A Model of Vascular Tumor Response to Chemotherapy Combined with Anti-Angiogenic Therapy

S. T. R. Pinho [a,*] F. S. Bacelar [b] R. F. S. Andrade [a]
H. I. Freedman [c]

[a] *Instituto de Física, Universidade Federal da Bahia, 40210-340, Salvador, Brazil*

[b] *IFISC(CSIC-UIB) Instituto de física Interdisicplinar y Sistemas Complejos, Campus Universitat Illes Balears, E-07122 Palma de Mallorca, Spain*

[c] *Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2G1*

Abstract

Angiogenesis is acknowledged as an essential mechanism for tumor spreading and metastasis of neoplastic diseases. Consequently, anti-angiogenic therapy has been proposed as a complementary or perhaps an alternative strategy to the traditional cytotoxic therapies. This work considers a model of ordinary differential equations that describe the dynamics of tumors at the vascular stage (after the angiogenic process has been triggered), under the action of chemical and anti-angiogenic therapies. Due to the increase of endothelial cells at the vascular stage, the cancer state prevails over the internal state in the no treatment situation. Results from the local stability analysis and numerical integration, indicate that the combination of chemotherapy and anti-angiogenic therapy is the best strategy to eliminate the tumor, reducing the cytotoxic effect. At a fixed infusion rate, the cure state may be reached when the combined therapy is considered but not for the anti-angiogenic therapy only. On the other hand, pure chemotherapy effectively destroys the tumor, but only when higher infusion doses are applied.

Key words: differential equations, cancer therapy

* Corresponding author: Instituto de Física, Universidade Federal da Bahia, Campus Universitário de Ondina, 40210-340, Salvador, Brazil, Tel: + 5571 32836658; fax: + 5571 32357730.

Email addresses: suani@ufba.br (S. T. R. Pinho), florabacelar@ifisc.uib-csic.es (F. S. Bacelar), randrade@ufba.br (R. F. S. Andrade), hfreedma@math.ualberta.ca (H. I. Freedman).

1 INTRODUCTION

Neoplastic diseases are responsible for 12% of deaths around the world. They constitute a most important issue in public health and puzzle the researchers of several disciplines with ever new and intriguing challenges. A malignant tumor corresponds to an assembly of ill-functioning cells. They suffer the lack of internal control that characterizes the normal cells of the tissues where they grow. They also lose the ability to perform tissue specific tasks, proliferate much faster than the normal cells, and finally provide mechanisms for their own reproduction. This includes metastatic activities and the development of specific irrigation vessels to warrant themselves the necessary nutrients for their rapid growth (Evans, 1991; Sherbet, 1982). Since the last decades of the 20th century, this last mechanism (usually called tumor angiogenesis) is pointed out as essential for spreading and metastasis of solid tumors (Folkman, 1971; Alberts et al., 2002). As a consequence, the anti-angiogenic therapy, which is much less drug resistant than chemotherapy (Hanahan and Folkman, 1996) has been proposed as an alternative, rather complementary than isolated, to the conventional therapies. Anti-angiogenic therapy may be particularly efficient for solid tumors that grow slowly (Beecken et al., 2001). Up to now, it has been applied both to malignant tumors (colon, metastatic kidney, metastatic colorectal) and benign tumors (hemangiomas). In the case of colorectal tumors, it is expressly recommended in association with chemotherapy (O'Dwyer, 2006).

The angiogenic process corresponds to the formation of new blood vessels (from a previous vascularization) due to the proliferation, migration and differentiation of endothelial cells (EC's) that revest the blood vessels. That process occurs during embriogenesis and tissue reparation, but the number of EC's can also be enhanced due to the emergence of some diseases like solid tumors, when new vessels are created to supply the tumors with oxygen and nutrients (Birkfalvi, 1995). After the tumor reaches 1-2 mm (pre-vascular stage), the cancer cells (CC's) induce a synthesis of several substances, generally called Tumor Angiogenic Factors (TAF). This includes the family of vascular endothelial growth factor (VEGF-A to VEGF-E), that stimulate the proliferation of new EC's (Bussolino et al., 2003). They also produce smaller amounts of inihibtors (TIF), as the protein TP53, thrombospondin, endostatin, and angiostin, all of which can regulate the density of EC's (Bussolino et al., 2003; Reilly et al., 1997), (Wodarz and Komarova, 2005). Some experiments show that the growth of EC's does not depend on the normal cells (Alberts et al., 2002). In general, the natural growth rate of EC's is much smaller than its growth due to the presence of a tumor (Alberts et al., 2002). The net result of TAF and TIF is proportional to the tumor size (Maggelakis, 1996).

The term angiogenesis has been traditionally used for the mechanism by which local EC's give rise to new EC's that build more blood cells. More recently, another mechanism, referred to as vasculogenesis, has been suggested (Wodarz et. al., 2005): TAF induces a circulating population of endothelial progenitor cells which migrate to the neighborhood of the tumor, and build new blood vessels locally. For both mechanisms, angiogenesis and vasculogenesis, the essential feature is the increasing of the number of EC's due to the tumor.

Folkman and collaborators (Folkman, 1971; Hahnfeldt et al., 1999; Hahnfeldt et al., 2003) focused their research on anti-angiogenic therapy. The anti-angiogenic drugs act on EC's instead of on CC's. This therapy is little drug resistant because EC's are genetically stable. Besides the reduction of EC's, the anti-angiogenic drugs also normalize the vascularization (Jain, 2001), optimizing the chemotherapy action. It is well known that vascularization is necessary for the flow of the chemotherapy drug, but it can not be so dense as to provide resistance to the flow (Kerbel et al. 2007). Nowadays some physicians accept that treating both CC's and EC's in a tumor may be more effective than treating CC's alone (Bussolino et al. 2003; Hanahan, 1998).

The understanding of angiogenic dynamics (Hanfeldt et al., 1999) is fundamental for both an accurate description of tumor growth at the vascular stage and for modelling therapies with the purpose of identifying the best treatment strategy. In this sense, a large number of continuous (Liu and Freedman, 2005) and discrete (Sansone et al., 2001; Scalerandi et al., 2001) models have been proposed to describe the essential aspects of cancer dynamics at the vascular stage, where the angiogenic process is taken into account. Most of the continuous models are based on reaction-diffusion partial differential equations (for a review, see Anderson and Chaplain, 1998, and a collection of papers by several authors in a book edited by Preziosi, 2003). However, models based on ordinary differential equations (ODE) may capture the therapy response (Magni et al., 2006), that is overlooked by other models, because it is simpler to make an optimization analysis of the therapy dose (Martin and Teo, 1994). Indeed Sachs (2001) argues that *'The simplest ODE models form the foundations of applied biological modelling in practice'*.

In a previous work (Pinho et al., 2002), some of us proposed a time delayed chemotherapy model of metastatic tumor but did not discuss the angiogenic process explicitly. In this work, we advance those previous investigations by considering the vascular stage of the tumor and by explicitly modelling the angiogenesis process, and by including the anti-angiogenic therapy in the former chemotherapy model. To this purpose, we add a new variable representing the quantity of new EC's, produced by the presence of TAF and TIF, to the previous model of competing CC's and normal cells (NC's). As in the previous model, it is reasonable to suppose that CC's win the competition against NC's for the no treatment situation (Pinho et al., 2002). At this point,

our main goal is to compare the isolated chemotherapy effect with the combined (chemo+anti-angiogenic) therapies in one single tissue, neglecting any metastatic effect.

In a recent paper (Nagy, 2004) the angiogenic process and the competition with normal cells were taken into account in a ODE model where, as in our model, there is an endothelial cell compartment. In another ODE model (Magni et al., 2006), the drug effect has been analysed. Our model has the advantage of including altogether the competition with normal cells, the angiogenic process and more than one kind of therapy (chemotherapy and anti-angiogenic therapy). Of course the assumptions of our model do not replace the role of spatial structure, but it helps to describe some features as the control action of the anti-angiogenic therapy (Hanfeldt et al. 2003), and the success of the combined therapy strategy as in the case of colorectal tumors.

This paper is organized as follows. In Section 2, we introduce the model; in Section 3, we discuss the cancer hypothesis at the vascular stage; the main analytical and numerical results are shown in Section 4 for the combined (C+A) therapy model and, as a particular case, the chemotherapy model. Finally, in Section 5, we present our conclusions and some perspectives.

