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Observation and control in a model of a cell population affected by radiation

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ABSTRACT

The effect of radiation on a cell population is described by a two-dimensional nonlinear system of differential equations. If the radiation rate is not too high, the system is known to have an asymptotically stable equilibrium. First, for the monitoring of this effect, the concept of observability is applied. For the case when the total number of cells is observed, without distinction between healthy and affected cells, a so-called observer system is constructed, which, at least near the equilibrium state, makes it possible to recover the dynamics of both the healthy and the affected cells, from the observation of the total number of cells without distinction.

Results of simulations with illustrative data are also presented. If we want to control the system into a required new equilibrium state, and maintain this new equilibrium by a constant control, a technique of theory of optimal control can be applied to construct a feedback control system.

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1. Introduction

Organisms can be exposed to radiation under different circumstances. For example, in case of a nuclear disaster, normal cells of the human body can be dangerously affected by radiation. In radiotherapy instead, killing cancerous cells is one of the most important treatments of malignant tumors. Although therapeutic radiation (both in external and internal treatment) targets specific areas where tumors are formed, it can also affect healthy cells in the immediate vicinity. In all cases the knowledge of the dynamics of the effect of radiation to a cell population is of crucial importance.

A primary effect of radiation is causing chromosome damage. As a result, the affected cells can not reproduce and will eventually die. It happens however, that some broken chromosomes recombine and in this way an affected cell, with certain probability, returns to normal, see Sachs et al. (1992); Schöllnberger et al. (1999); Nickoloff and Hoekstra (1998). This is an important information for the dynamical modeling of the effect of radiotherapy.

Over the last decades, mathematical modeling supporting different cancer therapy methods has gained growing attention. For a mathematical and simulation analysis of chemotherapy, see e.g. Pinho et al. (2002). Nani and Freedman (2000) dealt with the qualitative analysis of a dynamic model of immunotherapy. Sachs et al. (2001) surveyed various differential equation models supporting radiotherapy. A recent general overview of mathematical modeling of different cancer therapy methods can be obtained from the special issue Horn and Webb (2004).

In the present paper a single cell population exposed to radiation will be divided into the subpopulations of affected and unaffected cells, respectively. (Such a model, in principle, can be applied separately to the cancerous and to the healthy cells.) Specifically, in our model the terms healthy and irradiated (affected) cells correspond to the radiation of the normal (i.e. not cancerous) cells. However, the same methodology invariably applies to the case of the tumoral cell population. A more complex approach will be based on the model involving both cancerous and healthy cell populations, see Belostotski and Freedman (2005); Freedman (2006). The necessary stability analysis of such model has been recently published in Freedman and Pinho (2009).

Our investigations will be based on the model considered in Freedman and Pinho (2008), where a two-dimensional nonlinear system of ordinary differential equations describes the respective dynamics of the population of the healthy cells and those affected by radiation, and the irradiated cells at a certain rate recombine into healthy cells. In this model the growth of the healthy cells is supposed to be logistic.

Mathematical systems theory offers a methodology for the analysis of qualitative properties of the models of cancer therapy, such as stability of equilibria, controllability and observability. In Belostotski and Freedman (2005), Freedman and Pinho (2008, 2009) important results are published on the stability of cell populations under radiotherapy. We will also use some of these results. Concerning different radiation models, in Belostotski and Freedman

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(2005); Freedman and Pinho (2008, 2009) detailed theoretical discussion is given for the applicability of the simple radiation protocols as controls. A novelty of our contribution is the explicit calculation of a closed-loop control, steering the cell population to a desired equilibrium. To our knowledge, observability problems and the state estimation from the partial observation of the cell populations exposed to radiation have not been considered yet in the literature. As a first result in this direction, for the model of Freedman and Pinho (2008), we will construct an asymptotic state estimator using a so-called observer system, which is a new tool for monitoring of irradiated cell system.

