrium points. There are a total of five possible equilibrium points. The first equilibrium point we will discuss occurs at $x_{eq} = y_{eq} = z_{eq} = 0$. This corresponds to a total lack of both dormant and growing cancer cells, as well as of antibodies. This would be an ideal state to achieve; however, it corresponds to an unstable equilibrium point as the eigenvalue $r - m$ of the associated Jacobian is always positive.[4]

A second equilibrium point occurs when $x_{eq}, y_{eq} \neq 0$; $z_{eq} = 0$. It is given by:

$$x_{eq} = \frac{mK(1 - \frac{m}{r})}{\lambda}, \qquad y_{eq} = K(1 - \frac{m}{r}), \qquad z_{eq} = 0. \tag{5}$$

It corresponds to cancer proliferation in the total absence of an immune response; perhaps the immune system of the patient has been previously compromised. An analysis of the eigenvalues of the Jacobian at this point shows the condition for stability is

$$K\left(1 + m\frac{r - \lambda - m}{r\lambda}\right) < \frac{b}{\gamma}. \tag{6}$$

Under the assumption of an approximately equal rate of antibody production and antibody decay, $\frac{b}{\gamma} \approx 1$. If in addition, we assume that the rate of replication of active cancer cells is high compared to the death rate of quiescent cells in the absence of antibodies and the rate of initiation of cell cycle arrest, with a carrying capacity $K > 1$, we have that condition (6) is not satisfied and the point is unstable. We

[3] Notice that it might be never possible to measure such a value directly, even in mice experiments, as the mouse might be killed well before such a value is reached.

[4] The condition $r - m > 0$ physically corresponds to 'tumor growth in the absence of an immune response' (cf. pg. 315 of [16]) This situation is therefore not realistic since any perturbation, no matter how small, will lead to an uncontrolled growth of active cancer cells.

shall assume this to be the case. In fact, for the values of the parameters of [16] provided above in (4), this equilibrium point is unstable.

A third equilibrium point is given by:

$$x_{eq} = 0, \qquad y_{eq} = \frac{b}{\gamma} = K(1 - \frac{(\alpha + \alpha_1)m}{r\alpha_1}), \qquad z_{eq} = \frac{m}{\alpha_1}. \tag{7}$$

This equilibrium point exists only in the case when $\frac{b}{\gamma} = K(1 - \frac{(\alpha+\alpha_1)m}{r\alpha_1})$, so for generic values of parameters it does not exist.[5] It corresponds to a complete lack of quiescent cancer cells, with active tumor cells nonetheless proliferating and antibodies seeking to remove them. If one assumes the existence of some quiescent cancer cells as we do,[6], this equilibrium point is only of mathematical interest.[7]

The fourth and fifth possible equilibrium points occur when x_{eq}, y_{eq} and z_{eq} are all nonzero. This may correspond to a situation in which cancer cells are still proliferating and becoming quiescent, but the immune system is capable of keeping the rate of cancer cell proliferation low enough through antibody production, so that the patient survives. If we let $\beta = \alpha_1 + \alpha_3$, $\tau = \lambda + m$, $B = -K - \frac{K\alpha\tau}{r\beta} - \frac{\alpha_3 b}{\beta\gamma} + \frac{Km}{r}$, then the following are equilibrium points:

$$x_{eq} = \frac{b}{\gamma} - y_{eq} \tag{8}$$

$$y_{eq} = \frac{-B \pm \sqrt{B^2 - 4(\frac{K\alpha_3 b}{\beta\gamma} + \frac{K\alpha\lambda b}{r\beta\gamma} - \frac{\alpha_3 bmK}{r\gamma\beta})}}{2} \tag{9}$$

$$z_{eq} = \frac{r(1 - \frac{y_{eq}}{K}) - m}{\alpha} \tag{10}$$

In order for at least one of these two possible equilibrium points to exist, i.e., for the expression under the square root to be nonnegative and x_{eq}, y_{eq} and z_{eq} to be positive, we must have:

1. $m\alpha_3 \neq \lambda\alpha_1$
   Note that in a "real-world" scenario, this condition is likely to hold, as reasonable parameter values imply that $-B > 0$, since $r - m > 0$, so that $\frac{Km}{r} < K$.
2. $\alpha_3 r < K\beta(r - m)$
   The carrying capacity of the cancer cells is generally assumed to be large enough that this inequality holds. In particular, this is the case for the parameter values in (4).
3. $B^2 \geq 4(\frac{K\alpha_3 b}{\beta\gamma} + \frac{K\alpha\lambda b}{r\beta\gamma} - \frac{\alpha_3 bmK}{r\gamma\beta})$

Two equilibrium points with all coordinates non-zero exist if and only if the above three conditions hold and also:

$$\alpha\lambda < r\alpha_3.$$

[5] In fact, for the parameter values given in (4), the equilibrium point does not exist.

[6] One reason to justify the presence of quiescent cells is the existence of spatial and physical constraints of a tumor so that not all cancer cells are allowed to proliferate.