2 THE MODEL

The ODE model we propose to describe the cancer dynamics at the vascular stage includes the features considered in Pinho et al., 2002. To its basic structure we add three relevant features concerning the angiogenic process and the anti-angiogenic therapy action.

a) The endothelial compartment

We consider an EC compartment that depends on the tumor size (Sachs, 2001), since its number is associated with the net result of TAF and TIF. Based on the experimental observation that the natural growth rate of EC's on mice varies from months (liver) to years (brain) (Alberts et al., 1002), we consider that the natural birth rate of EC's is much smaller than its growth due to tumor angiogenesis (Sachs et al., 2001). The endothelial cells, which are responsible for the neo-vascularization, also helps the chemotherapy action whose flow depends strongly on the vascular system.

b) Dynamical carrying capacity

In Hanfeldt et al., 1999, the concept of a dynamical carrying capacity was

introduced to describe the feedback mechanism of angiogenesis: '... *a tumor regulates associated vascular growth or suppression, and the tumor vasculature in turn controls tumor growth through its usual nutritive functions*'. Since the tumor vasculature may be associated with the increase of EC's, we consider that its amount increases the carrying capacity of CC's K_2 by a term $\gamma z(t)$.

c) Action of anti-angiogenic drugs

The action of anti-angiogenic drugs reducing the amount of EC's is included into our model, as well as their additional action in helping the action of chemical drugs, which eventually normalize the vascularization. In the extreme situation, very high vascularization makes it more difficult for the chemical drugs to flow.

Let us first consider the no-therapy situation. The assumptions of the no-therapy model are: that both NC's and CC's exhibit logistic natural growth rates; NC's and CC's compete for available resources; new EC's, beyond the usual basal level, are regulated by the increase of TAF and the decrease of TIF produced by CC's as well as by a much slower death rate. Assuming the variables $x_1(t)$, $x_2(t)$ and $z(t)$ to represent the amount of the NC's, CC's and EC's at time t, we obtain the following model formed by three differential equations:

$$
\begin{aligned}
\dot{x}_1(t) &= \alpha_1 x_1(t) \left[1 - \frac{x_1(t)}{K_1} \right] - q_1\, x_1(t)\, x_2(t), \\
\dot{x}_2(t) &= \alpha_2 x_2(t) \left[1 - \frac{x_2(t)}{(K_2 + \gamma\, z(t))} \right] - q_2\, x_1(t)\, x_2(t), \\
\dot{z}(t) &= \beta\, x_2(t) + \alpha_3\, z(t) \left[1 - \frac{z(t)}{K_3} \right],
\end{aligned}
$$

$$\tag{1}$$

where all variables are non-negative for all $t \geq 0$. The initial conditions are such that $z(t = 0)) = 0$ and $x_1(t = 0) > x_2(t = 0) \geq 0$. The pre-vascular stage is recovered when $z = 0$.

All parameters are positive. They are defined as follows:

α_i, $i = 1, 2, 3$, the natural birth rates of the NC's, CC's, and EC's;
K_i, $i = 1, 2$, the respective carrying capacities;
q_i, $i = 1, 2$, the competition coefficients between x_1 and x_2;
β, the birth rate of new EC's due to an increase of TAF and a decrease of TIF;

γ, the proportion of EC's that contributes to neo-vascularization.

To obtain the therapy models, we add to system [1] variables to describe the amount of chemical and anti-angiogenic agents respectively. While the chemotherapeutic agent acts as a predator on both CC's and NC's with different intensities, the anti-angiogenic therapeutic agent acts on EC's only. As in (Pinho et al., 2002), we consider that both chemical and anti-angiogenic therapies are continuously injected into the individual. Although the periodic injection is more realistic, the continuous treatment at shorter intervals may avoid the regrowth of tumor cells due to the angiogenic process (Browder et al., 2001). We may assume that EC's are less drug resistant than the CC's (Browder et al., 2001). The effective quantity of drug decreases due to its action on the cells and also because of the washout rate for both therapies. According to these features, the efficiency of the chemotherapy depends both on the vascularization (EC's) and on its normalization (anti-angiogenic therapy). Finally, we consider that chemical and anti-angiogenic therapies are applied simultaneously (Reilly et al., 1997). Defining the variables $y(t)$ and $w(t)$ as the amount of chemical and anti-angiogenic agents at time t, the combined CA-model is given by:

$$
\begin{aligned}
\dot{x}_1(t) &= \alpha_1 x_1(t) \left[1 - \frac{x_1(t)}{K_1} \right] - q_1 x_1(t) x_2(t) - p_1(z(t), w(t)) \frac{x_1(t) y(t)}{a_1 + x_1(t)}, \\
\dot{x}_2(t) &= \alpha_2 x_2(t) \left[1 - \frac{x_2(t)}{K_2 + \gamma\, z(t)} \right] - q_2 x_1(t) x_2(t) - p_2(z(t), w(t)) \frac{x_2(t) y(t)}{a_2 + x_2(t)}, \\
\dot{z}(t) &= \beta\, x_2(t) + \alpha_3\, z(t) \left[1 - \frac{z(t)}{K_3} \right] - \frac{p_3\, z(t)\, w(t)}{a_3 + z(t)}, \\
\dot{y}(t) &= \Delta - \left[\xi + d_1(z(t), w(t)) \frac{x_1(t)}{a_1 + x_1(t)} + d_2(z(t), w(t)) \frac{x_2(t)}{a_2 + x_2(t)} \right] y(t), \\
\dot{w}(t) &= \Phi - \left[\eta + \frac{d_3 z(t)}{a_3 + z(t)} \right] w(t).
\end{aligned}
$$

$$(2)$$

where

$$
\begin{aligned}
p_i(z(t), w(t)) &= p_{i0} + \frac{p_{i1} z(t)}{b_1 + z(t)} + \frac{p_{i2} w(t)}{b_2 + w(t)} \\
d_i(z(t), w(t)) &= d_{i0} - \frac{d_{i1} z(t)}{c_1 + z(t)} - \frac{d_{i2} w(t)}{c_2 + w(t)}
\end{aligned}
$$

$$(3)$$

and $d_{i0} - d_{i1} - d_{i2} > 0$, with i=1,2.

As in the former no-therapy model, all variables are non-negative for all $t \geq 0$ and the initial conditions are the same as in system (1) with $y(t = 0) \geq 0$ and $w(t = 0) \geq 0$.

All additional parameters, listed below, are also positive:

- $p_{i,0}$, $i = 1, 2, 3$, the predation coefficients of y on NC's, CC's, and $EC's$ respectively;
- $p_{i,1}$, $i = 1, 2$, the rates of the neo-vascularization which aid chemotherapy action on x_i;
- $p_{i,2}$, $i = 1, 2$, the rates of the anti-angiogenic which aid chemotherapy action on x_i;
- a_i, $i = 1, 2, 3$, a saturation parameter to describe this effect on the predation action on z and x_j, $j = 1, 2$;
- $d_{i,0}$, $i = 1, 2, 3$, rates of the agents that act, respectively, on NC's, CC's, and EC's. Hence they are proportional to p_i, $i = 0, 1, 2$;
- $d_{i,1}$, $i = 1, 2$, the rates of the neo-vascularization which aid the chemotherapy agent due to interaction with x_i;
- $d_{i,2}$, $i = 1, 2$, the rates of the anti-angiogenic which aid the chemotherapy agent due to interaction with x_i;
- b_i, $i = 1, 2$, a saturation parameter to describe this effect on the cells of the neo-vascularization and anti-angiogenic actions, respectively, on chemotherapy action;
- c_i, $i = 1, 2$, a saturation parameter to describe this effect on the agent of the neo-vascularization and anti-angiogenic actions on the chemotherapy agent, respectively;
- Δ, the continuous infusion rate of the chemical agent;
- ξ, the washout rate of the chemical agent;
- Φ, the continuous infusion rate of the anti-angiogenic agent;
- η, the washout rate of the anti-angiogenic agent.

As in the model introduced in Pinho et al., 2002, we also impose certain restrictions on the parameter values. CC's grow at a faster rate than NC's ($\alpha_2 > \alpha_1$); the chemical agent must be considerably more effective in killing CC's than NC's ($p_2 > p_1$) (Dorr and Von Hoff, 1994; Silver et al., 1987). The birth rate of EC's due to the tumor is much larger than its natural death rate ($\beta \gg \alpha_3$). In addition, there are other inequalities related to competitive outcome, which we list in the next section as they depend on the equilibria of system (1).

Single therapy situations can be handled as particular cases of system 2. We can obtain a chemotherapy model (C-model), by imposing $w \equiv 0$ and eliminating the last equation of system (2). If $z \equiv 0$ in system (2), we recover the non-metastatic version of the model introduced in Pinho et al.(2002). Proceeding along the same lines, an anti-angiogenic (A-model) is obtained from

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(2) by setting $y \equiv 0$ and eliminating the fourth equation of (2).