The paper is organised as follows. In Section 2, we recall the description of the model and some stability results from Freedman and Pinho (2008). Section 3 is devoted to the problem of observation. First, in terms of the model parameters, we obtain a sufficient condition for local observability near equilibrium. Then we also prove a theorem concerning the construction of observer systems for different observation situations. The observer system makes it possible for us to asymptotically estimate unknown (i.e. not observed) components of the original system. Illustrative simulation results are also provided. For earlier applications of the concept of observability and observer systems, see e.g. Varga et al. (2003); López et al. (2007); Varga (2008) and Gámez et al. (2008). In Section 4 with illustrative data we will show how the number of healthy cells can be steered to a desired level, applying an appropriate feedback control. Finally, in Section 5 , the methodology and the results are discussed.

2. Description of the Model and Preliminaries

We consider a dynamic model describing the interaction between the populations of healthy and irradiated cells of an organ under the effect of a constant radiation. Let $x_1(t)$ be the number of healthy cells, and $x_2(t)$ the number of irradiated cells at time$t$. For this situation, from Freedman and Pinho (2008) we recall the following model:

$$\dot{x}_1 = rx_1\left(1-\frac{x_1}{K_0}\right) - \Delta x_1 + px_2, \quad \dot{x}_2 = \Delta x_1 - px_2 - \delta x_2. \tag{1}$$

In this systems it is supposed that the growth of the healthy cells is logistic as in Sachs et al. (1992) and Andronov et al. (1973). The number of irradiated cells with broken chromosomes are represented by Δx_1, where $\Delta > 0$ is the radiation rate determined by the corresponding protocol, $p > 0$ is the rate at which the irradiated cells recombine into healthy cells, $\delta > 0$ is the washout rate of irradiated cells, and finally, $r > 0$ is the Malthus parameter and $K_0 > 0$ the carrying capacity for the healthy cell population.

Freedman and Pinho (2008) proved that the system leaves the nonnegative orthant invariant. Moreover, they proved that system (1) has always a trivial equilibrium $(0, 0)$, and a "mathematical" equilibrium $x^* = (x_1^*, x_2^*)$, with

$$x_1^* = \frac{K_0[r(p+\delta)-\Delta\delta]}{r(p+\delta)}, \quad x_2^* = \frac{K_0\Delta[r(p+\delta)-\Delta\delta]}{r(p+\delta)^2}. \tag{2}$$

Obviously $x^* > 0$ if and only if

$$\Delta < \frac{r(p+\delta)}{\delta}. \tag{3}$$

Below from Freedman and Pinho (2008) we recall three statements. Later on, we will use the Jacobian of the right-hand side of (1) calculated at equilibrium x^*:

$$A = \begin{pmatrix} r - \dfrac{2rx_1^*}{K_0} - \Delta & p \\ \Delta & -p-\delta \end{pmatrix}. \tag{4}$$

Theorem 2.1.

(a) $x^* > 0$ *if and only if equilibrium* $(0, 0)$ *is unstable.*
(b) *If* $x^* > 0$, *it is globally asymptotically stable, with respect to* $\mathbb{R}^2_+ \setminus \{(0, 0)\}$.
(c) *System* (1) *persists* (*uniformly*) *if and only if we have* (3). *Otherwise the cell population becomes extinct.*

3. Observability Analysis of the Model

First we recall some known concepts and results concerning observation systems, to be used in this paper.

Given m, n positive integers, we suppose that the following functions

$$f : \mathbb{R}^n \to \mathbb{R}^n, \quad h : \mathbb{R}^n \to \mathbb{R}^m$$

are continuously differentiable and for some $x^* \in \mathbb{R}^n$ we have that $f(x^*) = 0$ and $h(x^*) = 0$.

We consider the following observation system

$$\dot{x} = f(x) \tag{5}$$

$$y = h(x) \tag{6}$$

where h is the observation function.

