OPTIMAL CONTROL APPLICATIONS AND METHODS
Optim. Control Appl. Meth. (2015)
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/oca.2164

Optimal control of a delayed breast cancer stem cells nonlinear model

Andrés Barrea and Matias E. Hernández*,†

CIEM, Centro de Investigación y Estudios de Matemática, University of Córdoba, Argentina

SUMMARY

In this article, we consider a nonlinear model, which is governed by an ordinary differential equations system with time delays in state and control. The model is used in order to describe the growth of breast cancer cells under therapy. We seek optimal therapies to minimize the number of cancer cells as well as the total quantity of drug used in the treatment. In this way, we formulate an optimal control problem. We prove the existence of an optimal therapy and use Pontryagin's maximum principle in order to find optimality conditions, which characterize such optimal therapy. At last, both numerical results and conclusion are presented. Copyright © 2015 John Wiley & Sons, Ltd.

Received 25 September 2014; Revised 6 January 2015; Accepted 9 February 2015

KEY WORDS: optimal control; cancer; maximum principle

1. INTRODUCTION

Breast cancer is a kind of cancer that develops from breast cells. This cancer has a heterogeneous distribution of cell types. Cancer stem cells (CSCs) have been identified in primary breast cancer tissues and cell lines. CSCs are defined as a small subset of cancer cells that possess own properties of the normal stem cells such as self-renew and replenish the heterogeneous lineage of cancer cells that comprise the tumor. A theory has suggested that stem cells cause relapse of patients and are responsible for metastasis. An important question is how the proportion of CSC population can be maintained at a relatively constant level in tumors [1–3]. CSC hypothesis suggests that CSCs possess the ability to divide symmetrically to yield two identically immortal CSCs as well as asymmetrically to simultaneously self-renew and yield one mortal non-stem cancer cell with finite replicative potential. It is believed that the proportion of CSCs remains constant, alternating between symmetric and asymmetric division.

There are a large number of mathematical models to study the previous issues, but the most important model with delayed state is presented in [3], which was corroborated with *in vivo* and *in vitro* experiments.

We include a therapy effects (control) with time delays into the model proposed in [3]. Also, we formulate an optimal control problem in order to minimize the number of breast cancer cells and amount of drugs used in the treatment. Other authors have studied similar problem [4–9].

The organization of this article is as follows: In section 2, we present the model used in [3] and incorporate the therapy effects on CSCs. In section 3, we apply Pontryagin's maximum principle to find optimal therapies. Section 4 is devoted to give some numerical result. At last, in section 5, we provide the conclusions.

*Correspondence to: Matias E. Hernández, CIEM, Centro de Investigación y Estudios de Matemática, University of Córdoba, Argentina.

†E-mail: hernandez@famaf.unc.edu.ar

Copyright © 2015 John Wiley & Sons, Ltd.

2. MATHEMATICAL MODEL FOR BREAST CANCER DYNAMICS

We assume that breast cancer is constituted by three main types of cells: CSCs, progenitor cells (PCs), and terminally differentiated cells (TDCs) [3]. When feedback control is not included, it is formulated in the following system of ordinary differential equations for the dynamics of the cell populations:

$$\begin{cases} \frac{dC(t)}{dt} = (p_0 - q_0)\nu_0 C(t) - d_0 C(t), \\ \frac{dP(t)}{dt} = (1 - p_0 + q_0)\nu_0 C(t) + (p_1 - q_1)\nu_1 P(t) - d_1 P(t), \\ \frac{dT(t)}{dt} = (1 - p_0 + q_0)\nu_0 P(t) - d_2 T(t), \\ (C(0), P(0), T(0)) = (C_0, P_0, T_0), \end{cases} \tag{1}$$

where $C(t)$, $P(t)$, and $T(t)$ denote, respectively, the number of CSCs, PCs, and TDCs at time t [3]. We also denote p_0 as the probability that a CSC is divided into a pair of CSCs, q_0 as the probability that a CSC is divided into a pair of PCs, p_1 as the probability that a PC is divided into a pair of PCs, and q_1 as the probability that a PC is divided into a pair of TDCs, respectively. Therefore, $1 - p_0 - q_0(1 - p_1 - q_1)$ denotes the probability that an asymmetric cell division takes place from CSCs (PCs) to PCs (TDCs). Finally, (C_0, P_0, T_0) is the initial condition of system (1).

Parameters ν_0 and ν_1 are called synthesis rates, and it represent the growth rates of each cell lineage. Parameters d_0, d_1, and d_2 are the degradation rates of CSCs, PCs, and TDCs, respectively, where d_0 and d_1 must be relatively small or negligible compared with d_2 [3].

Cell division and other mechanisms allow stem cells to regulate its population. One of these mechanisms is a Type-I feedback, which is proposed in [3]. According to this delayed feedback, the TDCs can regulate the synthesis rates of CSCs and PCs. In this case, the dynamical system has the following form:

$$\begin{cases} \frac{dC(t)}{dt} = (p_0 - q_0)\frac{\nu_0 C(t)}{1+\beta_0 T^2(t-\tau)} - d_0 C(t), \\ \frac{dP(t)}{dt} = (1 - p_0 + q_0)\frac{\nu_0 C(t)}{1+\beta_0 T^2(t-\tau)} + (p_1 - q_1)\frac{\nu_1 P}{1+\beta_1 T^2(t-\tau)} - d_1 P(t), \\ \frac{dT(t)}{dt} = (1 - p_1 + q_1)\frac{\nu_1 P}{1+\beta_1 T^2(t-\tau)} - d_2 T(t), \\ (C(t), P(t), T(t)) = (C_0, P_0, T_0), \forall t \in [-\tau, 0]. \end{cases} \tag{2}$$

In model (2), parameters ν_1 and ν_2 of model (1) have been replaced by a nonlinear decreasing Hill functions of the TDC population with time delay, τ, and strength parameters β_1 and β_2, respectively:

$$\frac{\nu_0}{1 + \beta_0 T^2(t-\tau)} \text{ and } \frac{\nu_1}{1 + \beta_1 T^2(t-\tau)}.$$