2.1 Boundedness and Dissipativity

In this subsection we establish two important properties of the solutions to system (2):

1. All solutions with positive values remain positive.

Proof.   Arguing uniqueness of solutions, no solution with $x_1(t) > 0$ at any time $t \geq 0$ can become zero in finite time since $x_1 \equiv 0$ is a solution of the first equation of (2). Similarly the same is true for $x_2(t)$. Since $\dot{y}(0) = \Delta > 0$, no solution $y(t)$ of (2) with $y(t) > 0$ can become zero. Similarly, since $\dot{w}(0) = \Phi > 0$, no solution $w(t)$ of (2) with $w(t) > 0$ can become zero. Finally, since $x_2 \equiv 0$ is a solution of the first equation of (2), $\dot{z}(0) = \beta x_2(0) = 0$.   □

2. System (2) is dissipative.

Proof.   Since the initial conditions are nonnegative, so are the solutions. From the first equation (2), it follows that

$$\dot{x}_1(t) \leq \alpha_1 x_1(t) \left(1 - \frac{x_1(t)}{K_1} \right).$$

From standard comparison theory we get

$$\limsup_{t \to \infty} x_1(t) \leq K_1.$$

Since $d_{i0} - d_{i1} - d_{i2} > 0$, $b_i > 0$, and $c_i > 0$, with i=1,2, we obtain from the fourth equation of (2):

$$\dot{y}(t) \leq \Delta - \xi y,$$

what implies

$$\limsup_{t \to \infty} y(t) \leq \frac{\Delta}{\xi}.$$

Similarly, from the fifth equation of (2),

$$\limsup_{t \to \infty} w(t) \leq \frac{\Phi}{\eta}.$$

After some calculations, the third equation of (2) leads to:

$$\limsup_{t \to \infty} z(t) \leq M_1,$$

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where

$$M_1 = \frac{K_3}{2}\left(1 + \frac{\gamma\beta}{\alpha_3}\right) + \frac{1}{2}\sqrt{K_3^2\left(1 + \frac{\beta\gamma}{\alpha_3}\right)^2 + \frac{4\beta K_2 K_3}{\alpha_3}}.$$

From the second equation of (2),

$$\limsup_{t\to\infty} x_2(t) \le K_2 + \gamma M_1.$$

Hence the region

$\mathcal{R} = \{(x_1, x_2, z, y, w) \in \mathbf{R}_+^5 \ / \ 0 \le x_1 \le K_1,\ 0 \le x_2 \le K_2 + \gamma M_1,\ 0 \le y \le \xi^{-1}\Delta,\ 0 \le z \le M_1,\ 0 \le w \le \eta^{-1}\Phi\}$ is an attracting invariant region, proving the property. $\qquad\square$

3 CANCER HYPOTHESIS

We assume the cancer hypothesis based on the local stability of the equilibria of system (1), with the same approach considered in Nani and Freedman (2000) and Pinho et al. (2002): without any therapy, CC's win the competition with NC's.

The equilibria of system (1) are:

$V_0 = (0,0,0), V_{10} = (K_1,0,0), V_1 = (K_1,0,K_3), V_2 = (0, K_2+\gamma\tilde{z}, \tilde{z}), V_3 = (x_1^*, x_2^*, z^*)$

with

$$\tilde{z} = \frac{\beta\gamma K_3 + \alpha_3 K_3 + \sqrt{(\beta\gamma K_3 + \alpha_3 K_3)^2 + 4\beta K_2 K_3 \alpha_3}}{2\alpha_3}\ . \tag{4}$$

The coordinates x_1^* and x_2^* of V_3 are given by

$$x_1^* = \frac{\alpha_2\left(-\alpha_3 z^{*2} + \beta\gamma K_3 z^* + K_3\alpha_3 z^* + \beta K_2 K_3\right)}{\beta\left(z^*\gamma + K_2\right)K_3 q_2},$$
$$x_2^* = \frac{z^*\left(z^* - K_3\right)\alpha_3}{\beta K_3},$$
$$\tag{5}$$

where z^* is any real solution of the cubic equation :

$$D_3 z^{*3} + D_2 z^{*2} + D_1 z^* + D_0 = 0 \tag{6}$$

with

$$D_3 = \alpha_3 \, q_1 \, q_2 \, K_1 \, \gamma$$
$$D_2 = \alpha_3 \, (K_1 \, K_2 \, q_1 \, q_2 + \alpha_1 \, \alpha_2) + K_3 \, \alpha_3 \, q_1 \, q_2 \, K_1 \, \gamma$$
$$D_1 = -K_3 \, \alpha_3 \, (K_1 \, K_2 \, q_1 \, q_2 + \alpha_1 \, \alpha_2) - \beta \, \gamma K_3 \, \alpha_1 \, K_2 \, (K_1 \, q_2 - \alpha_2)$$
$$D_0 = \beta \, K_3 \, \alpha_1 \, K_2 \, (-K_1 \, q_2 + \alpha_2).$$

$$(7)$$

In terms of equilibria, the cancer hypothesis is verified if the system evolves to V_2.

The Jacobian matrix for a generic equilibrium $V(\bar{x}_1, \bar{x}_2, \bar{z})$ is given by:

$$
\mathcal{J}_V = \begin{pmatrix} J_{11} & -q_1 \bar{x}_1 & 0 \\ -q_2 \bar{x}_2 & J_{22} & J_{23} \\ 0 & \beta & J_{33} \end{pmatrix},
\tag{8}
$$

with

$$J_{11} = \alpha_1 \left(1 - 2\bar{x}_1/K_1\right) - q_1 \bar{x}_2, \qquad J_{22} = \alpha_2 \left[1 - 2\bar{x}_2/(K_2 + \gamma \bar{z})\right] - q_2 \bar{x}_1$$

$$J_{23} = \gamma \alpha_2 \bar{x}_2^2/(K_2 + \gamma \bar{z})^2, \qquad J_{33} = \alpha_3 \left(1 - 2\bar{z}/K_3\right).$$

The local stability analysis of boundary equilibria leads to the following eigenvalues $(\lambda_1, \lambda_2, \lambda_3)$ associated with the corresponding equilibria:

$$V_0 : (\alpha_1, \alpha_2, \alpha_3)$$

$$V_{10} : (-\alpha_1, \alpha_2 - q_2 K_1, \alpha_3)$$
$$V_1 : (-\alpha_1, \alpha_2 - q_2 K_1, -\alpha_3)$$

Hence V_0 and V_{10} are locally unstable, while V_1 is locally unstable when $\alpha_2 > K_1 q_2$.

The first eigenvalue of V_2 is expressed by

$$\lambda_1 = \alpha_1 - K_2 q_1 - \frac{\beta K_3 q_1 \gamma^2}{2\alpha_3} - \frac{K_3 q_1 \gamma}{2} - \frac{q_1 \sqrt{K_3^2(\beta \gamma + \alpha_3)^2 + 4\beta K_2 K_3 \alpha_3 \gamma}}{2\alpha_3} \tag{9}$$

The other two eigenvalues of V_2 constitute the set

$$\sigma(\mathcal{B}_V) = \{\lambda_i \mid \lambda_i^2 - Tr(\mathcal{B}_V)\lambda + \det(\mathcal{B}_V) = 0, \ i = 2,3\} \tag{10}$$

where

$$\mathcal{B}_V = \begin{pmatrix} -\alpha_2 & \gamma\alpha_2 \\ \beta & \alpha_3 \left(1 - 2\tilde{z}/K_3\right) \end{pmatrix}, \tag{11}$$

According to (4), we have $\tilde{z} > K_3/2$. Therefore

$$Tr(\mathcal{B}_V) = -\alpha_2 + \alpha_3 \left(1 - \frac{2\tilde{z}}{K_3}\right) < 0$$

and

$$\det(\mathcal{B}_V) = -\alpha_2\alpha_3 \left(1 - \frac{2\tilde{z}}{K_3}\right) - \beta\gamma\alpha_2$$
$$= \frac{\alpha_2\sqrt{(\beta\gamma K_3 + \alpha_3 K_3)^2 + 4\beta K_2 K_3 \alpha_3}}{K_3} > 0.$$

Therefore, by the Routh-Hurwitz criterion (Coppel, 1965), the real parts of eigenvalues λ_2 and λ_3 are negative.