Definition 3.1. *Observation system* (5) and (6) *is called locally observable near the equilibrium* x^* *over a given time interval* $[0, T]$, *if there exists* $\epsilon > 0$, *such that for any two different solutions* x *and* $\bar{x}$ *of system* (5) *with* $|x(t) - x^*| < \epsilon$ *and* $|\bar{x}(t) - x^*| < \epsilon (t \in [0, T])$, *the observed functions* $h \circ x$ *and* $h \circ \bar{x}$ *are different.* ($\circ$ *denotes the composition of functions. For brevity, the reference to* $[0, T]$ *will be omitted.*)

For the formulation of a sufficient condition for local observability consider the linearization of the observation system (5) and (6) around x^*, consisting in the calculation of the Jacobians

$$A := f'(x^*) \quad \text{and} \quad C := h'(x^*).$$

Theorem 3.2 ((Lee and Markus, 1971)). *Suppose that*

$$rank[C|CA|CA^2|\cdots|CA^{n-1}]^{\mathrm{T}} = n. \tag{7}$$

Then the observation system (5) and (6) *is locally observable near the equilibrium* x^*.

Definition 3.3. A matrix $A \in \mathbb{R}^{n\times n}$ will be called stable, if all its eigenvalues have negative real parts.

We remind then how it is possible to construct the observer of a system. Now, the construction of an observer system will be based on Sundarapandian (2002).

Definition 3.4. Given a continuously differential function $G : \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}^n$, dynamical system described by

$$\dot{z} = G(z, y), \tag{8}$$

is called a local asymptotic (respectively, exponential) observer for observation system (5) and (6), if the composite system (5), (6) and (8) satisfies the following two requirements.

(i) If $x(0) = z(0)$, then $x(t) = z(t)$, for all $t \geq 0$.
(ii) There exists a neighborhood V of the equilibrium x^* of $\mathbb{R}^n$ such that for all $x(0), z(0) \in V$, the estimation error $z(t) - x(t)$ decays asymptotically (respectively, exponentially) to zero.

Theorem 3.5 ((Sundarapandian, 2002)). *Suppose that* x^* *is a Lyapunov stable equilibrium of system* (5), *and that there exists a matrix* K *such that matrix* A-KC *is stable, where* $A = f'(x^*)$ *and* $C = h'(x^*)$. *Then dynamic system defined by*

$$\dot{z} = f(z) + K[y - h(z)] \tag{9}$$

is a local exponential observer for observation system (5) and (6).

For the application of the above construction we will suppose $x^* > 0$.

Case 1. We assume that the total number of cells is observed, i.e. the observation function is

$$h(x_1, x_2) := x_1 + x_2 - x_1^* - x_2^*. \tag{10}$$

Then for the observation system (1)–(10) we calculate the linearization around the equilibrium x^*:

$$A = \begin{pmatrix} -r + \dfrac{2\Delta\delta}{p+\delta} - \Delta & p \\ \Delta & -p-\delta \end{pmatrix}, \quad C = (1\ 1).$$

It is easy to prove that $rank[C|CA]^{\mathrm{T}} = 2$ if and only if $\Delta \neq ((r-\delta)(p+\delta)/2\delta)$. In this case, by Theorem 3.2 system (1)–(10) is locally observable.

Case 2. Now we present another result on observability, where only the irradiated cells are observed. Then the observation function is given by,

$$h(x_1, x_2) := x_2 - x_2^*. \tag{11}$$

Hence, for the linearization of the observation system (1)–(11) we have

$$A = \begin{pmatrix} -r + \dfrac{2\Delta\delta}{p+\delta} - \Delta & p \\ \Delta & -p-\delta \end{pmatrix}, \quad C = (0\ 1).$$

Now we have $rank[C|CA]^{\mathrm{T}} = 2$ without any further condition. Therefore, again by Theorem 3.2 system (1)–(11) is locally observable.

For the construction of observer systems corresponding to Cases 1 and 2, we will prove the following theorem.