There is another type of feedback mechanism with time delays, which assume that the probability of symmetric cell division is regulated by the population of TDCs. This feedback is known as Type-II feedback and responds the following delay differential equations:

$$\begin{cases} \frac{dC(t)}{dt} = \left(\frac{p_0}{1+\gamma_1^0 T^2(t-\tau)} - \frac{q_0}{1+\gamma_2^0 T^2(t-\tau)}\right)\nu_0 C(t) - d_0 C(t), \\ \frac{dP(t)}{dt} = \left(1 - \frac{p_0}{1+\gamma_1^0 T^2(t-\tau)} + \frac{q_0}{1+\gamma_2^0 T^2(t-\tau)}\right)\nu_0 C(t) \\ + \left(\frac{p_1}{1+\gamma_1^1 T^2(t-\tau)} - \frac{q_1}{1+\gamma_2^1 T^2(t-\tau)}\right)\nu_1 P(t) - d_1 P(t), \\ \frac{dT(t)}{dt} = \left(1 - \frac{p_1}{1+\gamma_1^1 T^2(t-\tau)} + \frac{q_1}{1+\gamma_2^1 T^2(t-\tau)}\right)\nu_1 P(t) - d_2 T(t), \\ (C(t), P(t), T(t)) = (C_0, P_0, T_0), \forall t \in [-\tau, 0]. \end{cases} \tag{3}$$

Copyright © 2015 John Wiley & Sons, Ltd.

DOI: 10.1002/oca

As can be noted from model (3), division probabilities are modeled by nonlinear decreasing Hill functions controlled by TDC levels with time delay, τ, and feedback strength parameters γ :

$$\frac{p_0}{1+\gamma_1^0 T^2(t-\tau)},\ \frac{q_0}{1+\gamma_2^0 T^2(t-\tau)},$$

$$\frac{p_1}{1+\gamma_1^1 T^2(t-\tau)} \text{ and } \frac{p_0}{1+\gamma_1^2 T^2(t-\tau)}.$$

When Type-I and Type-II feedback mechanisms are combined, then the governing system of equations takes the form [3]:

$$\begin{cases} \frac{dC(t)}{dt} = \underbrace{\left(\frac{p_0}{1+\gamma_1^0 T^2(t-\tau)} - \frac{q_0}{1+\gamma_2^0 T^2(t-\tau)}\right)}_{G_1(t-\tau)} \underbrace{\frac{\nu_0 C(t)}{1+\beta_0 T^2(t-\tau)}}_{H_1(t,t-\tau)} - d_0 C(t), \\ \frac{dP(t)}{dt} = \left(1 - \frac{p_0}{1+\gamma_1^0 T^2(t-\tau)} + \frac{q_0}{1+\gamma_2^0 T^2(t-\tau)}\right) \frac{\nu_0 C(t)}{1+\beta_0 T^2(t-\tau)} + \\ \qquad \underbrace{\left(\frac{p_1}{1+\gamma_1^1 T^2(t-\tau)} - \frac{q_1}{1+\gamma_2^1 T^2(t-\tau)}\right)}_{G_2(t-\tau)} \underbrace{\frac{\nu_1 P(t)}{1+\beta_1 T^2(t-\tau)}}_{H_2(t,t-\tau)} - d_1 P(t), \\ \frac{dT(t)}{dt} = \left(1 - \frac{p_1}{1+\gamma_1^1 T^2(t-\tau)} + \frac{q_1}{1+\gamma_2^1 T^2(t-\tau)}\right) \frac{\nu_1 P(t)}{1+\beta_1 T^2(t-\tau)} - d_2 T(t), \\ (C(t), P(t), T(t)) = (C_0, P_0, T_0), \forall t \in [-\tau, 0]. \end{cases} \tag{4}$$

We consider a control, $u(t)$, in order to model the dynamics of the cancer cells under therapy. Function $u(t)$ represents the drug doses administered at time t in such a way as to $u = 0$ corresponds to no drug being applied, while $u = 1$ occurs with a full dose. The generalized model is given by the following:

$$\begin{cases} \frac{dC(t)}{dt} = G_1(t-\tau) H_1(t, t-\tau) - d_0 C(t) - e_0 u(t-\tau) C(t-\tau), \\ \frac{dP(t)}{dt} = (1 - G_1(t-\tau))\, H_1(t, t-\tau) + G_2(t-\tau) H_2(t, t-\tau) - d_1 P(t) - e_1 u(t-\tau) P(t-\tau), \\ \frac{dT(t)}{dt} = (1 - G_2(t-\tau))\, H_2(t, t-\tau) - d_2 (T(t) - e_2 u(t-\tau) T(t-\tau), \\ (C(t), P(t), T(t)) = (C_0, P_0, T_0), u(t) = 0, \forall t \in [-\tau, 0], \end{cases} \tag{5}$$

where e_0, e_1, and e_2 are the drug sensitivities of the cancer cells CSCs, PCs, and TDCs, respectively. We assume that $u(t) \in U_{ad}$, where

$$U_{ad} = \left\{u : u(t) \text{ is measurable and } 0 < u(t) \leqslant 1, \forall t \in [0, T_f]\right\},$$

and $T_f < \infty$ is the time horizon.

Figure 1 shows the free evolution of the cancer cells CSCs, PCs, and TDCs over a period of 100 days obtained from model (4) with the values of Table I, which are shown in the numerical results section (i.e. section 4). Initial conditions are $C(t) = C_0, P(t) = P_0$, and $T(t) = T_0$, $\forall t \in [-\tau, 0]$, where $C_0 = 10^5$, $P_0 = 0$, $T_0 = 0$, and $\tau = 2$.

2.1. Existence of solutions of system (5)

In order to prove that system (5) has a solution, it is rewritten as follows:

$$\dot{X}(t) \doteq F(X(t), X(t-\tau)) = AX(t) + K(X(t), X(t-\tau)), \tag{6}$$

Copyright © 2015 John Wiley & Sons, Ltd.