We conclude that the conditions

$$\alpha_2 > K_1 \tag{12}$$

and

$$\alpha_1 < K_2 q_1 + \frac{\beta K_3 q_1 \gamma^2}{2\alpha_3} + \frac{K_3 q_1 \gamma}{2} + \frac{q_1 \sqrt{K_3^2 (\beta\gamma + \alpha_3)^2 + 4\beta K_2 K_3 \alpha_3}\gamma}{2\alpha_3} \tag{13}$$

guarantee the cancer hypothesis. If inequality (13) holds, it follows that $D_0 < 0$ as expressed in (7). Since $D_3 > 0$ always, the interior solution V_3 does not exist in the positive cone. In conclusion, this proves the following theorem.

Theorem 1 *Conditions (12) and (13) guarantee the cancer hypothesis: V_2 is asymptotically stable, V_1 is locally unstable and V_3 does not exist in the positive cone.*
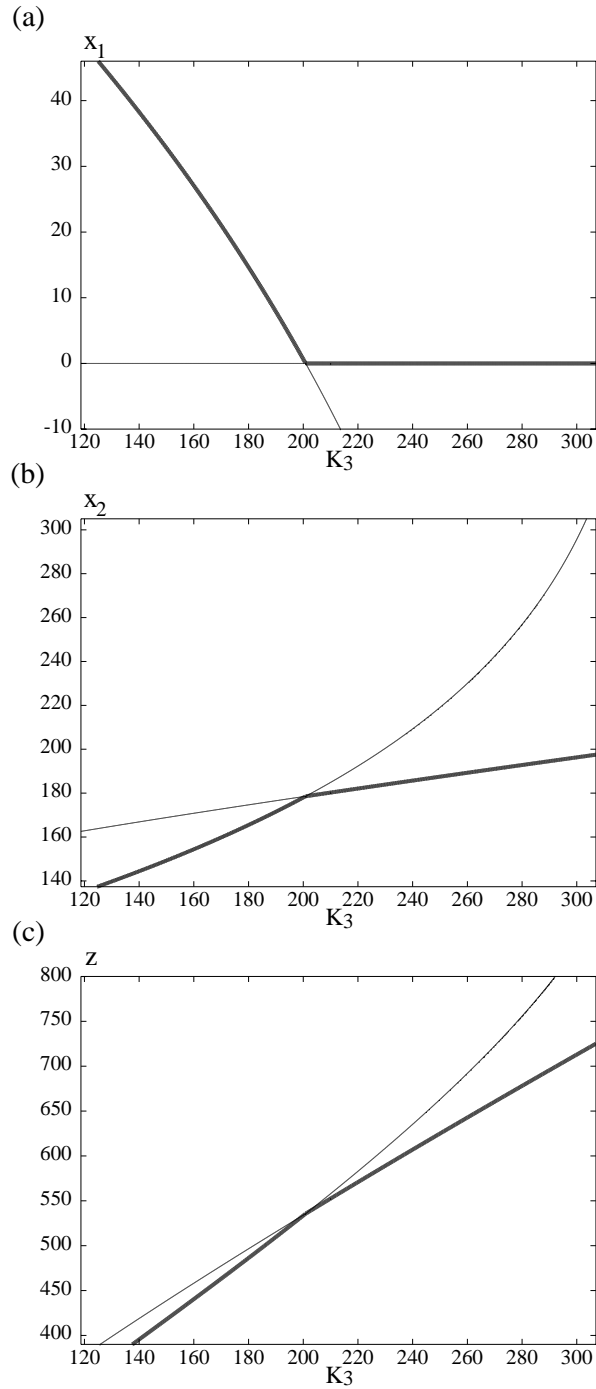
(a)

(b)

(c)

Fig. 1. Bifurcation analysis of the no-therapy model with respect to the parameter K_3. The parameter values are shown in Table 1, except for the value of K_3. The transcritical bifurcation occurs at $K_3^\star = 200.893$. The bifurcation diagram for NC's, CC's and, EC's are represented by (a), (b) and (c) respectively.

Condition (13) sets up the threshold value of K_3 for the existence and stability of the internal solution. In this case, there is a transcritical bifurcation between

the internal state V_3 and the cancer state V_2 at

$$K_3^\star = \frac{(K_2 q_1 - \alpha_1)^2 \alpha_3}{\gamma q_1 \left[\beta \gamma \alpha_1 + \alpha_3(\alpha_1 - K_2 q_1)\right]}.$$
(14)

Table 1
Parameters of the no-therapy model

NC's natural birth rate	α_1	15
CC's natural birth rate	α_1	25
EC's natural birth rate	α_3	10
NC's carrying capacity	k_1	200
CC's carrying capacity	k_2	125
EC's carrying capacity	k_3	210
competition coefficients for NC's	q_1	0.084
competition coefficients for CC's	q_2	0.08
neo-vascularization parameter	γ	0.1
rate of TAF and TIF production	β	50

In Figure 1, we show a transcritical bifurcation for the parameter values shown in Table 1 except for K_3 that is allowed to vary. The diagram bifurcation was obtained numerically (Doedel, 1997). The parameter values obey the cancer hypothesis conditions (12) and (13). The transcritical bifurcation occurs at a threshold value of K_3, $K_3^\star = 200.893$. Below this value, the internal state V_3 is stable. From this value on, the cancer state V_2 is stable. In Figure 1a, it is easy to note that, above the threshold value, the internal state does not exist in the positive cone.

In the next section, we perform a comparative study of the action of therapies based on analytical and numerical results for the C-model, A-model and CA-model.

4 ACTION OF THE THERAPY: ANALYTICAL AND NUMERICAL RESULTS

To better analyze the therapeutic models, this section is divided into subsections where each of the different treatment strategies, including one or more therapies, are considered individually. Our analysis is based on local stability theory and numerical integration of the ODE's system (2).

4.1 CHEMOTHERAPY MODEL (C-MODEL - $w \equiv 0$)

The equilibria of the C-model are:

$$C_0 = \left(0, 0, 0, \frac{\Delta}{\xi}\right), \quad C_{03} = \left(0, 0, K_3, \frac{\Delta}{\xi}\right),$$

$$C_{10} = (\hat{x}_1, 0, 0, \hat{y}), C_1 = (\hat{\hat{x}}_1, 0, K_3, \hat{\hat{y}}), C_2 = \left(0, \tilde{x}_2, \tilde{z}_2, \tilde{y}\right), C_3 = (x_1^{**}, x_2^{**}, z^{**}, y^{**}).$$

The equilibria C_0 and C_{03} always exist, but have no actual relevance from the clinical point of view.

The coordinates $\hat{x}_1$ and $\hat{y}$ of C_{10} are the solutions of the quadratic equation:

$$\alpha_1(\xi + d_{10})\hat{x}_1^2 + [\xi a_1 - K_1(\xi + d_{10})]\alpha_1 \hat{x}_1 + K_1(p_1\Delta - \alpha_1 \xi a_1) = 0$$

given by

$$\hat{x}_1 = \frac{\alpha_1[K_1(\xi + d_{10}) - \xi a_1] \pm \{\alpha_1^2[K_1(\xi + d_1) + \xi a_1]^2 - 4K_1 p_1 \Delta(\xi + d_{10})\}^{1/2}}{2\alpha_1(\xi + d_{10})},$$

and

$$\hat{y} = \frac{\Delta(a_1 + \hat{x}_1)}{[\xi a_1 + (\xi + d_{10})\hat{x}_1]}.$$

Thus the equilibrium C_{10} exists, when the following conditions are satisfied (Pinho et al., 2002):

$$p_{10}\Delta < \alpha_1 \xi a_1$$
$$\text{or}$$
$$\{\xi a_1 < K_1(\xi + d_{10}) \text{ and } \xi a_1 \alpha_1 < p_{10}\Delta\}.$$

For the first condition, there is just one positive equilibrium C_{10}. For the set of second conditions, there are two positive equilibria C_{10}.