[7] In a situation in which this equilibrium point exists, its stability may be determined by using the Routh-Hurwitz criterion for asymptotic stability on the coefficients of the characteristic polynomial of the Jacobian. If we let: $d_2 = \frac{\alpha_3 m}{\alpha_1} + \lambda + r - \frac{(\alpha+\alpha_1)m}{\alpha_1}$, $d_1 = (\frac{\alpha_3 m}{\alpha_1} + \lambda)(r - \frac{(\alpha+\alpha_1)m}{\alpha_1}) - \varepsilon mb + \frac{\alpha\varepsilon mb}{\alpha_1}$, $d_0 = \frac{\alpha\varepsilon mb(\frac{\alpha_3 m}{\alpha_1} + \lambda + 2m)}{\alpha_1} - \varepsilon mb(r - \frac{(\alpha+\alpha_1)m}{\alpha_1})$, the characteristic polynomial of the Jacobian is then given by $c_J(t) = t^3 + d_2 t^2 + d_1 t + d_0$. This equilibrium point is then stable provided that $d_i \geq 0$ for $i = 0, 1, 2$ and $d_2 d_1 > d_0$.

We can determine the stability of these points by examining the characteristic equation of the Jacobian using the Routh-Hurwitz conditions for stability. Let:

$$b_2 = (\alpha_3 + \alpha)z_{eq} + \frac{2ry_{eq}}{K} + \tau - r \tag{11}$$

$$b_1 = (\alpha_3 z_{eq} + \lambda)(\frac{2ry_{eq}}{K} + \alpha z_{eq} - r + m) + \varepsilon\gamma z_{eq}(\alpha_3 x_{eq} - (\alpha - \alpha_1)y_{eq}) \tag{12}$$

$$b_0 = \alpha\varepsilon\gamma y_{eq} z_{eq}(\beta z_{eq} + \tau) + \varepsilon\gamma z_{eq}(\alpha_3 x_{eq} - \alpha_1 y_{eq})(\frac{2ry_{eq}}{K} + \alpha z_{eq} - r + m) \tag{13}$$

The characteristic equation of the Jacobian is then given by $c_J(t) = t^3 + b_2 t^2 + b_1 t + b_0$. Whichever of the two equilibrium points we are analyzing (corresponding to a choice of '+' or '−' in (9)) is stable provided that $b_i \geq 0$ for $i = 0, 1, 2$, and $b_2 b_1 > b_0$. For the parameter values (4), the equilibrium point corresponding to a '−' in (9) exists and is asymptotically stable. It is assumed that this equilibrium point corresponds to a non-lethal situation in which the immune system of a patient balances the cancer. Therefore, this equilibrium point corresponds to non-lethal *cancer dormancy*. This, then, will be the situation to which we attempt to drive the state of the system using a control function $u = u(t)$. For the parameters (4), the equilibrium point corresponding to a '+' in (9) also exists; however it corresponds to a high cancer load with $y_{eq} \approx 11.0804$, and is asymptotically unstable.

There are no more possible equilibrium points. If one attempts to find an equilibrium point with $y_{eq} = 0$ and $x_{eq}, z_{eq} \neq 0$, then a contradiction is obtained; namely, it is found that $z_{eq} = \frac{-\lambda}{\alpha_3} < 0$, which is impossible as the variables x, y, and z necessarily achieve only non-negative values. For every case with any two of x_{eq}, y_{eq}, or z_{eq} taken to be zero, it is easily found that it is always necessary that the third one also be zero, a case which has already been discussed.

3.1. **Change of coordinates.** Given an equilibrium point (x_{eq}, y_{eq}, z_{eq}), we perform a shift in the coordinates (x, y, z) to transfer the equilibrium point to the origin. By defining $(\tilde{x}, \tilde{y}, \tilde{z}) := (x - x_{eq}, y - y_{eq}, z - z_{eq})$, and using the fact that each of the right hand sides of (1), (2), (3) is zero when we replace (x, y, z) with (x_{eq}, y_{eq}, z_{eq}), we obtain the differential equations for $\tilde{x}$, $\tilde{y}$ and $\tilde{z}$ (where we define $\gamma' := \epsilon\gamma$, $b' := \epsilon b$):

$$\frac{d\tilde{x}}{dt} = -(\lambda + \alpha_3 z_{eq})\tilde{x} + (m + \alpha_1 z_{eq})\tilde{y} + (\alpha_1 y_{eq} - \alpha_3 x_{eq})\tilde{z} + \alpha_1 \tilde{z}\tilde{y}. \tag{14}$$

$$\frac{d\tilde{y}}{dt} = (-m + r - \frac{2r}{K}y_{eq} - \alpha z_{eq})\tilde{y} - \alpha y_{eq}\tilde{z} - \alpha\tilde{z}\tilde{y} - \frac{r}{K}\tilde{y}^2, \tag{15}$$

$$\frac{d\tilde{z}}{dt} = \gamma' z_{eq}(\tilde{x} + \tilde{y}) + \gamma'\tilde{z}(\tilde{x} + \tilde{y}) + (-b' + \gamma'(x_{eq} + y_{eq}))\tilde{z} + u(t). \tag{16}$$

Equations (14)-(16) simplify in an obvious way if $z_{eq} = 0$. Moreover if $z_{eq} \neq 0$, from (3) we obtain $\gamma'(x_{eq} + y_{eq}) = b'$, which gives for (16):

$$\frac{d\tilde{z}}{dt} = \gamma' z_{eq}(\tilde{x} + \tilde{y}) + \gamma'\tilde{z}(\tilde{x} + \tilde{y}) + u(t). \tag{17}$$

For the sake of comparison with the results in [16], we provide the system obtained by using the parameters given above in (4) and the equilibrium point discussed above corresponding to a '−' in (9); This equilibrium point is $(x_{eq}, y_{eq}, z_{eq}) \approx (.1713, .8287, .0743)$. The system (14), (15), (17) becomes:

$$\frac{d\tilde{x}}{dt} = -0.0843\tilde{x} + 0.01742\tilde{y} - 0.0885\tilde{z} + .1\tilde{y}\tilde{z} \tag{18}$$

$$\frac{d\tilde{y}}{dt} = -0.0083\tilde{y} - 0.9115\tilde{z} - 1.1\tilde{y}\tilde{z} - .01\tilde{y}^2 \tag{19}$$

$$\frac{d\tilde{z}}{dt} = .00007428(\tilde{x} + \tilde{y}) + .001\tilde{z}(\tilde{x} + \tilde{y}) \tag{20}$$

As this is the most interesting case, describing a dynamic situation where a nonzero antibody population exactly balances the growing of the tumor cells at a presumably survivable level, we shall concentrate on the problem of stabilization of this equilibrium point in the following.