DOI: 10.1002/oca

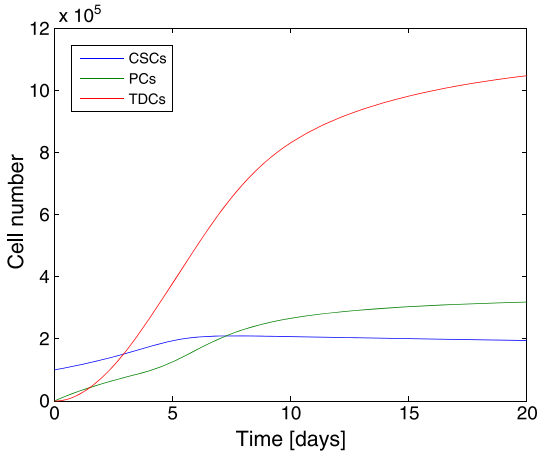

Figure 1. Free dynamic of the cancer cells CSCs (blue), PCs (green), and TDCs (red). Parameters used are listed in Table I. CSCs, cancer stem cells; PCs, progenitor cells; TDCs, terminally differentiated cells.

Table I. Tumor parameters.

p_0	q_0	p_1	q_1	$\frac{\nu_0}{\nu_1}$	$\frac{d_2}{\nu_1}$	$\frac{d_0}{d_2}$	$\frac{d_1}{d_2}$	γ_1^0	γ_2^0	γ_1^1	γ_2^1	β_0	β_1
0.5	0.2	0.1	0.5	0.5	0.05	0.1	0.5	10^{-11}	2×10^{-12}	4×10^{-10}	5×10^{-11}	8×10^{-12}	4×10^{-12}

where we have defined

$$X(t) \doteq \begin{pmatrix} C(t) \\ P(t) \\ T(t) \end{pmatrix}, X(t-\tau) \doteq \begin{pmatrix} C(t-\tau) \\ P(t-\tau) \\ T(t-\tau) \end{pmatrix},$$

$$A \doteq \begin{pmatrix} -(e_0u(t-\tau)+d_0) & 0 & 0 \\ 0 & -(e_1u(t-\tau)+d_1) & 0 \\ 0 & 0 & -(e_2u(t-\tau)+d_2) \end{pmatrix},$$

and $K(X(t), X(t-\tau))$ is defined by the following function:

$$\begin{pmatrix} \left(\frac{p_0}{1+\gamma_1^0T^2(t-\tau)} - \frac{q_0}{1+\gamma_2^0T^2(t-\tau)}\right)\frac{\nu_0C(t)}{1+\beta_0T^2(t-\tau)} \\ \left(1-\frac{p_0}{1+\gamma_1^0T^2(t-\tau)}+\frac{q_0}{1+\gamma_2^0T^2(t-\tau)}\right)\frac{\nu_0C(t)}{1+\beta_0T^2(t-\tau)} + \left(\frac{p_1}{1+\gamma_1^1T^2(t-\tau)} - \frac{q_1}{1+\gamma_2^1T^2(t-\tau)}\right)\frac{\nu_1P(t)}{1+\beta_1T^2(t-\tau)} \\ \left(1-\frac{p_1}{1+\gamma_1^1T^2(t-\tau)}+\frac{q_1}{1+\gamma_2^1T^2(t-\tau)}\right)\frac{\nu_1P(t)}{1+\beta_1T^2(t-\tau)} \end{pmatrix}.$$

Theorem 2.1
There is a solution of system (5).

Proof 2.1
We use the following classical result: if F is uniformly Lipschitz continuous, then there is a solution of system (5). The proof of this result can be found in standard ordinary differential equations with delay textbooks [10–12]. Therefore, the plan is to show that F is uniformly Lipschitz continuous.

It is obvious that $AX(t)$ is uniformly Lipschitz continuous, then we only need to prove that $K(X(t), X(t-\tau))$ is uniformly Lipschitz continuous. In other words, we will prove that

$$|K(X_1(t), X_1^\tau(t)) - K(X_2(t), X_2^\tau(t))| \leqslant M\left(|X_1(t)-X_2(t)| + |X_1^\tau(t)-X_2^\tau(t)|\right).$$

Copyright © 2015 John Wiley & Sons, Ltd.

DOI: 10.1002/oca

For simplicity, we denote $X_1(t-\tau)$ and $X_2(t-\tau)$ by $X_1^\tau(t)$ and $X_2^\tau(t)$, respectively.

We begin by checking that the right-hand side of (2) is uniformly Lipschitz continuous. Therefore, we rewrite (2) as follows:

$$\dot{X} = \tilde{A}X(t) + \tilde{K}(X(t), X^\tau(t)),$$

where

$$\tilde{A} \doteq \begin{pmatrix} -d_0 & 0 & 0 \\ 0 & -d_1 & 0 \\ 0 & 0 & -d_2 \end{pmatrix}$$

and $\tilde{K}(X(t), X(t-\tau))$ is defined as follows:

$$\begin{pmatrix} (p_0 - q_0)\frac{\nu_0 C(t)}{1+\beta_0 T^2(t-\tau)} \\ (1 - p_0 + q_0)\frac{\nu_0 C(t)}{1+\beta_0 T^2(t-\tau)} + (p_1 - q_1)\frac{\nu_1 P(t)}{1+\beta_1 T^2(t-\tau)} \\ (1 - p_1 + q_1)\frac{\nu_1 P(t)}{1+\beta_1 T^2(t-\tau)} \end{pmatrix}.$$

Once again, we only need to prove that

$$\left|\tilde{K}(X_1(t), X_1^\tau(t)) - \tilde{K}(X_2(t), X_2^\tau(t))\right| \leq M\left(|X_1(t) - X_2(t)| + |X_1^\tau(t) - X_2^\tau(t)|\right).$$

If we denote $\tilde{K}(X_1(t), X_1^\tau(t)) - \tilde{K}(X_2(t), X_2^\tau(t)) = (I_1, I_2, I_3)^T$, then

$$\left|\tilde{K}(X_1(t), X_1^\tau(t)) - \tilde{K}(X_2(t), X_2^\tau(t))\right| = |I_1| + |I_2| + |I_3|.$$

We observe that the first term,$|I_1|$, is equal to

$$\underbrace{\left|\left(\frac{(p_0 - q_0)\nu_0 C_1(t)}{1 + \beta_0 T_1^2(t-\tau)}\right) - \left(\frac{(p_0 - q_0)\nu_0 C_2(t)}{1 + \beta_0 T_2^2(t-\tau)}\right)\right|}_{|I_1|}$$

and in turn, it is equal to

$$\underbrace{\left|\frac{D_1 C_1(t)(1 + \beta_0 T_2^2(t-\tau)) - D_1 C_2(t)(1 + \beta_0 T_1^2(t-\tau))}{(1 + \beta_0 T_1^2(t-\tau))(1 + \beta_0 T_2^2(t-\tau))}\right|}_{|\tilde{I}_1|},$$

where $D_1 \doteq (p_0 - q_0)\nu_0$.