The coordinates $\hat{\hat{x}}_1$ of C_1, a cure state with the presence of EC's, are the solutions of the quadratic equation

$$D_2 \hat{\hat{x}}_1^2 + D_1 \hat{\hat{x}}_1 + D_0 = 0,$$

where

$$D_2 = -(b_1 + K_3) \left[c_1 \left(\xi + d_{10} \right) + \left(\xi + d_{10} - d_{11} \right) K_3 \right] \alpha_1$$
$$D_1 = -(b_1 + K_3) \left\{ \xi a_1 \left(c_1 + K_3 \right) - K_1 \left[c_1 \left(\xi + d_{10} \right) + \left(\xi + d_{10} - d_{11} \right) K_3 \right] \right\} \alpha_1$$
$$D_0 = -K_1 \left(c_1 + K_3 \right) \left[b_1 \left(\Delta p_{10} - \xi a_1 \alpha_1 \right) + K_3 \left(\Delta p_{10} + \Delta p_{11} - \xi a_1 \alpha_1 \right) \right] .$$
$$\text{(15)}$$

They are expressed by

$$\hat{\hat{x}}_1 = \frac{-(b_1 + K_3) \left\{ \xi a_1 \left(c_1 + K_3 \right) + K_1 \left[-c_1 \left(\xi + d_{10} \right) - \left(\xi + d_{10} - d_{11} \right) K_3 \right] \right\} \alpha_1}{2 \left(b_1 + K_3 \right) \left[c_1 \left(\xi + d_{10} \right) + \left(\xi + d_{10} - d_{11} \right) K_3 \right] \alpha_1} \pm$$

$$\pm \frac{\sqrt{-(b_1 + K_3) \alpha_1 4 \Delta K_1 \left(c_1 + K_3 \right) \left[c_1 \left(\xi + d_{10} \right) + \left(\xi + d_{10} - d_{11} \right) K_3 \right] \left[\left(b_1 + K_3 \right) p_{10} + K_3 p_{11} \right] -}}{2 \left(b_1 + K_3 \right) \left[c_1 \left(\xi + d_{10} \right) + \left(\xi + d_{10} - d_{11} \right) K_3 \right] \alpha_1}$$

$$\frac{\sqrt{-(b_1 + K_3) \left\{ \xi a_1 \left(c_1 + K_3 \right) + K_1 \left[c_1 \left(\xi + d_{10} \right) + \left(\xi + d_{10} - d_{11} \right) K_3 \right] \right\}^2 \alpha_1}}{2 \left(b_1 + K_3 \right) \left[c_1 \left(\xi + d_{10} \right) + \left(\xi + d_{10} - d_{11} \right) K_3 \right] \alpha_1}$$

$$\hat{\hat{y}} = \frac{\Delta (a_1 + \hat{x}_1)}{\left\{ \xi a_1 + \left[\xi + d_{10} - d_{11} K_3 / \left(c_1 + K_3 \right) \right] \hat{x}_1 \right\}} .$$

The equilibria C_1 exist when the coefficients of equation (15), D_0, D_1 and D_2 are such that $(D_2 > 0, \ D_0 < 0)$, or $(D_2 > 0, \ D_1 < 0, \ D_0 > 0)$.

For the first condition there is just one positive equilibrium C_1. For the set of second conditions, there are two positive equilibria C_1.

The equilibria C_2 and C_3 result from the solutions of polynomial equations of 6th and 11th order in z respectively. They are obtained numerically as we will discuss in the bifurcation analysis.

The Jacobian matrix of the C-model for a generic equilibrium is given by:

$$\mathcal{J}_C = \begin{pmatrix} J_{11} & -q_1 x_1 & J_{13} & J_{14} \\ -q_2 x_2 & J_{22} & J_{23} & J_{24} \\ 0 & \beta & \alpha_3 \left(1 - 2z / K_3 \right) & 0 \\ J_{41} & J_{42} & J_{43} & J_{44} \end{pmatrix} , \tag{16}$$

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$$J_{11} = -\frac{y\,a_1\,[(z+b_1)\,p_{10} + z\,p_{11}]}{(z+b_1)\,(a_1+x_1)^2} - q_1\,x_2 + \alpha_1\left(1 - \frac{2\,x_1}{K_1}\right);$$

$$J_{13} = -\frac{y\,b_1\,p_{11}\,x_1}{(z+b_1)^2\,(a_1+x_1)}; \qquad J_{14} = -\frac{[(z+b_1)\,p_{10} + z\,p_{11}]\,x_1}{(z+b_1)\,(a_1+x_1)};$$

$$J_{22} = -q_2\,x_1 - \frac{y\,a_2\,[(z+b_1)\,p_{20} + z\,p_{21}]}{(z+b_1)\,(a_2+x_2)^2} + 1 - \frac{2\,x_2\,\alpha_2}{K_2+z\,\gamma};$$

$$J_{23} = x_2\left[-\left(\frac{y\,b_1\,p_{21}}{(z+b_1)^2\,(a_2+x_2)}\right) + \frac{\gamma\,x_2\,\alpha_2}{(z\,\gamma+K_2)^2}\right];$$

$$J_{24} = x_2\left[-\left(\frac{\Delta\,b_1\,p_{21}}{\xi\,(z+b_1)^2\,(a_2+x_2)}\right) + \frac{\gamma\,x_2\,\alpha_2}{(z\,\gamma+K_2)^2}\right];$$

$$J_{41} = -\frac{y\,a_1\,[(z+c_1)\,d_{10} - z\,d_{11}]}{(z+c_1)\,(a_1+x_1)^2}; \qquad J_{42} = -\frac{y\,a_2\,[(z+c_1)\,d_{20} - z\,d_{21}]}{(z+c_1)\,(a_2+x_2)^2};$$

$$J_{43} = \frac{y\,c_1\,[a_2\,d_{11}\,x_1 + (a_1\,d_{21} + (d_{11}+d_{21})\,x_1)\,x_2]}{(z+c_1)^2\,(a_1+x_1)\,(a_2+x_2)};$$

$$J_{44} = -\xi - \frac{d_{10}\,x_1}{a_1+x_1} + \frac{z\,d_{11}\,x_1}{(z+c_1)\,(a_1+x_1)} - \frac{d_{20}\,x_2}{a_2+x_2} + \frac{z\,d_{21}\,x_2}{(z+c_1)\,(a_2+x_2)}.$$

The eigenvalues, obtained from (16), $(\lambda_1, \lambda_2, \lambda_3, \lambda_4)$ associated with the equilibria C_0 and C_{03} are respectively:

$$C_0 : \left(-\frac{\Delta\,p_{10}}{\xi\,a_1} + \alpha_1, \; -\frac{\Delta\,p_{20}}{\xi\,a_2} + \alpha_2, \; \alpha_3, \; -\xi\right)$$

$$C_{03} : \left(-\frac{\Delta\,p_{10}}{\xi\,a_1} - \frac{\Delta\,K_3\,p_{11}}{\xi\,a_1\,(b_1+K_3)} + \alpha_1, \; -\frac{\Delta\,p_{20}}{\xi\,a_2} - \frac{\Delta\,K_3\,p_{21}}{\xi\,a_2\,(b_1+K_3)} + \alpha_2, \; -\alpha_3, \; -\xi\right)$$

So, C_0 is always locally unstable. C_{03} is also locally unstable if

$$\alpha_1 > \frac{\Delta\, p_{10}}{\xi\, a_1} + \frac{\Delta\, K_3\, p_{11}}{\xi\, a_1\, (b_1 + K_3)} \text{ or } \alpha_2 > \frac{\Delta\, p_{20}}{\xi\, a_2} + \frac{\Delta\, K_3\, p_{21}}{\xi\, a_2\, (b_1 + K_3)}. \tag{17}$$

One of the eigenvalues of C_{10} is $\lambda = \alpha_3 > 0$; so C_{10} is also locally unstable. Under restriction (17), the system may evolve to C_1, C_2 or C_3 depending on the values of the parameters and on the initial conditions. There are different regions of parameter space for which C_1, C_2 and C_3 are asymptotically stable.

Table 2
Parameters of the C-model.

saturation rate of the agent on NC's	a_1	10
saturation rate of the agent on CC's	a_2	801
saturation rate on the cells of vascularization on the agent	b_1	100
saturation rate on the agent of vascularization on the agent	c_1	100
rate of the agent on NC's	d_{10}	0.5
rate of vascularization on agent, due to interaction with NC's	d_{11}	0.1
rate of the agent on CC's	d_{20}	36
rate of vascularization on agent, due to interaction with CC'	d_{21}	0.5
predation coefficient on NC's	p_{10}	0.05
rate of the vascularization on chemotherapy action on NC's	p_{11}	0.01
predation coefficient on CC's	p_{20}	18
rate of the vascularization on chemotherapy action on CC's	p_{21}	5
chemical infusion rate	Δ	vary
chemical washout rate	ξ	50