Theorem 3.6. *If for* $k_1, k_2 \in \mathbb{R}$ *inequalities*

(i) $k_2 > \max\{r,\ \delta\}$
(ii) $k_1 > p(\delta + (rk_2/\Delta))$

hold, then with the corresponding choice of h, for systems (1)–(10) *and* (1)–(11), *a local observer is given by*

$$\dot{z}_1 = rz_1\left(1 - \frac{z_1}{K_0}\right) - \Delta z_1 + pz_2 + k_1[y - h(z)]$$
$$\dot{z}_2 = \Delta z_1 - pz_2 - \delta z_2 + k_2[y - h(z)].$$

Proof. In both cases, denoting $K := col(k_1, k_2)$ and applying the Routh-Hurwitz criterion for $n = 2$, we have to guarantee that the coefficients of the normed characteristic polynomial of matrix $A - KC$ are positive, i.e. in Cases 1 and 2, the following inequalities should hold:

Case 1.

$$r - \frac{2\Delta\delta}{p+\delta} + \Delta + p + \delta + k_1 + k_2 > 0, \tag{12}$$

$$\left(-r + \frac{2\Delta\delta}{p+\delta} - \Delta - k_1\right)\left(-p-\delta-k_2\right) - (\Delta - k_2)(p - k_1) > 0. \tag{13}$$

Case 2.

$$r - \frac{2\Delta\delta}{p+\delta} + \Delta + p + \delta + k_2 > 0, \tag{14}$$

$$\left(-r + \frac{2\Delta\delta}{p+\delta} - \Delta\right)\left(-p-\delta-k_2\right) - \Delta(p - k_1) > 0. \tag{15}$$

Now, from (3) we immediately get $-r + ((2\Delta\delta)/(p+\delta)) < r$, furthermore, (*i*) and (*ii*) imply $k_1 + k_2 > r$. Hence we easily obtain (12) and (14). Based on this, to see (13) it is enough to show that

$$k_1 > \frac{(r-\Delta)(\delta + k_2)}{\Delta}. \tag{16}$$

By (*i*) we have $r\delta < rk_2$, implying

$$(r-\Delta)(\delta + k_2) < 2rk_2 + 2\Delta\delta + \Delta p$$
$$\Rightarrow \frac{(r-\Delta)(\delta + k_2)}{\Delta} < p + 2\left(\delta + \frac{rk_2}{\Delta}\right).$$

Hence, applying (*ii*) we obtain (16).

Finally, to see (15), it is enough to show

$$\frac{2\Delta\delta}{p+\delta}(-p-\delta-k_2) - \Delta(p - k_1) > 0.$$

For the latter it is sufficient to prove inequality

$$k_1 > 2\delta + \frac{2\delta k_2}{p+\delta} + p,$$

which is implied by (*ii*), since from (3) we have

$$p + 2\left(\delta + \frac{rk_2}{\Delta}\right) > 2\delta + \frac{2\delta k_2}{p+\delta} + p.$$

Now, the application of Theorem 3.5 concludes the proof. □

Example. For an illustration set $\Delta := 2, r := 2.1, K_0 := 100, p := 1, \delta := 0.1$ In this case $x^* > 0$ and is globally stable. Moreover, we easily get the corresponding rank condition for local observability in both Cases 1 and 2. On the other hand, for these parameter values, the conditions (*i*) and (*ii*) of Theorem 3.6 are satisfied:

$$k_2 > 2.1, \quad k_1 > 1 + 2(0.1 + 1.05k_2).$$

Therefore, with $K := col(150, 50)$ we obtain the following observer system:

$$\begin{aligned} \dot{z}_1 = &\ 2.1z_1\left(1 - \frac{z_1}{100}\right) - 2z_1 + z_2 + 150(y - h(z)) \\ \dot{z}_2 = &\ 2z_1 - z_2 - 0.1z_2 + 50(y - h(z)). \end{aligned} \tag{17}$$

Let us consider Case 1, and solve systems (1) and (17) with the respective initial conditions $x(0) = (100, 0)$ and $z(0) = (150, 50)$, with observation function (10).