Now, we have that

$$\begin{aligned}
|\tilde{I}_1| &\leq \left|D_1 C_1(t)(1 + \beta_0 T_2^2(t-\tau)) - D_1 C_2(t)(1 + \beta_0 T_1^2(t-\tau))\right| \\
&\leq \left|D_1 C_1(t) + D_1\beta_0 C_1(t) T_2^2(t-\tau) - D_1 C_2(t) - D_1\beta_0 C_2(t) T_1^2(t-\tau)\right| \\
&\leq |D_1|\,|C_1(t) - C_2(t)| + \left|D_1\beta_0 C_1(t) T_2^2(t-\tau) - D_1\beta_0 C_1(t) T_1^2(t-\tau)\right| \\
&\quad + \left|D_1\beta_0 C_1(t) T_1^2(t-\tau) - D_1\beta_0 C_2(t) T_1^2(t-\tau)\right| \\
&\leq |D_1|\,|C_1(t) - C_2(t)| + |D_1\beta_0 C_1(t)|\left|T_2^2(t-\tau) - T_1^2(t-\tau)\right| \\
&\quad + \left|D_1\beta_0 T_1^2(t-\tau)\right|\,|C_1(t) - C_2(t)| \\
&\leq |D_1|\left(1 + |D1||\beta_0|\left|T_1^2(t-\tau)\right|\right)|C_1(t) - C_2(t)| \\
&\quad + |D_1\beta_0 C_1(t)|\,|T_2(t-\tau) + T_1(t-\tau)|\,|T_2(t-\tau) - T_1(t-\tau)|.
\end{aligned}$$

Copyright © 2015 John Wiley & Sons, Ltd.

DOI: 10.1002/oca

However, from the right-hand side of (2), it is easy to prove that there is a finite non-negative constant $R < \infty$ such that $N(t) < R, \forall t \in [0, T_f]$, where $N(t) = C(t) + P(t) + T(t)$ and $T_f < \infty$ is the time horizon. Then $|T_1^2(t-\tau)| < R^2$ and $|T_2(t-\tau) + T_1(t-\tau)| < 2R$. Therefore,

$$|I_1| = |\tilde{I}_1| \leqslant M_1 \left(|C_1(t) - C_2(t)| + |T_1(t-\tau) - T_2(t-\tau)|\right),$$

where $M_1 \doteq \max\left\{|D_1|\left(1 + |D1||\beta_0|\left|R^2\right|\right)|, |D_1\beta_0|\, R^3\right\}$.

Similarly, we have the following inequalities:

$$|I_2| \leqslant M_2 \left(|C_1(t) - C_2(t)| + |T_1(t-\tau) - T_2(t-\tau)|\right),$$

and

$$|I_3| \leqslant M_3 \left(|C_1(t) - C_2(t)| + |T_1(t-\tau) - T_2(t-\tau)|\right).$$

Let M be the max $\{M_1, M_2, M_3\}$. Then, $|I_1|+|I_2|+|I_3| \leqslant M \left(|C_1(t)-C_2(t)| + |T_1(t) - T_2(t)|\right)$, and the right-hand side of (2) is uniformly Lipschitz continuous.

Similar to the previous case, it is possible to prove that the right-hand side of (3) is uniformly Lipschitz continuous.

The fact that the right-hand sides of (2) and (3) are uniformly Lipschitz continuous, it is used in order to prove that K is also uniformly Lipschitz continuous (therefore, F will be uniformly Lipschitz continuous). We begin by