The eigenvalues of the cure state C_1 are:

$$\begin{cases} \lambda_2^{(1)} & = \alpha_2 - q_2\hat{\hat{x}}_1 - a_2^{-1}\hat{\hat{y}}\left[p_{20} + K_3 p_{21}/(b_1 + K_3)\right] \\ \lambda_3^{(1)} & = -\alpha_3 \\ \sigma(\mathcal{B}_c) & = \{\lambda_i^{(1)} \mid \lambda^2 - Tr(\mathcal{B}_c)\lambda + \det(\mathcal{B}_c) = 0,\ i = 1, 4\} \end{cases}$$

where $\mathcal{B}_c$ is the sub-matrix of the Jacobian (16) with the restriction that only lines and columns 1 and 4 at the C_1 equilibrium are considered, i.e.,

$$\mathcal{B}_C = \begin{pmatrix} J_{11}(C_1) & J_{14}(C_1) \\ J_{41}(C_1) & J_{44}(C_1) \end{pmatrix}, \tag{18}$$

with

$$J_{11}(C_1) = -\frac{\hat{\hat{y}}\, a_1\, [(K_3 + b_1)\, p_{10} + K_3\, p_{11}]}{(K_3 + b_1)\, (a_1 + \hat{\hat{x}}_1)^2} + \alpha_1 \left(1 - \frac{2\,\hat{\hat{x}}_1}{K_1}\right);$$

$$J_{14}(C_1) = -\frac{[(K_3 + b_1)\, p_{10} + K_3\, p_{11}]\, \hat{\hat{x}}_1}{(K_3 + b_1)\, \left(a_1 + \hat{\hat{x}}_1\right)};$$

$$J_{41}(C_1) = -\frac{\hat{\hat{y}}\, a_1\, [(K_3 + c_1)\, d_{10} - K_3\, d_{11}]}{(K_3 + c_1)\, \left(a_1 + \hat{\hat{x}}_1\right)^2};$$

$$J_{44}(C_1) = -\xi - \frac{d_{10}\, \hat{\hat{x}}_1}{a_1 + \hat{\hat{x}}_1} + \frac{K_3\, d_{11}\, \hat{\hat{x}}_1}{(K_3 + c_1)\, \left(a_1 + \hat{\hat{x}}_1\right)}.$$

Therefore, analogously to Theorem 5 of Pinho et al., 2002, the Routh-Hurwitz criterion (Coppel, 1965) requires that $Tr(\mathcal{B}_c) < 0$ and $\det(\mathcal{B}_c) > 0$ in order that the cure state is locally stable. Thus we prove the following theorem.

Theorem 2 . *Suppose that $\hat{\hat{x}}_1 > K_1/2$ and $d_{10}c_1 > (d_{11} - d_{10})K_3$. If $\alpha_2 < q_2\hat{\hat{x}}_1 - a_2^{-1}\hat{\hat{y}}\, [p_{20} + K_3 p_{21}/(b_1 + K_3)]$, then C_1 is locally asymptotically stable. If $\alpha_2 > q_2\hat{\hat{x}}_1 - a_2^{-1}\hat{\hat{y}}\, [p_{20} + K_3 p_{21}/(b_1 + K_3)]$, then C_1 is hyperbolic saddle point.*

The bifurcation analysis of the C-model is illustrated in Figure 2 for the parameter values shown in Tables 1 and 2. Beside satisfying the cancer hypothesis, the parameter values obey the conditions for existence of equilibria C_1, C_2 and C_3. It is reasonable to choose the infusion rate Δ as a control parameter. On increasing Δ, there is a transcritical bifurcation between the cancer state (C_2) and the internal state C_3: below a threshold value Δ_1 the cancer state is stable and the internal state does not exist in the positive cone. Above Δ_1 and below another threshold value Δ_2, the three relevant equilibria exist; the internal state becomes stable while the cancer state becomes unstable. Finally above Δ_2, the internal state does not exist and the cure state becomes stable.
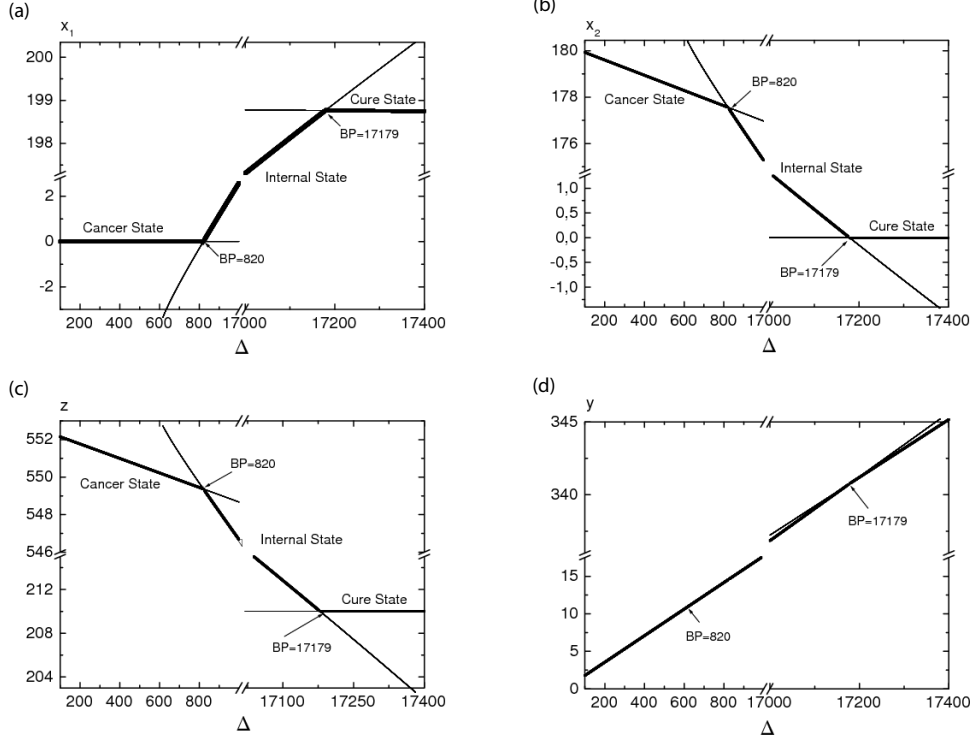
Fig. 2. Bifurcation analysis of the C-model with respect to infusion rate Δ. The set of parameter values is shown in Tables 1 and 2, except the value of Δ. There are two transcritical bifurcations: the first one between cancer and internal states at $\Delta_1 = 820$ value and, the second one between the internal and cure states at $\Delta_2 = 17179$ value. The bifurcation diagram for NC's, CC's, EC's and chemotherapy agent are represented by (a), (b), (c) and (d) respectively.

The transcritical bifurcation between the cure state and the internal state is regulated by the first eigenvalue shown in (18) which depends on different parameters. As shown in Figure (2), depending on the value of Δ, the system can also evolve to cancer state C_2 for low doses, to internal state C_3 for intermediate values, and to cure state (C_1) for high values.

4.2 ANTI-ANGIOGENIC THERAPY MODEL (A-MODEL - $y \equiv 0$)

The equilibria of the A-model are:

$$A_0 = \left(0, 0, 0, \frac{\Phi}{\eta}\right), \quad A_{10} = \left(K_1, 0, 0, \frac{\Phi}{\eta}\right), \quad A_1 = (K_1, 0, \gamma\check{z}, \check{w})$$

$$A_2 = (0, \check{x}_2, \check{z}, \check{w}), \quad A_3 = (x_1^\dagger, x_2^\dagger, z^\dagger, w^\dagger).$$

The equilibria A_0 and A_{10} always exist. The cure state A_1 is such that the

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coordinate $\check{z}$ is the solution of the following quadratic equation:

$$\alpha_3(\eta + d_3)\check{z}^2 + \alpha_3[\eta(a_3 - K_3) - K_3 d_3]\check{z} + K_3(p_3 - \alpha_3 a_3) = 0$$

given by:

$$\check{z} = \frac{K_3}{2} - \frac{\eta a_3}{2(\eta + d_3)} \pm \frac{\sqrt{\alpha_3^2\left[-\eta a_3 + K_3(\eta + d_3)\right]^2 + 4\alpha_3 K_3(\eta + d_3)(\eta a_3 \alpha_3 - \Phi p_3)}}{2\alpha_3(\eta + d_3)}$$

and

$$\check{w} = \frac{\Phi(a_3 + \check{z})}{[\eta a_3 + (\eta + d_3)\check{z}]}.$$

The cancer states A_2 are solutions of the cubic equation:

$$E_3 \check{z}^3 + E_2 \check{z}^2 + E_1 \check{z} + E_0 = 0$$

where

$$
\begin{aligned}
E_3 &= (\eta + d_3)\,\alpha_3 \\
E_2 &= -(\eta + d_3)\,K_3\,(\beta\gamma + \alpha_3) - \eta\,a_3\alpha_3 \\
E_1 &= -K_3\left[\beta\,(\eta + d_3)\,K_2 - \Phi p_3 + \eta a_3\,(\beta\,\gamma + \alpha_3)\right] \\
E_0 &= -\beta\eta a_3 K_2 K_3
\end{aligned}
$$

(19)

and

$$\check{x}_2 = K_2 + \gamma\check{z} \text{ and } \check{w} = \frac{\Phi(a_3 + \check{z})}{[\eta a_3 + (\eta + d_3)\check{z}]}.$$

The equilibria A_3 result from the solutions of polynomial equations of 4th order in z. They are obtained numerically as we will discuss in the bifurcation analysis.