In Fig. 1 we can see that the observer system (17) asymptotically recovers the solution of the original system.

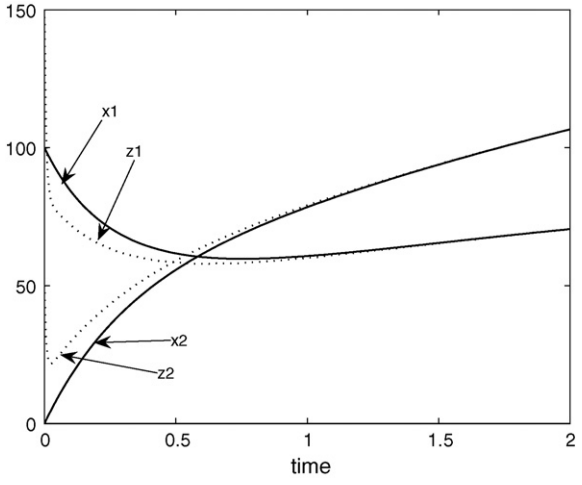

Fig. 1. Solutions of (1) and (17) with initial conditions $x(0) = (100,\ 0)$ and $z(0) = (150,\ 50)$ with observation function (10).

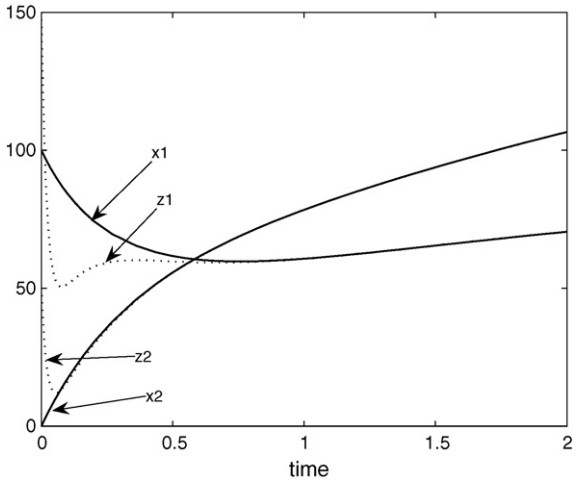

Fig. 2. Solutions of (1) and (17) with initial conditions $x(0) = (100, 0)$ and $z(0) = (150, 50)$ with observation function (11).

Similarly, if we consider now Case 2, i.e. observation function (11), and solve system (17) with $z(0) = (150, 50)$, solution z approaches the solution of the original system (1) with the initial condition $x(0) = (100, 0)$ (see Fig. 2).

4. Linear Feedback Control for the Radiation

For $n, r \in \mathbb{N}$, $L \in \mathbb{R}^{n\times n}$, $B \in \mathbb{R}^{n\times r}$, and continuously differentiable function $g : \mathbb{R}^n \to \mathbb{R}^n$, consider the control system

$$\dot{x} = Lx + g(x) + BU, \tag{18}$$

where U is a continuous control function. Assume that to a constant control $u^* \in \mathbb{R}^r$, there corresponds an equilibrium state x^*, i.e.,

$$Lx^* + g(x^*) + Bu^* = 0. \tag{19}$$

Then, from (18) and (19), for the new variables

$$y := x - x^*; \quad u := U - u^*$$

we have

$$\dot{y} = Ly + q(y) + Bu, \quad \text{with} \quad q(y) := g(y + x^*) - g(x^*). \tag{20}$$

A feedback control will be given below which asymptotically steers system (20) into the zero equilibrium.

Theorem 4.1 ((Rafikov et al., 2008)). *If there exist matrices P, Q, $R \in \mathbb{R}^{n\times n}$; P positive definite and Q symmetric, such that the function*

$$l(y) := y^{\mathrm{T}}Qy - q^{\mathrm{T}}(y)Py - y^{\mathrm{T}}Pq(y) \quad (y \in \mathbb{R}^n)$$

is positive definite, and P satisfies the equation

$$PL + L^{\mathrm{T}}P - PBR^{-1}B^{\mathrm{T}}P + Q = 0. \tag{21}$$

Then the linear feedback

$$u(y) := -R^{-1}B^{\mathrm{T}}Py \quad (y \in \mathbb{R}^n) \tag{22}$$

asymptotically steers any initial state $y(0)$ to zero.