$$K(X_1(t), X_1^\tau(t)) - K(X_2(t), X_2^\tau(t)) = (J_1, J_2, J_3)^T.$$

Therefore,

$$|K(X_1(t), X_1^\tau(t)) - K(X_2(t), X_2^\tau(t))| = |J_1| + |J_2| + |J_3|.$$

For the first term, $|J_1|$, we have

$$\begin{aligned}
|J_1| &\leqslant |\left(\frac{p_0}{1+\gamma_1^0 T_1^2(t-\tau)} - \frac{q_0}{1+\gamma_2^0 T_1^2(t-\tau)}\right)\frac{\nu_0 C_1(t)}{1+\beta_0 T_1^2(t-\tau)} - \left(\frac{p_0}{1+\gamma_1^0 T_1^2(t-\tau)} - \frac{q_0}{1+\gamma_2^0 T_1^2(t-\tau)}\right)\frac{\nu_0 C_1(t)}{1+\beta_0 T_1^2(t-\tau)}| \\
&= |\left(\frac{p_0}{1+\gamma_1^0 T_1^2(t-\tau)} - \frac{q_0}{1+\gamma_2^0 T_1^2(t-\tau)}\right)\frac{\nu_0 C_1(t)}{1+\beta_0 T_1^2(t-\tau)} - \left(\frac{p_0}{1+\gamma_1^0 T_1^2(t-\tau)} - \frac{q_0}{1+\gamma_2^0 T_1^2(t-\tau)}\right)\frac{\nu_0 C_1(t)}{1+\beta_0 T_1^2(t-\tau)} \\
&\quad + \left(\frac{p_0}{1+\gamma_1^0 T_2^2(t-\tau)} - \frac{q_0}{1+\gamma_2^0 T_2^2(t-\tau)}\right)\frac{\nu_0 C_2(t)}{1+\beta_0 T_1^2(t-\tau)} - \left(\frac{p_0}{1+\gamma_1^0 T_2^2(t-\tau)} - \frac{q_0}{1+\gamma_2^0 T_2^2(t-\tau)}\right)\frac{\nu_0 C_2(t)}{1+\beta_0 T_1^2(t-\tau)} \\
&\quad + \left(\frac{p_0}{1+\gamma_1^0 T_2^2(t-\tau)} - \frac{q_0}{1+\gamma_2^0 T_2^2(t-\tau)}\right)\frac{\nu_0 C_1(t)}{1+\beta_0 T_1^2(t-\tau)} - \left(\frac{p_0}{1+\gamma_1^0 T_2^2(t-\tau)} - \frac{q_0}{1+\gamma_2^0 T_2^2(t-\tau)}\right)\frac{\nu_0 C_1(t)}{1+\beta_0 T_1^2(t-\tau)}| \\
&\leqslant \frac{|\nu_0|}{|1+\beta_0 T_1^2(t-\tau)|}|\left(\frac{p_0}{1+\gamma_1 T_1^2(t-\tau)} - \frac{q_0}{1+\gamma_2 T_1^2(t-\tau)}\right)C_1(t) - \left(\frac{p_0}{1+\gamma_1 T_2^2(t-\tau)} - \frac{q_0}{1+\gamma_2 T_2^2(t-\tau)}\right)C_2(t)| \\
&\quad + |\frac{p_0}{1+\gamma_1 T_2^2(t-\tau)} - \frac{q_0}{1+\gamma_2 T_2^2(t-\tau)}||\frac{\nu_0}{1+\beta_0 T_1^2(t-\tau)}C_1(t) - \frac{\nu_0}{1+\beta_0 T_2^2(t-\tau)}C_2(t)| \\
&\quad + |\frac{\nu_0}{1+\beta_0 T_1^2(t-\tau)}||\frac{p_0}{1+\gamma_1 T_2^2(t-\tau)} - \frac{q_0}{1+\gamma_2 T_2^2(t-\tau)}||C_2(t) - C_1(t)| \\
&\leqslant |\nu_0| M_1(|C_1(t) - C_2(t)| + |T_1(t-\tau) - T_2(t-\tau)|) + (|p_0| + |q_0|)M_2(|C_1(t) - C_2(t)| \\
&\quad + |T_1(t-\tau) - T_2(t-\tau)|) + |\nu_0|(|p_0| + |q_0|)(|C_1(t) - C_2(t)| + |T_1(t-\tau) - T_2(t-\tau)|) \\
&= \tilde{M}_1((|C_1(t) - C_2(t)| + |T_1(t-\tau) - T_2(t-\tau)|)),
\end{aligned}$$

where $0 < M_1, M_2 < \infty$, and $\tilde{M}_1 = \max\{|\nu_0|M_1, (|p_0| + |q_0|)M_2, |\nu_0|(|p_0| + |q_0|)\}$. It is also possible to prove that

$$|J_2| \leqslant \tilde{M}_2 \left(|C_1(t) - C_2(t)| + |T_1(t-\tau) - T_2(t-\tau)|\right),$$

Copyright © 2015 John Wiley & Sons, Ltd.

DOI: 10.1002/oca

and

$$|J_3| \leqslant \tilde{M}_3 \left(|C_1(t) - C_2(t)| + |T_1(t-\tau) - T_2(t-\tau)|\right).$$

Thus, K is uniformly Lipschitz continuous and completes the proof of the theorem. □

3. FORMULATION OF THE OPTIMAL CONTROL PROBLEM

It is important in order to minimize the number of cancer cells by using a minimal amount of drugs in the treatment. Then, we formulate the following functional

$$J(u) = \int_0^{T_f} \left\{w_1 C(t) + w_2 P(t) + w_3 T(t) + \tfrac{1}{2} w_4 u^2(t)\right\} dt. \tag{7}$$

We arrive at the optimal control problem that follows

$$\min_{u \in U_{ad}} J(u), \tag{8}$$

subject tosystem (5), where T_f is the fixed terminal time,

$$U_{ad} = \{u : 0 \leqslant u(t) \leqslant 1, \forall t \in [0, T_f], \text{and } u \text{ is Lebesgue measurable}\}.$$

Theorem 3.1
There is an optimal control, $u^* \in U_{ad}$, of the problem (8) subject to system (5).

Proof 3.1
A proof of the earlier theorem can be made by checking the following items: (i) U_{ad} is closed and convex; (ii) the integrand of $J(u)$, $L(C, P, T, u)$, is convex on u; (iii) there are constants $c_1, c_2 > 0$, and $\rho > 1$ such that $c_2 + c_1 \left(|u|^2\right)^{\rho/2} \leqslant L(C, P, T, u)$; (iv) the right-hand side of the state system is bounded by a linear function in the state and control variables; and (v) the set of controls and corresponding state variables are nonempty [13].

It is easy to prove that the properties (i)–(v) are valid. □

We have proved that there is an optimal control, u^*, of the problem (8) subject to system (5). We will derive a necessary condition for u^* by using the Pontryagin's maximum principle with delays, and in order to simplify notation, we will not write the superscripts $*$ for the optimal control, trajectory, and so on.

We begin by defining the Hamiltonian, H, as follows:

$$\begin{aligned} H(C, P, T, \lambda_1, \lambda_2, \lambda_3, u) = {} & w_1 C(t) + w_2 P(t) + w_3 T(t) + \tfrac{1}{2} w_4 u^2(t) + \lambda_1(t)\dot{C}(t) \\ & + \lambda_2(t)\dot{P}(t) + \lambda_3(t)\dot{T}(t), \end{aligned} \tag{9}$$

where λ_1, λ_2, and λ_3 are adjoint functions, which satisfy the following differential equations

$$\dot{\lambda_1}(t) = -\frac{\partial H(t)}{\partial C(t)} - \chi_{[0, T_f - \tau]}(t) \frac{\partial H(t+\tau)}{\partial C(t-\tau)}, \tag{10}$$

$$\dot{\lambda_2}(t) = -\frac{\partial H(t)}{\partial P(t)} - \chi_{[0, T_f - \tau]}(t) \frac{\partial H(t+\tau)}{\partial P(t-\tau)}, \tag{11}$$

$$\dot{\lambda_3}(t) = -\frac{\partial H(t)}{\partial T(t)} - \chi_{[0, T_f - \tau]}(t) \frac{\partial H(t+\tau)}{\partial T(t-\tau)}, \tag{12}$$

with the conditions $\lambda_1(T_f) = \lambda_2(T_f) = \lambda_3(T_f) = 0$. We use Hamiltonian (9) and system (5) to calculate the functions $\dot{\lambda_1}(t)$, $\dot{\lambda_2}(t)$, and $\dot{\lambda_3}(t)$.