To analyze the local stability of equilibria, we consider the Jacobian matrix for a generic equilibrium $A(\bar{x}_1, \bar{x}_2, \bar{z}, \bar{w})$, which is written as

$$\mathcal{J}_A = \begin{pmatrix} J_{11} & -q_1\bar{x}_1 & 0 & 0 \\ -q_2\bar{x}_2 & J_{22} & \gamma\alpha_2\bar{x}_2^2/(K_2 + \bar{z})^2 & 0 \\ 0 & \beta & J_{33} & -p_3\bar{z}/(a_3 + \bar{z}) \\ 0 & 0 & -d_3\bar{w}a_3/(a_3 + \bar{z})^2 & J_{44} \end{pmatrix},$$

(20)

$$J_{11} = \alpha_1 \left(1 - \frac{2\bar{x}_1}{K_1}\right) - q_1\bar{x}_2; \qquad J_{22} = \alpha_2 \left(1 - \frac{2\bar{x}_2}{K_2 + \gamma\bar{z}}\right) - q_2\bar{x}_1;$$

$$(21)$$

$$J_{44} = -\eta - \frac{d_3\bar{z}}{a_3 + \bar{z}}; \qquad J_{33} = -\left(\frac{\bar{w}\,a_3\,p_3}{(\bar{z} + a_3)^2}\right) + \left(1 - \frac{2\,\bar{z}}{K_3}\right)\alpha_3.$$

$$(22)$$

The spectra of A_0 and A_{10}, $(\lambda_1, \lambda_2, \lambda_3, \lambda_4)$, are respectively:

$$A_0 : (\alpha_1, \alpha_2, -\delta - p_3\Phi/(a_3\eta), -\eta)$$
$$A_{10} : (-\alpha_1, \alpha_2 - q_2K_1, \alpha_3 - \Phi p_3/\eta a_3, -\eta)$$
$$A_1 : (-\alpha_1, \alpha_2 - q_2K_1, \lambda_3^{(1)}, \lambda_4^{(1)})$$

where $\{\lambda_i^{(1)} \mid \lambda^2 - Tr(\mathcal{B}_A)\lambda + \det(\mathcal{B}_A) = 0,\ i = 3, 4\}$ with

$$\mathcal{B}_A = \begin{pmatrix} -[\check{w}\,a_3\,p_3/(\check{z} + a_3)^2] + \alpha_3\,(1 - 2\,\check{z}/K_3) & -p_3\check{z}/(a_3 + \check{z}) \\ -d_3\check{w}a_3/(a_3 + \check{z})^2 & -\eta - d_3\check{z}/(a_3 + \check{z}) \end{pmatrix} \quad (23)$$

A_0 is always locally unstable. Theorem 1 requires that $\alpha_2 - q_2K_1 > 0$. This shows that A_{10} and A_1 are both locally unstable because of their second eigenvalues.

Therefore we enunciate the following theorem:

Theorem 3 *Assuming condition (12), the cure equilibria A_{10} and A_1 are hyperbolic saddle points.*

Table 3
Parameters of the A-model.

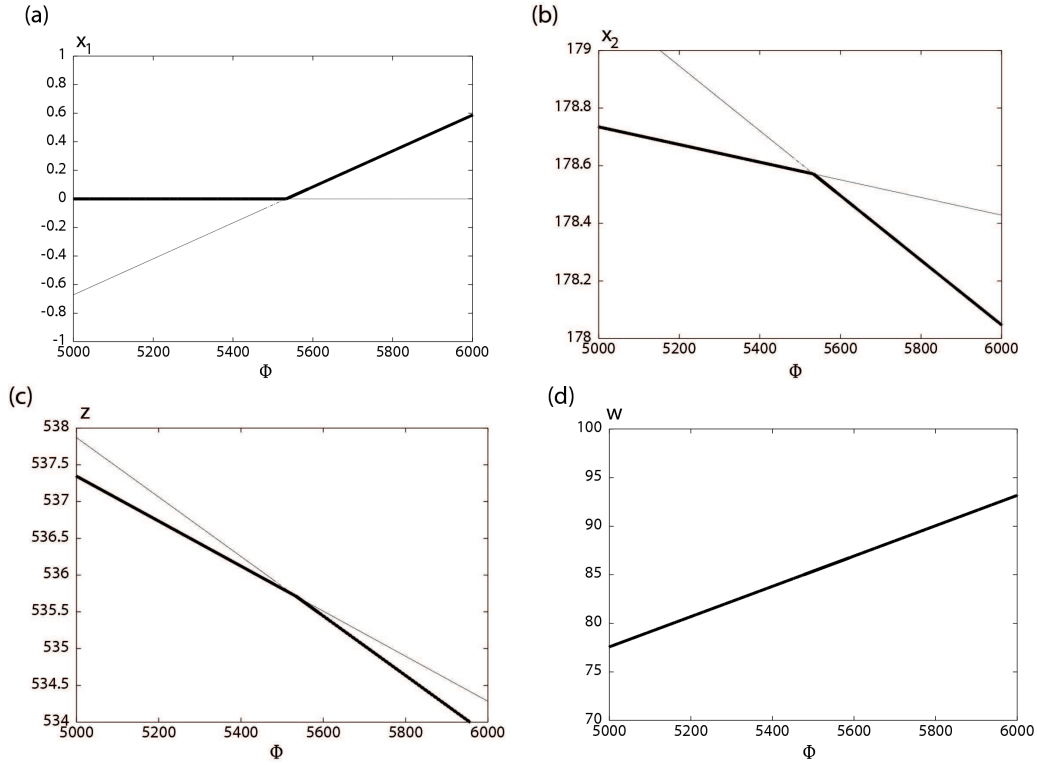|		
saturation rate of the agent on EC's	a_3	801
predation coefficients on EC's	p_3	18
rate of vascularization on EC's	d_3	36
anti-angiogenic infusion rate	Φ	1000
anti-angiogenic washout rate	η	50

Fig. 3. Bifurcation analysis of the A-model with respect to anti-angiogenic infusion rate Φ. The set of parameter values are shown in Tables 1 and 3, except the value of Φ . There is a transcritical bifurcation between A_2 and A_3, at the value $\Phi^\star = 5533.123$. The bifurcation diagram for NC's, CC's, EC's and anti-angiogenic agent are represented by (a), (b), (c) and (d) respectively.

There are different regions of parameter space in which both A_2 and A_3 are asymptotically stable. Hence, in general, the system may evolve to A_2 or A_3, depending on the values of the parameters and on the initial conditions.

The bifurcation analysis of the A-model is illustrated in Figure 3 for parameter values shown in Tables 1 and 3. There we illustrate a transcritical bifurcation between the cancer state A_2 and the internal state A_3: below a threshold value of the infusion rate Φ, $\Phi^\star$, the cancer state is stable and the internal state does not exist.

We recall that, as A_1 is not asymptotically stable, it is very unlikely to reach this cure state. The isolated effect of the anti-angiogenic agent is to reduce the tumor. The previous results for the C-model had shown that, due to angiogenesis, only for some values of infusion doses, chemotherapy is able to eliminate the tumor (see Figure2). Hence, in the next subsection we will investigate the combined therapy (Browder et al., 2001), as an efficient strategy to eliminate the tumor with lower doses of chemotherapy.

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4.3 COMBINED THERAPY MODEL (CA-MODEL)

The equilibria of the combined chemo+anti-angiogenic (C+A) therapy model are:

$$CA_0 = (0, 0, \check{z}, \Delta/\xi, \check{w},), \quad CA_1 = (\check{x}_1, 0, \check{z}, \check{y}, \check{w}),$$
$$CA_2 = (0, \check{x}_2, \check{z}, \check{y}, \check{w}), \quad CA_3 = (x_1^\ddagger, x_2^\ddagger, z^\ddagger, y^\ddagger, w^\ddagger),$$

The coordinates $\check{z}$ and $\check{w}$ of equilibria CA_0 and CA_1 are the same of equilibria A_1. The coordinates $\check{x}_1$ of CA_1 are given by:

$$\check{x}_1 = \frac{-\xi a_1 (\check{z} + c_1) (\check{w} + c_2)}{c_1 [c_2 (\xi + d_{10}) + \check{w} (\xi + d_{10} - d_{12})] + \check{z} [c_2 (\xi + d_{10} - d_{11}) + \check{w} (\xi + d_{10} - d_{11} - d_{12})]}$$

$$\check{y} = \frac{\Delta (a_1 + \check{x}_1)}{\xi a_1 + [\xi + d_{10} - \check{z} d_{11}/(\check{z} + c_1) - \check{w} d_{12}/(\check{w} + c_2)] \check{x}_1}$$

The equilibria CA_2 and CA_3 result from the solutions of polynomial equations of 8th and 11th order in z respectively. They are obtained numerically as we will discuss in the bifurcation analysis.