4. **Estimate of the region of attraction.** System (14), (15), (17) has the structure

$$\frac{d\vec{w}}{dt} = F_1(\vec{w}) + F_2(\vec{w}), \tag{21}$$

where $\vec{w} := (\tilde{x}, \tilde{y}, \tilde{z})^T$ and F_1 and F_2 are homogeneous polynomials of degrees 1 and 2, respectively. In particular, $F_1(\vec{w}) = A\vec{w}$. If all the eigenvalues of A have negative real part, then the origin is asymptotically stable, i.e., there exists a connected, simply connected [6], open set $\Omega \subseteq \mathbf{R}^3$ containing the origin in its interior such that the solution of (21) converges to the origin for every initial condition in Ω. This region is commonly referred to as the *Region of Attraction (ROA)* [6],[18].

The equilibrium point we are interested in is the stable one representing the (survivable) situation where the antibodies exactly balance the proliferating cancer cells and keep the tumor under control. To design the control strategy, we obtain a large enough estimate of the ROA and then use minimal control, i.e., a (continuous) modification of rate of growth of antibodies to drive the state of the system to the ROA. From that point on, the state will converge towards the desired equilibrium point.

Because of the polynomial nature of the equations in (21), it is natural to use the classical method of Zubov [25] [26] (cf. also [23] for developments and improvements). The central object of the method is a *Lyapunov function* $V(\vec{w})$ solution of the Zubov equation, which, for system (21), takes the form

$$\frac{d}{dt}V(\vec{w}) = \nabla V(\vec{w})(F_1(\vec{w}) + F_2(\vec{w})) = -\phi(\vec{w})(1 - V(\vec{w})), \tag{22}$$

where $\phi(\vec{w})$ is an arbitrary positive definite function which we will take to be quadratic: $\phi(\vec{w}) = \vec{w}^T Q \vec{w}$, for Q a positive definite matrix. In Zubov's method the function V is sought as a series $V(\vec{w}) = \sum_{j=2}^{\infty} V_j(\vec{w})$, where $V_j(\vec{w})$ is a homogeneous polynomial of degree j. The $\binom{j+2}{2}$ coefficients characterizing the function $V_j(\vec{w})$ are in general computed solving the equation (cf. (22))

$$\sum_{j=2}^{\infty} \nabla V_j F_1 + \sum_{j=2}^{\infty} \nabla V_j F_2 = -\phi + \sum_{j=2}^{\infty} \phi V_j. \tag{23}$$

This can be solved recursively by equating polynomials with the same degree on the left and the right hand side. In particular, for polynomials of degree 2, we obtain[8]

$$\nabla V_2 F_1 = -\phi. \tag{24}$$

[8]This is the equation used in the proof of asymptotic stability and leads to a Lyapunov matrix equation (see, e.g., [8]) $A^T P + PA = -Q$.

In practice the method uses the partial sum of order m

$$\tilde{V}_m(\vec{w}) = \sum_{j=2}^{m} V_j(\vec{w}), \tag{25}$$

as an approximation of the desired Lyapunov function. Consider the boundary $\partial\Omega_m$ of the set Ω_m where Ω_m is the largest connected neighborhood of the origin where

$$\nabla\tilde{V}_m(F_1 + F_2)(\vec{w}) \leq 0. \tag{26}$$

Let C_m^* be the minimum of $\tilde{V}_m$ on $\partial\Omega$. Then the surface defined by

$$\tilde{V}_m(\vec{w}) = C^*, \tag{27}$$

is the boundary of a region $\Gamma_m := \{\vec{w}|\tilde{V}_m(\vec{w}) \leq 0\}$ which is included in the ROA. Therefore, the region Γ_m is a (conservative) estimate of the ROA. Zubov has shown that as $m \to \infty$, Γ_m converges (although not uniformly)[9] to the ROA. Therefore a good estimate of the ROA can be obtained by calculating $\tilde{V}_m$ for m sufficiently large.

We have used Zubov's method, as described above, to obtain an estimate of the region of attraction for the system described by (18), (19), (20). We found that in our case we do not have a significant improvement by considering polynomials of order low but bigger than two.[10] We therefore find it convenient to consider as a Lyapunov function a polynomial of degree 2. Using $\phi(\tilde{x}, \tilde{y}, \tilde{z}) = \tilde{x} + 10^4\tilde{y} + 10^8\tilde{z}$ as the positive definite function in (22), we compute the Lyapunov function:

$$V_2(\vec{w}) := \tilde{V}_2(\vec{w}) := V(\tilde{x}, \tilde{y}, \tilde{z}) = \vec{w}^T P\vec{w}, \tag{28}$$

which gives[11] $P \approx$

$$\begin{bmatrix} 12922.583 & 57069.649 & 14655447.234 \\ 57069.649 & 1202407.259 & 53431010.706 \\ 14655447.234 & 53431010.706 & 17343982544.476 \end{bmatrix}.$$

An estimate of the region of attraction is obtained by finding a value k such that $V = k$ is completely contained inside of the region $\dot{V} \leq 0$. Then everything inside of the surface $V = k$ is in the interior of the ROA. We find that given our equation (28), a maximal such value is $k = 10^5$. This region estimating the ROA has the shape of a tilted ellipsoid.