Remark 4.2. The statement $\lim_\infty y = 0$ is obviously equivalent to $\lim_\infty x = x^*$.

Remark 4.3. According to Rafikov et al. (2008), the feedback control (22) also minimizes the functional

$$\phi(y) := \int_0^\infty [l(y(t)) + u^{\mathrm{T}}(y(t))Ru(y(t))]\,\mathrm{d}t, \tag{23}$$

however, we will not use this statement.

Corollary 4.4. *Using the notation of the previous theorem, let us suppose that function l is locally positive definite. Then there exists a neighbourhood V of zero in $\mathbb{R}^n$ such that for all $x(0) \in V$, for the solution x of system (19) we have $\lim_\infty x = x^*$.*

Proof. The proof of Theorem 4.1 available in Rafikov et al. (2008), is based on the observation that under the conditions of the mentioned theorem, $W(y) = y^{\mathrm{T}}Py$ is a Lyapunov function implying (global) asymptotic stability of the zero equilibrium of system (20). It is not hard to see that a similar reasoning implies the following statement. If function W is locally positive definite, then the zero equilibrium of system (20) is locally asymptotically stable. Hence, the statement of the Corollary follows.

Now, we are going to apply the above corollary to system (1) to control cell populations, utilizing the following control system

$$\begin{aligned} \dot{x}_1 &= rx_1\left(1 - \frac{x_1}{K}\right) - \Delta x_1 + px_2 \\ \dot{x}_2 &= \Delta x_1 - px_2 - \delta x_2 + U, \end{aligned} \tag{24}$$

corresponding to system (18).

Our objective is to find a feedback control that steers the population of healthy cells to a desired level $x_1^* = x_{1d}$. The corresponding value $x_2^* = x_{2d}$ and u^* can be calculated solving the following system of linear equations:

$$\begin{aligned} rx_1^*\left(1 - \frac{x_1^*}{K}\right) - \Delta x_1^* + px_2^* &= 0 \\ \Delta x_1^* - px_2^* - \delta x_2^* + u^* &= 0. \end{aligned} \tag{25}$$

We note that u^* is interpreted as a constant radiation rate that would maintain the desired level $x_1^* = x_{1d}$ of healthy cells.

Now, for systems (21) and (22), we can choose

$$L := \begin{pmatrix} r - \Delta & p \\ \Delta & -(p + \delta) \end{pmatrix}$$

and

$$h(y) := \begin{pmatrix} -\dfrac{r}{K}(y_1^2 + 2y_1x_1^*) \\ 0 \end{pmatrix} \quad (y \in \mathbb{R}^2).$$

If the conditions of Theorem 4.1 are satisfied, the required feedback control can be obtained by (22).

For the parameters considered in previous model simulations $r := 1$, $\Delta := 5$, $K := 100$, $p := 1$, and $\delta := 0.1$, it is easy to prove that system (1) has an asymptotically stable equilibrium, where $x_1 = 54$. Now, we suppose that the objective is to increase the number of healthy cells, for example to a level $x_{1d} = 80$. To this end, from system (25) we calculate $x_{2d} = 344$ and $u^* = 21.6$. For matrices L and B we have

$$L = \begin{bmatrix} -4 & 1 \\ 5 & -1.1 \end{bmatrix}, \quad B = \begin{bmatrix} 0 \\ 1 \end{bmatrix}.$$