Copyright © 2015 John Wiley & Sons, Ltd.

DOI: 10.1002/oca

Now, in order to characterize the optimal control, u, we use the following optimality condition [4]:

$$\frac{\partial H}{\partial u} + \chi_{[0,T_f-\tau]}(t)\frac{\partial H(t+\tau)}{\partial u(t-\tau)} = 0. \tag{13}$$

From (13), we find that the optimal control is

$$u(t) = \chi_{[0,T_f-\tau]}(t)\left(\frac{\lambda_1(t+\tau)\tilde{d}_0 C(t) + \lambda_2(t+\tau)\tilde{d}_1 P(t) + \lambda_3(t+\tau)\tilde{d}_2 T(t)}{w_4}\right).$$

At last, it is easy to prove that optimal control has the following form:

$$u(t) = \max\left\{\min\left\{\frac{\lambda_1(t+\tau)\tilde{d}_0 C(t)+\lambda_2(t+\tau)\tilde{d}_1 P(t)+\lambda_3(t+\tau)\tilde{d}_2 T(t)}{w_4}\chi_{[0,T_f-\tau]}(t), 1\right\}, 0\right\}. \tag{14}$$

Next, in the context of two numerical examples, we use the Newton method to solve (5), (10), (11), and (12) with initial and terminal conditions $(C(0), P(0), T(0)) = (C_0, P_0, T_0)$ and $\lambda_1(T_f) = \lambda_2(T_f) = \lambda_3(T_f) = 0$, respectively. Optimal control $u(t)$ is equal to the right-side hand side of (14).

4. NUMERICAL RESULTS

In this section, we discuss the numerical results of the problem (8), whose optimal control and states are found from (5), (10), (11), (12), and (14). We use the Newton method in order to solve (5)-(14) [14]. Initial conditions are given by $C(t) = C_0, P(t) = P_0, T(t) = T_0$, and $u(t) = 0$, $\forall t \in [-\tau, 0]$, where $C_0 = 10^5$, $P_0 = 0$, $T_0 = 0$, and $\tau = 2$. We also assume that $T_f = 20$, $\lambda_1(t) = \lambda_2(t) = \lambda_3(t) = 0, \forall t \in [T_f, T_f + \tau]$, $w_1 = w_2 = w_3 = 1$, and $w_4 = 10^7$. CSCs are the most resistant to chemotherapeutic drugs, then we assume that $e_0 \leqslant e_1, e_2$ [3]. Table I contains the tumor parameters.

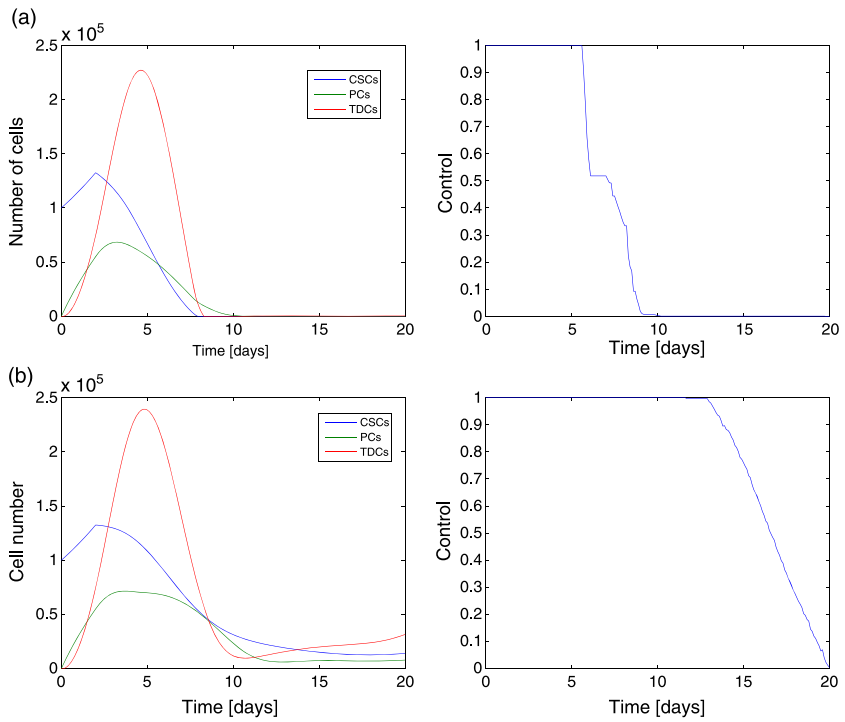

Figure 2. Optimal states and controls. In (a), $e_0 = 0.3$, $e_1 = 0.3$, and $e_2 = 0.5$. In (b), $e_0 = 0.2$, $e_1 = 0.3$, and $e_2 = 0.5$. Parameters used are listed in Table I. CSCs, cancer stem cells; PCs, progenitor cells; TDCs, terminally differentiated cells.

Copyright © 2015 John Wiley & Sons, Ltd.

DOI: 10.1002/oca

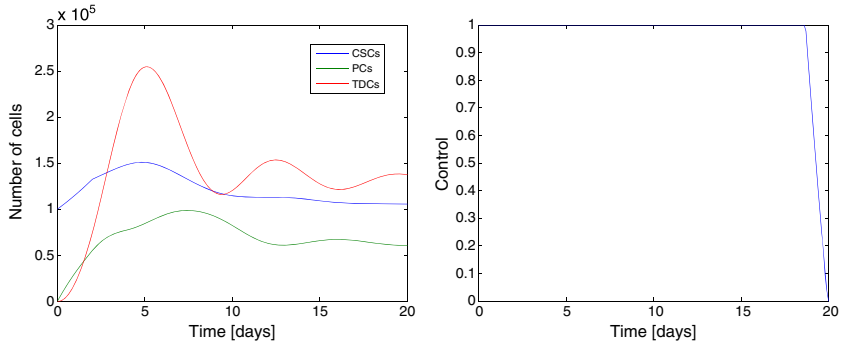

Figure 3. Optimal state and control with $e_0 = 0.1$, $e_1 = 0.3$, and $e_2 = 0.5$. Parameters used are listed in Table I. CSCs, cancer stem cells; PCs, progenitor cells; TDCs, terminally differentiated cells.