5. **Design and performance of the control law.** In [16], the model with the parameters (4) is assumed to predict lethality when the maximum value of y (representing the density of proliferating cancer cells) is greater than 1.8. On the other hand, in a situation in which the system evolves in such a way that the patient survives, the state of the model converges towards the 'dormant' equilibrium point discussed above, without hitting this maximum value. One situation where lethality is predicted is simulated in [16] and replicated here in Figure 2, where the initial conditions of the model are:

$$x_0 = 0, \qquad y_0 = 1, \qquad z_0 = .001 \tag{29}$$

We would like to design a control law $u = u(t) \geq 0$, i.e., to increase the rate of production of antibodies (cf. equation (3)), with these initial conditions so that

[9] Convergence here means that for every point $P \in ROA$ there exists M such that $P \in \Gamma_m$, for every $m > M$. However this convergence is in general not uniform, i.e., M might depend on P.

[10] For polynomials of high order the number of coefficients to calculate grows too large.

[11] Calculations were performed in MATLAB using the function 'Lyap'.

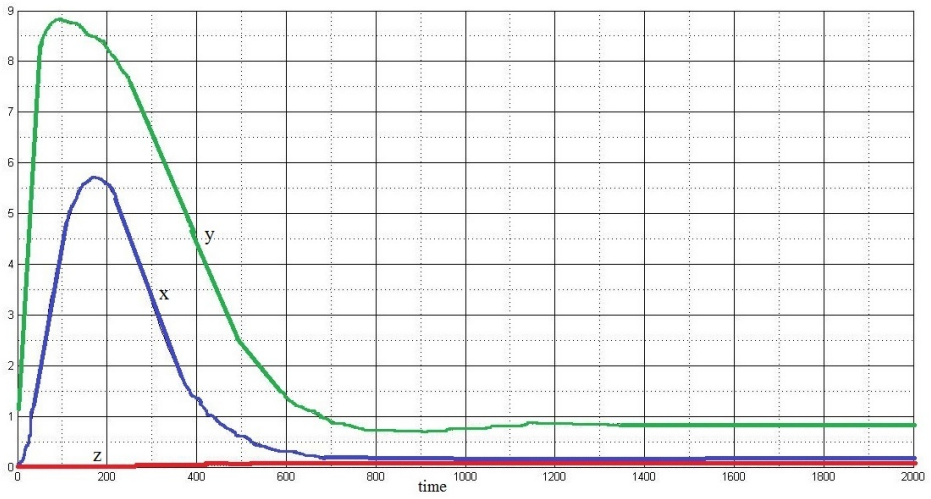

FIGURE 2. Initial conditions $x_0 = 0.0$, $y_0 = 1.0$, $z_0 = .001$ and no controls as in [16]. This situation is presumed to lead to patient lethality.This is s replication of the model simulations shown in Figure 7 of [16].The horizontal axis corresponds to time, and the vertical axis to antibody concentration, density of active tumor cells, and density of quiescent cancer cells.

lethality does not occur, and, at the same time, to drive the state into the region of attraction of the dormancy equilibrium point.

In order to stabilize the state of the system to a given equilibrium point, the most common technique is *Lyapunov control design* (see, e.g., [9]) where one uses the Lyapunov function V itself (which we used to find the estimate of the ROA) and design the control law so that the directional derivative along the vector field defining the dynamics is negative (cf. equation (26)). This way, the Lyapunov function is decreasing along the dynamics and the state will eventually enter the region characterized by $V \leq k$, which is included in the ROA. This approach for us presents a few problems. The control function is typically given in *feedback form*, i.e., u is a function of x, y, and z, which are not available for observation in practical experiments or clinical applications. One way around this is to integrate numerically the resulting equations and then use the result for x, y and z in u. It is however difficult with this method to control the size of u, as we do not want to introduce too many antibodies, the size of y that, as we have said, cannot go over a certain threshold, and at the same time make sure that the resulting u satisfies the condition $u \geq 0$. We therefore employ a different approach which relies more on analytic calculations and the structure of the equations (14), (15), (17) or equivalently (1), (2), (3).

We notice that, once the profile of z is decided, equation (2) is a (time varying) Riccati equation, whose solution can be written explicitly as

$$y(t) = \frac{y_0 e^{\int_0^t L(s)ds}}{1 + \frac{ry_0}{K}\int_0^t e^{\int_0^s L(\zeta)d\zeta}ds}, \tag{30}$$

where $L(t) := r - m - \alpha z(t)$ and y_0 is the initial condition for y. We can therefore decide a profile for z and from (30) obtain the corresponding profile of y or decide a profile for y and from (2) obtain the corresponding profile for z. Once z and y are determined, we can substitute them into (1) which becomes a linear equation in x and therefore can be explicitly integrated. Then we may substitute in x, y, and z into (3) and obtain the control law u. With a sequence of trials and errors on the initial choice we can make sure that all the variables will evolve in such a way that the whole state eventually enters the region of attraction and the condition $u(t) \geq 0$, $\forall t$, is satisfied. The condition on the maximum value of y will be automatically satisfied if our profile for y is chosen appropriately. One key feature of the model of [16] that we explicitly use in this procedure is the fact that the x variable does not enter the equation for $\dot{y}$, which means that the quiescent cells are assumed not to go back to proliferating again.