Choosing

$$Q := \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}, \quad R = \begin{bmatrix} 1 \end{bmatrix},$$

we calculate the matrix Riccati Eq. (21), and using the function LQR of *MATLAB*^{TM} v 7.0, we obtain a solution

$$P = \begin{bmatrix} 1.2362 & 0.9862 \\ 0.9862 & 0.9451 \end{bmatrix}.$$

Obviously P and Q are positive definite symmetric matrices. Furthermore, it is easy to verify analytically that $(0, 0)$ is a local minimum point for function l (see also Fig. 3), and by the Corollary to Theorem 4.1, we have the local asymptotic stability of the zero

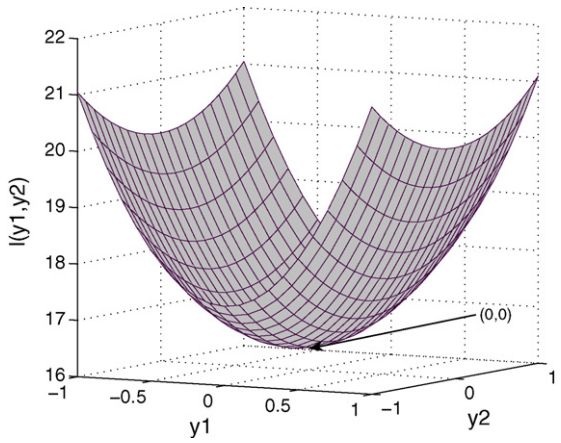

Fig. 3. Function $l(y)$ near equilibrium $(0, 0)$.

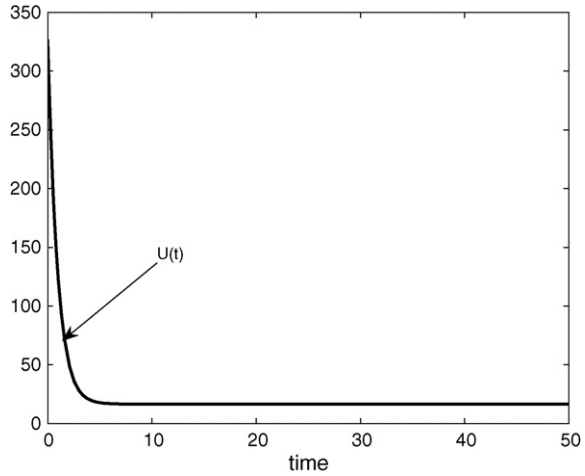

Fig. 5. Function $U(t)$ in the controlled system (27).

equilibrium of system (20). Therefore, applying (22), we obtain the required feedback control

$$u = -0.9862y_1 - 0.9451y_2 \tag{26}$$

Hence, from inequalities $x = x^* + y$ and $U = u^* + u$, we can calculate the closed loop control system

$$\begin{aligned} \dot{x}_1 &= x_1\left(1 - \frac{x_1}{100}\right) - 5x_1 + x_2 \\ \dot{x}_2 &= 4.0138x_1 - 2.045x_2 + 425.576. \end{aligned} \tag{27}$$

Fig. 4 shows how the second coordinate of the solution of the controlled system asymptotically reaches the desired value $x_{1d} = 80$.

In Fig. 5 we show the evolution of function $U(t)$ in the controlled system.

As seen from Fig. 5, function $U(t)$ is always positive, which corresponds to its physical interpretation as radiation intensity.

5. Discussion and Outlook

Using known results on the existence of an asymptotically stable equilibrium in a cell radiation model, in the paper sufficient conditions have been obtained for the local observability and for the observer design, corresponding to different observation situations. As a result, on the one hand, we can estimate both the population of healthy cells and those affected by the radiation, provided the total number of cells is observed. On the other hand, similarly, from the observation of the irradiated cells we can recover the number of healthy cells. In both cases, by an appropriate choice of two auxiliary parameters, we achieve a quite rapid convergence to asymptotic estimation.