We consider the following cases: *(i)* $e_0 = 0.3$, $e_1 = 0.3$, $e_2 = 0.5$; *(ii)* $e_0 = 0.2$, $e_1 = 0.3$, $e_2 = 0.5$; and *(iii)* $e_0 = 0.1$, $e_1 = 0.3$, $e_2 = 0.5$. In each case, we have solved (4)–(14). Figures 2 and 3 show the dynamics of CSCs, PCs, and TDCs with optimal controls. It shows that the optimal therapies reduce notably cancer cells. One very interesting thing to observe is that therapies are supplied in decreasing doses.

In case *(i)*, $C(T_f) = P(T_f) = T(T_f) = 0$. This means that the disease is cured. In case *(ii)*, we assume that CSCs are more resistant than the CSCs considered in case *(i)*, therefore, the disease has not been cured, and we have $C(T_f) = 1.4160\times10^4$, $P(T_f) = 8.0161$, and $T(T_f) = 3.1632\times10^4$.

Finally, in case *(iii)*, $C(T_f) = 1.0554\times10^5$, $P(T_f) = 6.0612\times10^4$, and $T(T_f) = 1.3735\times10^5$, and therefore, although $u(t) \approx 1, \forall t \in [0, T_f]$, the disease progresses (Figure 3).

5. CONCLUSION

This paper proposes a delayed model (5) to study breast cancer stem cells growth under therapy. In subsection 2.1, we have proved that model (5) has a solution. In order to minimize the number of cancer cells and the amount of drug used over treatment, we have proposed the optimal control problem (8), and the existence of an optimal control, u^*, is proven. After, we have used the Pontryagin's maximum principle to encounter an explicit expression of the optimal therapy. Finally, we have presented three numerical examples and Table I shows the parameters used into the model. All of the examples show that the optimal therapies are supplied in decreasing doses.

APPENDIX A: EQUILIBRIUM POINTS AND STABILITY OF SYSTEM (4)

We begin by observing that there are only three possible equilibrium points of system (4). They have the following form: *(i)* $x^* = (x_1^*, x_2^*, x_3^*)$, where $x_1^* = x_2^* = x_3^* = 0$; *(ii)* $y^* = (y_1^*, y_2^*, y_3^*)$, where $y_1^* \neq 0$, $y_2^* \neq 0$ and $y_3^* \neq 0$; and *(iii)* $z^* = (z_1^*, z_2^*, z_3^*)$, where $z_1^* = 0$, $z_2^* \neq 0$ and $z_3^* \neq 0$. It is clear that y^* and z^* depend on the parameters of system (4). Therefore, finding an analytic expression to y^* and z^* involves a lengthy and cumbersome process. For example, in order to find an analytic expression to y^*, we should solve the following nonlinear system:

$$\begin{cases} \left(\frac{p_0}{1+\gamma_1^0 y_3^2} - \frac{q_0}{1+\gamma_2^0 y_3^2}\right)\frac{v_0 y_1}{1+\beta_0 y_3^2} - d_0 y_1 = 0 \\ \left(1 - \frac{p_0}{1+\gamma_1^0 y_3^2} + \frac{q_0}{1+\gamma_2^0 y_3^2}\right)\frac{v_0 y_1}{1+\beta_0 y_3^2} + \left(\frac{p_1}{1+\gamma_1^1 y_3} - \frac{q_1}{1+\gamma_2^1 y_3}\right)\frac{v_1 y_2}{1+\beta_1 y_3} - d_1 y_2 = 0 \\ \left(1 - \frac{p_1}{1+\gamma_1^1 y_3} + \frac{q_1}{1+\gamma_2^1 y_3}\right)\frac{v_1 y_2}{1+\beta_1 y_3} - d_2 y_3 = 0. \end{cases}$$

Copyright © 2015 John Wiley & Sons, Ltd.

DOI: 10.1002/oca

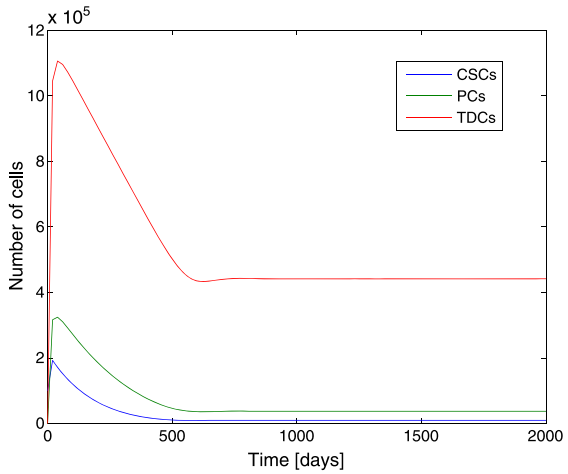

Figure A.4. Evolution of the system for a period of 2000 days. The system is stabilized in $y^* = (5.4920 \times 10^3, 3.9198 \times 10^4, 4.4160 \times 10^5)$. Parameters used are listed in Table I. CSCs, cancer stem cells; PCs, progenitor cells; TDCs, terminally differentiated cells.