Not all the functional forms of y may be imposed in (30), not only because $y(0)$ is fixed to y_0, and y is bounded by the carrying capacity, but also because the derivative of y at time $t = 0$ has to be related to $z(0) = z_0$ by formula (2).

We have chosen a family of functions for $y = y(t)$

$$y(t) := (1 - e^{-at})y_{eq} + (1 + ct)e^{-at}y_0, \tag{31}$$

with parameters a, and c. These functions have the property that $y(0) = y_0$, and $\lim_{t\to\infty} y(t) = y_{eq}$.

Using the initial conditions, we may relate the above parameters a and c as:

$$a = \frac{(\frac{1}{\alpha}(r - m - \frac{r}{K}) - z_0 - c)y_0}{y_{eq} - y_0} \tag{32}$$

For the parameters (4) and the initial conditions (29), we have chosen $c = .185$ and $a \approx .6611$. In order for a to be positive in the above equation, it is necessary that $c > .0717$, and simulations indicate a good value of c is around the value we have chosen. For values of c higher than about .2, too many antibodies are introduced, and for values of c less than about .17, too few are introduced, and y can grow large. Under the choice $c = .185$, we also obtain a control function $u(t)$ which when applied from $t = 0$ to $t = 1$ as in Figure 3 and then removed yields the profile given in Figure 4.

Simulations show that this control function $u(t)$ is non-negative over the interval on which it is applied. Figure 5 shows what happens when a patient is inoculated with an additional .099 concentration of antibodies, as in [16]. Under the inoculation, the system is within the ROA by time $t = 1700$, and have a maximum value of proliferating cancer cells at approximately 1.5. A comparison between our controlled evolution (in Figure 4) with the result of [16] (in Figure 5) shows a lower maximum y value in our case. Furthermore, our control law yields an additional antibody concentration of $\int_0^1 u(t)dt \approx .03763$, significantly less than the .099 inoculation used in [16]. We are also in the ROA by time $t = 600$ since $V(x, y, z) \leq 10^5$.

An alternative approach is to choose the function $u(t)$ directly, then use simulations to ensure that the state of the model evolves to be within our estimation of the ROA and the maximum of $y(t)$ is sufficiently low. This method is convenient in that it may be possible to choose a very simple form for $u(t)$, and, after a good estimate of the region of attraction is obtained, simulations are relatively simple to perform and compare.

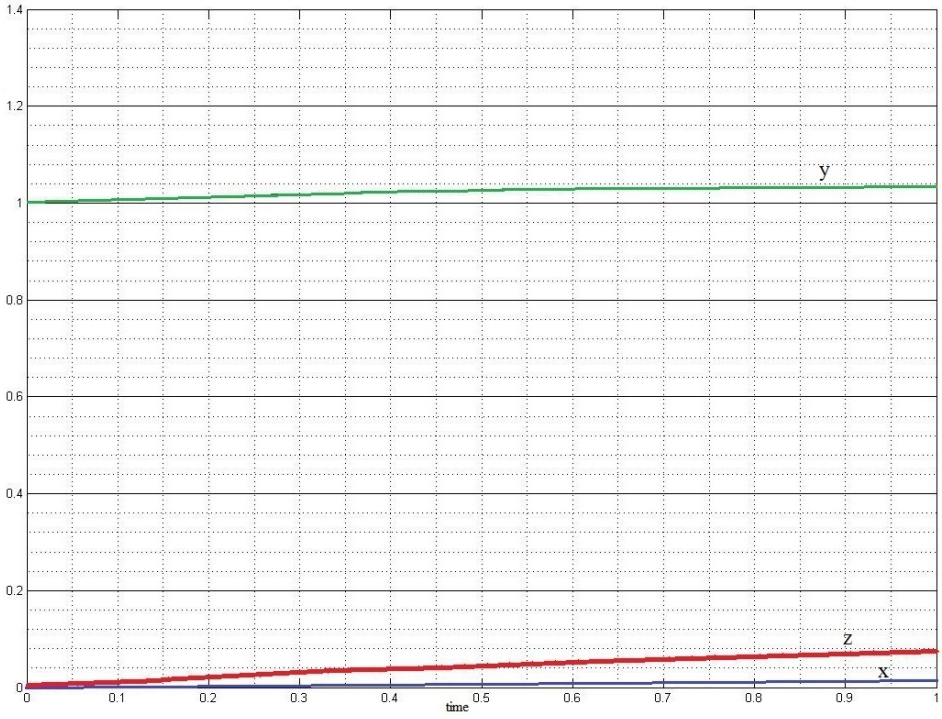

FIGURE 3. Using the same initial conditions as in 2, we apply a control $u(t)$ obtained by solving the equation $\dot{y}$ as a Riccati equation and choosing a profile for y as in (31) . The control is applied for $0 \leq t \leq 1$. The total concentration of additional antibody applied is $\approx .03763$. The horizontal axis corresponds to time, and the vertical axis to antibody concentration, density of active tumor cells, and density of quiescent cancer cells.

We have chosen $u(t) = t/6$ for $t \in [0, 1]$ and $u(t) \equiv 0$ otherwise. Then, we let the system evolve until $t = 1400$. Simulations show that the state of the system is inside the region of attraction at time $t = 1400$. Furthermore, prior to that moment, we never obtain a lethal value of y. This is again a better result than the vaccination presented in [16], as using the control function we have constructed, we not only have a smaller maximum value of $y(t)$, but we also increase the antibody concentration by only $\int_0^1 \frac{t}{6} dt \approx .0833$. See Figures 6 and 7.