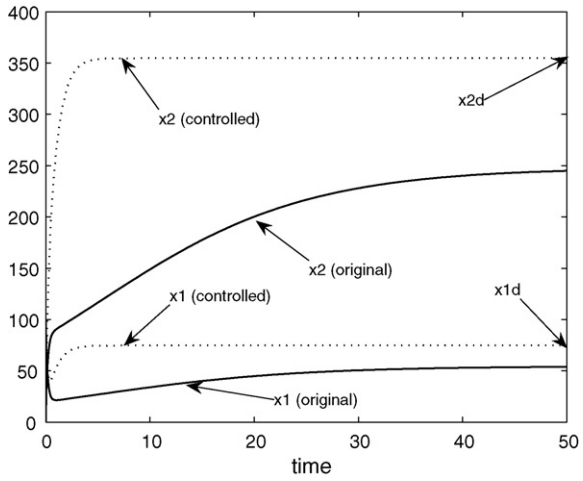

Fig. 4. Solutions of (1) and (27) with the same initial value $x(0) = (100, 0)$.

For an efficient therapy the decisions should be made on the basis of the information on the response of the cells to the applied radiation protocol. This is obviously a technically involved problem, and in the literature there are several methods of *in vivo* monitoring an evaluation of the cell populations exposed to radiation. These methods are traditionally based on computer tomography (CT) and magnetic resonance imaging (MRI). In recent years, the so-called biological imaging methods visualizing metabolic pathways have been developed. These methods provide complementary imaging of various aspects of tumour biology. Nowadays, the most advanced biological imaging system is positron emission tomography (PET), whose diagnostic capacities have clinically been evaluated over the last years. Nestle et al. (2009) is the most recent review on the monitoring technique of PET in radiotherapy. The monitoring methodology based on the construction of an observer system, suggested in the present paper, may contribute to the further development of the methodology of monitoring the response of the cell populations exposed to radiotherapy.

We have also shown, how a desired number of healthy cells can be achieved, using a feedback control. The latter means that the applied radiation intensity is defined in function of the current state of the cell population. We note that in the resulting closed-loop control the system practically reaches the corresponding equilibrium much more quickly than in the original system.

In the following, for an outlook, we briefly overview the possible extensions of the methods and results of the paper.

Our results have been obtained under the hypothesis that the growth of the population of unaffected (healthy) cells can be described by the classical logistic model. The logistic equation is the simplest density-dependent population growth model where the relative growth rate $\dot{N}/N$ is a decreasing linear function of N/K_0, the ratio of population size to carrying capacity. Depending on the biological situation, a more precise approximation (a more realistic model) can be obtained supposing this density-dependence to be of the more general form $F(N/K_0)$, where F is a smooth decreasing function and $F(1) = 0$.

Based on clinical and laboratory experience, in Sachs et al. (2001) it was pointed out, that this model fits to most solid tumors. (In particular, for breast tumors, it is a good approximation if the mentioned linear dependence of the logistic model is substituted by an appropriate power function.) Since the above function F implies

asymptotic stability of the population size equal to the carrying capacity, all results of the paper requiring this asymptotic stability have a good chance to be extended to the case of the above cell dynamics, more general than the logistic one.

As a further development of the results of the present paper, the applied methodology will be extend to the case of more complex radiotherapy models, when competing cancerous and healthy cell populations grow according to a logistic equation, see Freedman (2006), and the radiation affects both population but with different rates, as it is recently considered in Freedman and Pinho (2009). Another possibility of extension is considering cancer treatments other than radiotherapy. In fact, chemotherapy model of Pinho et al. (2002), immunotherapy model of Nani and Freedman (2000) are possible candidates for application of our methods.

Finally, we note that similarly to other recent papers presenting new methodological developments based on mathematical models, like Belostotski and Freedman (2005); Freedman and Pinho (2008, 2009), the numerical presentation of the results and the corresponding simulation analysis is carried out with illustrative rather than real data. Nevertheless, they contribute to the better understanding of the mechanism of radiotherapy. For the implementation of the methods offered in these methodological papers, including ours, in our view, a project concerning further *in vitro* studies and *in vivo* animal experiments would be necessary.

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