From the first equation, in order to find y_3, we should solve the following cubic equation:

$$u^3 + au^2 + bu + c = 0,$$

where

$$a = \frac{\nu_0}{d_0\gamma_1^0\gamma_2^0\beta_0}\left(\frac{d_0\gamma_1^0\gamma_2^0}{\nu_0} + \frac{d_0\gamma_2^0\beta_0}{\nu_0} + \frac{d_0\gamma_1^0\beta_0}{\nu_0}\right),$$

$$b = \frac{\nu_0}{d_0\gamma_1^0\gamma_2^0\beta_0}\left(\frac{d_0\gamma_2^0}{\nu_0} + \frac{d_0\gamma_1^0}{\nu_0} + \frac{d_0\beta_0}{\nu_0} - p_0\gamma_2^0 + q_0\gamma_1^0\right),$$

$$c = \frac{\nu_0}{d_0\gamma_1^0\gamma_2^0\beta_0}\left(\frac{d_0}{\nu_0} + q_0 - p_0\right),$$

and $u = y_3^2$. Then, we must use Cardano's rule to find u. Next, we may find $y_3 = \sqrt{u}$ as a function of parameters of system (4). Variables y_1 and y_2 are encountered from the other equations. It is an evident that it is a very complex task.

Rather, considering the parameters of Table I, we found numerical approximations of y^* and z^*. Values obtained are the following:

$$y^* = \begin{pmatrix} 5.4920 \times 10^3 \\ 3.9198 \times 10^4 \\ 4.4160 \times 10^5 \end{pmatrix}$$

and

$$z^* = \begin{pmatrix} 0 \\ 5.7375 \times 10^3 \\ 1.0687 \times 10^5 \end{pmatrix}.$$

Initial conditions determine the point equilibrium towards which the system tends. Figure A.4 is an extension of Figure 1 and shows that with parameters of Table I and initial conditions such as the ones listed earlier, the equilibrium point of system (4) is exactly y^*.

Copyright © 2015 John Wiley & Sons, Ltd.

DOI: 10.1002/oca

Let us now study the type of stability of y^*. So we consider the nonlinear functional differential equation

$$\dot{x}(t) = F(x(t), x(t-\tau)), \tag{15}$$

where $F : D \times D \longrightarrow \mathbb{R}^n$ is continuously differentiable and $D \subset \mathbb{R}^n$ is open. If $F(x_0, x_0) = 0$ for some $x_0 \in D$, then $x(t) = x_0$, $t \in \mathbb{R}$ is an equilibrium solution of (15). The linearized system about x_0 for (15) is

$$\dot{x}(t) = Ax(t) + Bx(t-\tau), \tag{16}$$

where $A = f_{xx}(x_0, x_0)$ and $B = f_{yy}(x_0, x_0)$.

There is a theorem according to which if $\Delta(\lambda)$ denotes the characteristic equation corresponding to system (16) and suppose that

$$-\sigma = \max_{\Delta(\lambda)=0} \Re(\lambda) < 0,$$

then x_0 is a locally asymptotically stable steady state of (15) [12].

In the context of system (4), with parameters of Table I, we found that $-\sigma = -0.5110 < 0$. Now, applying previous theorem, numerical results suggest that y^* could be a locally asymptotically stable steady state of (4).

Let $N(t) \doteq C(t) + P(t) + T(t)$ and $y_{max} \doteq \max_{t\in[0,\infty]} N(t)$. The system tends to y^*, where $y_1^* + y_2^* + y_3^* < y_{max}$, but first, the system reaches the maximum y_{max} (Figure A.4). Now, there is an umbral $y_d < y_{max}$ (it is possible that $y_d < y_1^* + y_2^* + y_3^*$), which the total cancer cells must not exceed. This is because if $N(t) > y_d$, the patient's life is at risk. If therapy is performed, then it is expected that $N(t) < y_d$.

REFERENCES

1. Al-Hajj M, Wicha M, Hernández B, Morrison A, Clarke M. Prospective identification of tumorigenic breast cancer cells. *Proceedings of the National Academy of Sciences of the United States of America* 2003; **100**(7):3983–3988.
2. Lliopoulus D, Hirsch H, Wang G, Struhl K. Inducible formation of breast cancer stem cells and their dynamic equilibrium with non-stem cancer cells via II6 secretion. *Proceedings of the National Academy of Sciences of the United States of America* 2011; **108**(4):1397–1402.
3. Liu X, Johnson S, Liu S, Kanojia D, Yue W, Singh U, Wang Q, Wang Q, Nie Q, Chen H. Nonlinear growth kinetics of breast cancer stem cells: implications for cancer stem cell targeted therapy. *Scientific Reports* 2013; **3**(2473):1–9.
4. Göllmann L, Kern D, Maurer H. Optimal control problems with delays in state and control variables subject to mixed control-state constraints. *Optimal Control Applications and Methods* 2008; **30**(4):1–25.
5. Hattaf K, Yousfi N. Optimal control of a delayed HIV infection model with immune response using an efficient numerical method. *ISRN Biomathematics* 2012; **30**(5402):1–7.
6. Laarabi H, Rachik M, El Kahlaoui O, Labriji E. Optimal vaccination strategies of an SIR epidemic model with a saturated treatment. *Universal Journal of Applied Mathematics* 2013; **1**(3):185–191.
7. Mohamed E, Rachik M, Benlahmar E. Optimal control of an SIR model with delay in state and control variables. *Hindawi Publishing Corporation ISRN Biomathematics* 2013; **2013**:1–7.
8. Pathak S, Maiti A, Samanta G. Rich dynamics of an SIR epidemic model. *Nonlinear Analysis: Modelling and Control* 2010; **15**(1):71–81.
9. Sadiq SF, Khan MA, Islam S, Zaman G, Jung IH, Khan SA. Optimal control of an epidemic model of leptospirosis with nonlinear saturated incidences. *Annual Review and Research in Biology* 2014; **4**(3):560–576.
10. Bellen A, Zennaro M. *Numerical Methods for Delay Differential Equations*. Clarendon Press: Oxford, 2005.
11. Shampine L, Thompson S. Solving DDEs in matlab. *Applied Numerical Mathematics* 2001; **37**(4):441–458.
12. Smith H. *An Introduction to Delay Differential Equations with Applications to the Life Sciences*. Springer: New York, 2011.
13. Fleming W, Rishel R. Deterministic and stochastic optimal control. *Bulletin of the American Mathematical Society* 1976; **82**:869–870.
14. Grüne L. Numerical methods for nonlinear optimal control problems, Mathematical Institute, University of Bayreuth, 95440 Bayreuth, Germany, 2012; 1–15.

Copyright © 2015 John Wiley & Sons, Ltd.

DOI: 10.1002/oca