6. **Discussion.** There are many mathematical models of cancer-immune system dynamics and reviews are given for example in [4], [24]. A recent meeting focusing on this topic was [27]. Not all the models use differential equations (see, e.g., [22]). However models using differential equations are quite popular due to their flexibility, and their clear interpretation. Moreover these models are natural candidates for the application of control theoretic methods. For example, the models in [21], modified with a Gompertzian law as in [14], [15], were used in [12], [13], to formulate cancer immunotherapy as an *optimal control problem* where the control variables were modeling a combined action of chemotherapy and immuno-therapy. Papers [12],

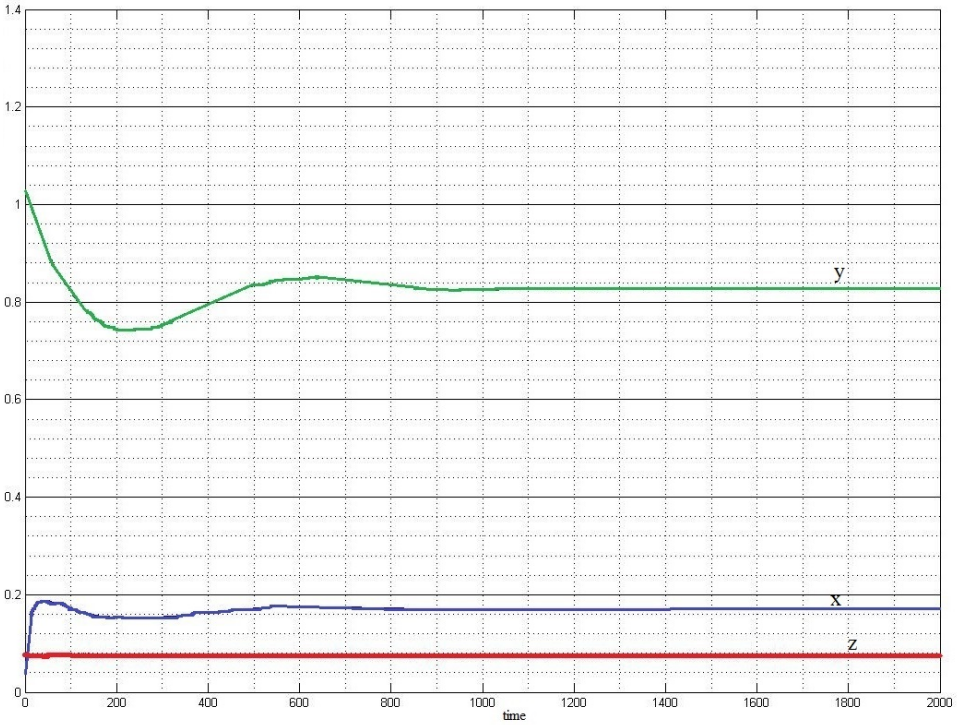

FIGURE 4. After removing the control function described in 3, the system evolves as shown. We are inside of the ROA of the 'dormant' all non-zero fixed point by time $t = 600$.The horizontal axis corresponds to time, and the vertical axis to antibody concentration, density of active tumor cells, and density of quiescent cancer cells.

[13] are in the same spirit as this paper as far as the use of control theoretic idea is concerned. General models of immune systems were also formulated in [2] and in the work of Kuznetsov and co-authors [10], [11], who also provided parameter estimates based on experiments with mice. All these models try to capture some of the main features observed clinically and in experiments characterizing cancer-immune system interaction. Although the presence of *dormancy* is a generally accepted fact, other aspects of tumor-antibody interaction need to be better understood and mathematical models definitely have an important role in that. In particular, many phenomena can be explained and controlled via a combination of experiments and mathematical models. These include: different types of interactions with *different immune cells* (e.g., innate or adaptive), the existence of an *immune barrier*, below which the immune response is not activated, the mechanisms involved in *escape* [3], which is the capability of tumor cells of restart proliferating after a period of dormancy, the possibility of quiescent tumor cells to become proliferating (and therefore a distinction between *quiescent* and *senescent* cells), and the delay between tumor development and immune response. Models also have to take into account spatial effects, especially for tumors, which are highly localized, as well as the effect of the micro-environment on tumor cell development.

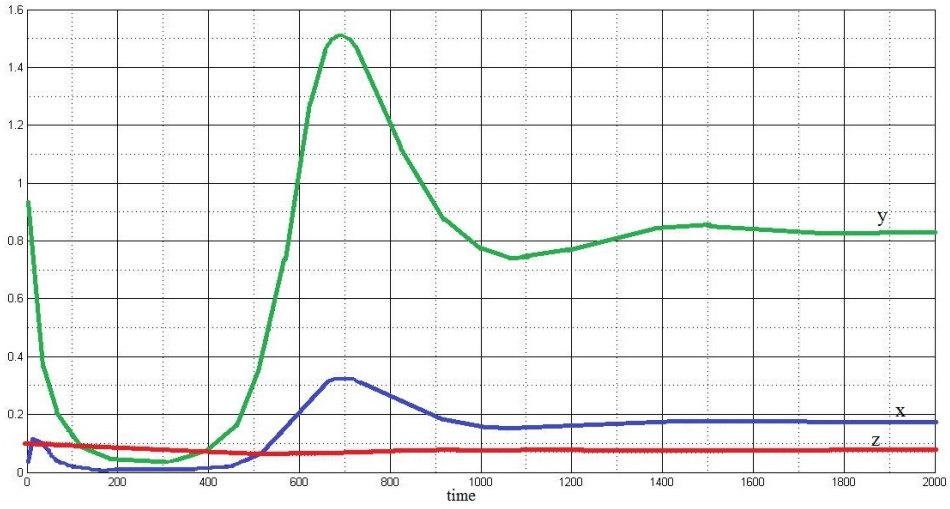

FIGURE 5. Initial conditions $x_0 = 0$, $y_0 = 1$, $z_0 = 0.1$ and no control. This situation amounts to a vaccination, as discussed in [16]. The total concentration of additional antibodies applied is .099. We are inside of the ROA of the 'dormant' all non-zero fixed point by time $t = 1700$. This also is s replication of the model simulations shown in Figure 7 of [16].The horizontal axis corresponds to time, and the vertical axis to antibody concentration, density of active tumor cells, and density of quiescent cancer cells.

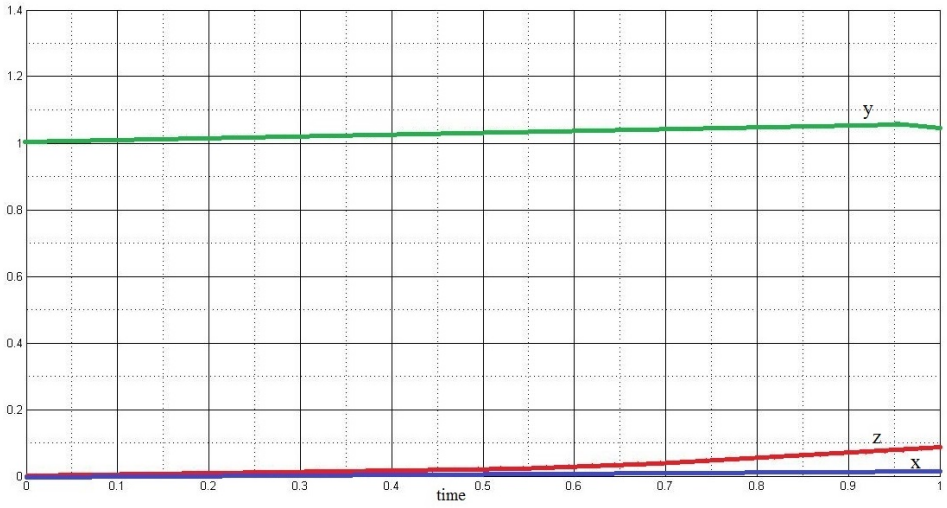

FIGURE 6. Using the same initial conditions as in 2, we apply a control $u(t) = t/6$ for $0 \leq t \leq 1$. The total concentration of additional antibody applied is $\approx .0833$. The horizontal axis corresponds to time, and the vertical axis to concentration of antibodies, density of active tumor cells, and density of quiescent cancer cells.

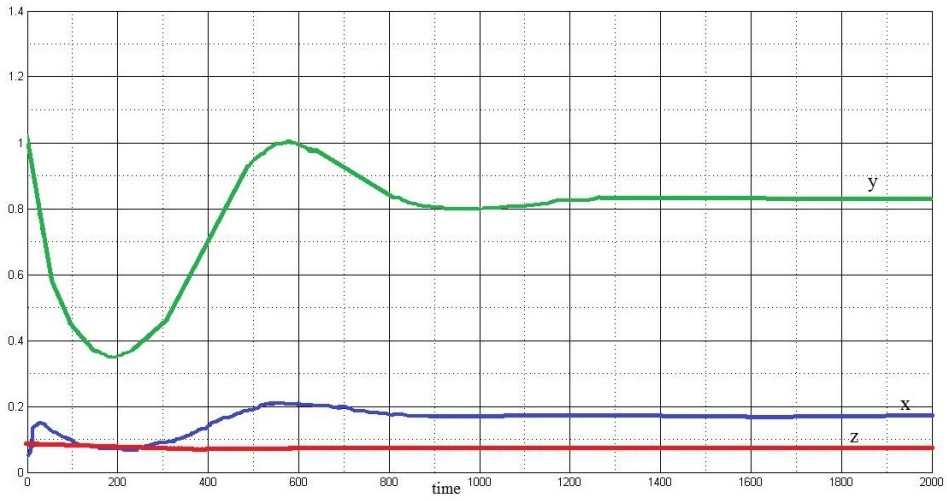

FIGURE 7. Model simulations using the control $u(t) = t/6$. After time $t = 1$, we set $u(t) = 0$. We are within the ROA of the 'dormant' all non-zero fixed point by time $t = 1400$. The horizontal axis corresponds to time, and the vertical axis to concentration of antibodies, density of active tumor cells, and density of quiescent cancer cells.

The model [16] we have analyzed in this paper was originally motivated and introduced to study the effect of vaccination in cancer immunotherapy. This model contains several improvements as compared to the simplest Lotka-Volterra type of models [24], e.g., the introduction of a logistic law for the growth of the proliferating cancer cell, and the explicit introduction of quiescent cells as a compartment in the system of equations. It is difficult to determine, at this stage, whether this model is more realistic and whether it will be more useful in the future, as compared to other models in the literature such as the ones reviewed in [4], [24]. However, the fact that the authors explicitly study the effect of vaccination, which translates into the initial condition of the antibody density, in the dynamical evolution of the tumor, motivated the question of whether a continuous control action could improve over the results of simple vaccination and we have seen, in this paper, that this is indeed the case.

We have demonstrated that using control-theoretic methods, and by closely examining the equations describing the dynamical system, we can more effectively and efficiently rescue a lethal situation. The results indicate that continuously administering antibodies over a short time may be preferable to simply inoculating a patient with a new initial dose of antibodies. Not only are less antibodies used in the control functions we have constructed, but the system evolves to be in the ROA more quickly than under an inoculation, and with a lower cancer load as well. These results may thus be more clinically feasible.

The challenge in the future will be not only to further improve the control laws presented here but also, and more importantly, to determine the real parameters and improve the model to translate mathematical prediction into clinical practice. We believe that more advanced techniques of control theory such as *adaptive control*

and parameter identification [19], as well as more nuanced techniques in optimal and Lyapunov control will play an important role in this.

REFERENCES

[1] A. M. Baker, et. al. Lysyl Oxidase Plays a Critical Role in Endothelial Cell Stimulation to Drive Tumor Angiogenesis *Cancer Research*, **73** (2013), 583–594.

[2] A. D'Onofrio, A general framework for modeling tumor-immune system competition and immuno-therapy, mathematical analysis and biomedical inferences, *Physica D*, **208** (2005), 220–235.

[3] G. P. Dunn, L. J. Old and R. D. Schreiber The three E's of cancer immuno-editing, *Annu. Rev. Immunol.*, **22** (2004), 329–360.

[4] R. Eftimie, J. L. Bramson and D. J. Earn, Interactions between the immune systems and cancer: A brief review of non-spatial mathematical models, *Bull. Math. Biol.*, **73** (2011), 2–32.

[5] J. Erler, et. al., Lysyl oxidase is essential for hypoxia-induced metastasis, *Nature*, **440** (2006), 1222–1226.

[6] R. Genesio, M. Tartaglia and A. Vicino, On the estimation of asymptotic stability regions: State of the art and new proposals, *IEEE Transactions on Automatic Control*, **30** (1985), 747–755.

[7] W. Hahn, *Stability of Motion*, Springer Verlag, Heidelberg-Berlin, 1967.

[8] T. Kailath, *Linear Systems*, Prentice-Hall Information and System Sciences Series. Prentice-Hall, Inc., Englewood Cliffs, N.J., 1980.

[9] M. Krstić, I. Kanellakopoulos and P. V. Kokotović, *Nonlinear and Adaptive Control Design*, John Wiley and Sons, 1995.

[10] V. A. Kuznetsov, Mathematical modeling of the development of dormant tumors and immune stimulation of their growth, *Cybern. syst. Anal*, **23** (1988), 556–564.

[11] V. A. Kuznetsov, I. A. Makalkin, M. A. Taylor and A. S. Perelson, Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis, *Bull. Math. Biol*, **56** (1994), 295–321.

[12] U. Ledzewicz, M. Faraji and H. Schaettler, Mathematical model of tumor-immune interactions under chemotherapy with immune boost, *Discrete and Continuous Dynamical Systems, Series B,* **18** (2013), 1031–1051.

[13] U. Ledzewicz, M. Naghneian and H. Schaettler, Optimal response to chemotherapy for a mathematical model of tumor-immune dynamics, *Journal of Mathematical Biology*, **64** (2012), 557–577.

[14] L. Norton and R. Simon, Growth curve of an experimental solid tumor following radiotherapy, *J. of the National Cancer Institute*, **58** (1977), 1735–1741.

[15] L. Norton, A Goempertzian model of human breast cancer growth, *Cancer Research*, **48** (1988), 7067–7071.

[16] K. Page and J. Uhr, Mathematical models of cancer dormancy, *Leukemia and Lymphoma*, **46** (2005), 313–327.

[17] G. Phan et. al., Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma, *PNAS*, **100** (2003), 8372–8377.

[18] S. Ratschan and Z. She, Providing a basin of attraction to a target region of polynomial systems by computation of Lyapunov-like functions, *SIAM J. Control Optim.*, **48** (2010), 4377–4394.

[19] S. Sastry and M. Bodson, *Adaptive Control: Stability, Convergence and Robustness*, Prentice-Hall, Advanced Reference Series (Engineering), 1989.

[20] A. Scott, J. Wolchock and L. Old, Antibody therapy of cancer, *Nature Reviews Cancer*, **12** (2012), 278–287.

[21] N. V. Stepanova, Course of the immune reaction during the development of a malignant tumor, *Biophysics*, **24** (1980), 917–923.

[22] T. Takayanagi, H. Kawamura and A. Ohuchi, Cellular automaton model of a tumor tissue consisting of tumor cells, cytoxic T lymphocytes (CTLs), and cytokine produced by CTLs, *IPSJ Trans Math Model Appl.*, **47** (2006), 61–67.

[23] A. Vannelli and M. Vidyasagar, Maximal Lyapunov functions and domains of attraction for autonomous nonlinear systems, *Automatica*, **21** (1985), 69–80.

[24] K. P. Wilkie, *A Review of Mathematical Models of Cancer-Immune Interactions in the Context of Tumor Dormancy*, Systems Biology of Tumor Dormancy, Springer, New York, 2013.
[25] V. I. Zubov, *Mathematical Methods for the Study of Automatic Control Systems,* Israel Jerusalem Academic Press, 1962.
[26] V. I. Zubov, *Methods of A.M. Lyapunov and Their Application*, the Netherlands, Noordhoff, 1964.
[27] *Sydney International Workshop on Math Models of Tumor-Immune System Dynamics*, January 7-10, 2013.

Received July 24, 2014; Accepted February 16, 2015.

E-mail address: bsheller@iastate.edu
E-mail address: daless@iastate.edu