The Jacobian matrix for a generic equilibrium $CA(x_1, x_2, z, y, w)$ is given by

$$\mathcal{J}_{CA} = \begin{pmatrix} J_{11} & -q_1 x_1 & J_{13} & J_{14} & 0 \\ -q_2 x_2 & J_{22} & J_{23} & J_{24} & J_{25} \\ 0 & \beta & J_{33} & 0 & -p_3 z/(a_3 + z) \\ J_{41} & J_{42} & J_{43} & J_{44} & J_{45} \\ 0 & 0 & -d_3 w a_3/(a_3 + z)^2 & 0 & -\eta - d_3 z/(a_3 + z) \end{pmatrix}, \quad (24)$$

$$J_{11} = \left(1 - \frac{2x_1}{K_1}\right) \alpha_1 + \frac{y a_1 \{-[(w + b_2) ((z + b_1) p_{10} + z p_{11})] - w (z + b_1) p_{12}\}}{(z + b_1) (w + b_2) (a_1 + x_1)^2} - q_1 x_2;$$

$$J_{13} = -\frac{y b_1 p_{11} x_1}{(z + b_1)^2 (a_1 + x_1)}; \qquad J_{14} = \frac{x_1 \{w (z + b_1) p_{12} + (w + b_2) [(z + b_1) p_{10} + z p_{11}]\}}{(z + b_1) (w + b_2) (a_1 + x_1)};$$

$$J_{22} = 1 - \frac{2x_2 \alpha_2}{z\gamma + K_2} - q_2 x_1 + \frac{y a_2 \{-[w (z + b_1) p_{22}] - (w + b_2) [(z + b_1) p_{20} + z p_{21}]\}}{(z + b_1) (w + b_2) (a_2 + x_2)^2};$$

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$$J_{23} = x_2 \left\{ -\left[\frac{y\, b_1\, p_{21}}{(z+b_1)^2\, (a_2+x_2)} \right] + \frac{\gamma\, x_2\, \alpha_2}{(z\,\gamma+K_2)^2} \right\};$$

$$J_{24} = -\frac{x_2\, [w\,(z+b_1)\,p_{22} + (w+b_2)\,((z+b_1)\,p_{20} + z\,p_{21})]}{(z+b_1)\,(w+b_2)\,(a_2+x_2)};$$

$$J_{25} = \frac{y\, b_2\, p_{22}\, x_2}{(w+b_2)^2\,(a_2+x_2)}; \qquad J_{33} = -\frac{w\, a_3\, p_3}{(z+a_3)^2} + \left(1 - \frac{2\,z}{K_3}\right)\alpha_3;$$

$$J_{41} = \frac{y\, a_1\, \{(w+c_2)\,[-((z+c_1)\,d_{10}) + z\,d_{11}] + w\,(z+c_1)\,d_{12}\}}{(z+c_1)\,(w+c_2)\,(a_1+x_1)^2}$$

$$J_{42} = \frac{y\, a_2\, \{(w+c_2)\,[-((z+c_1)\,d_{20}) + z\,d_{21}] + w\,(z+c_1)\,d_{22}\}}{(z+c_1)\,(w+c_2)\,(a_2+x_2)^2};$$

$$J_{43} = \frac{y\, c_1\, \{a_2\, d_{11}\, x_1 + [d_{11}\, x_1 + d_{21}\,(a_1+x_1)]\, x_2\}}{(z+c_1)^2\,(a_1+x_1)\,(a_2+x_2)};$$

$$J_{44} = -\xi - \frac{d_{10}\, x_1}{a_1+x_1} + \frac{z\, d_{11}\, x_1}{(z+c_1)\,(a_1+x_1)} - \frac{[(z+c_1)\,d_{20} - z\,d_{21}]\, x_2}{(z+c_1)\,(a_2+x_2)} + \frac{w\left(\frac{d_{12}\, x_1}{a_1+x_1} + \frac{d_{22}\, x_2}{a_2+x_2}\right)}{w+c_2};$$

$$J_{45} = \frac{y\, c_2\, \{a_2\, d_{12}\, x_1 + [d_{12}\, x_1 + d_{22}\,(a_1+x_1)]\, x_2\}}{(w+c_2)^2\,(a_1+x_1)\,(a_2+x_2)}.$$

The eigenvalue spectra of CA_1, $(\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5)$, are such that:

$$\begin{cases} \lambda_2^{(1)} &= -\breve{y}\,\{p_{20} + [\breve{z}\,p_{21}/(\breve{z}+b_1)] + [\breve{w}p_{22}/(\breve{w}+b_2)]\}/a_2 - q_2\,\breve{x}_1 + \alpha_2 \\ \sigma(\mathcal{B}_{CA}) &= \{\lambda_i^{(1)}/\lambda^2 - Tr(\mathcal{B}_{CA}) + \det(\mathcal{B}_{CA}) = 0,\ i = 1, 4\} \\ \sigma(\mathcal{D}_{CA}) &= \{\lambda_i^{(1)}/\lambda^2 - Tr(\mathcal{D}_{CA}) + \det(\mathcal{D}_{CA}) = 0,\ i = 3, 5\}. \end{cases}$$

$\mathcal{B}_{CA}$ is the sub-matrix of the Jacobian formed by lines and columns 1 and 4 at the CA_1 equilibrium:

$$\mathcal{B}_{CA} = \begin{pmatrix} J_{11}(CA_1) & J_{14}(CA_1) \\ J_{41}(CA_1) & J_{44}(CA_1) \end{pmatrix}, \tag{25}$$

with

$$J_{11}(CA_1) = \left(1 - \frac{2\,\check{x}_1}{K_1}\right)\alpha_1 - \frac{\check{y}\,a_1\,\{[(\check{w}+b_2)\,((\check{z}+b_1)\,p_{10} + \check{z}\,p_{11})] + \check{w}\,(\check{z}+b_1)\,p_{12}\}}{(\check{z}+b_1)\,(\check{w}+b_2)\,(a_1+\check{x}_1)^2};$$

$$J_{14}(CA_1) = \frac{\check{x}_1\,\{\check{w}\,(\check{z}+b_1)\,p_{12} + (\check{w}+b_2)\,[(\check{z}+b_1)\,p_{10} + \check{z}\,p_{11}]\}}{(\check{z}+b_1)\,(\check{w}+b_2)\,(a_1+\check{x}_1)};$$

$$J_{41}(CA_1) = \frac{\check{y}\,a_1\,\{(\check{w}+c_2)\,[-((\check{z}+c_1)\,d_{10}) + \check{z}\,d_{11}] + \check{w}\,(\check{z}+c_1)\,d_{12}\}}{(\check{z}+c_1)\,(\check{w}+c_2)\,(a_1+\check{x}_1)^2};$$

$$J_{44}(CA_1) = -\xi - \frac{d_{10}\,\check{x}_1}{a_1+\check{x}_1} + \frac{\check{z}\,d_{11}\,\check{x}_1}{(\check{z}+c_1)\,(a_1+\check{x}_1)} + \frac{\check{w}\,d_{12}\,\check{x}_1}{(a_1+\check{x}_1)(\check{w}+c_2)}.$$

According to the Routh-Hurwitz criterion (Coppel, 1965), the real part of $\lambda_3^{(1)}$ and $\lambda_5^{(1)}$ are negative when $Tr(\mathcal{B}_{CA}) < 0$ and $\det(\mathcal{B}_{CA}) > 0$. So their real part are negative if and only if

$$d_{10} > \frac{\check{z}d_{11}}{\check{z}+c_1} + \frac{\check{w}d_{12}}{\check{w}+c_2} \tag{26}$$

and

$$K_1/2 < \check{x}_1 < \frac{a_1\xi(\check{z}+c_1)(\check{w}+c_2)}{\check{w}(\check{z}+c_1)d_{12} - (\check{w}+c_2)[(\check{z}+c_1)(\xi+d_{10}) - \check{z}d_{11}]} \tag{27}$$

$\mathcal{D}_{CA}$ is the sub-matrix of the Jacobian formed by lines and columns 3 and 5 at the CA_1 equilibrium:

$$\mathcal{D}_{CA} = \begin{pmatrix} -[\check{w}\,a_3\,p_3/(\check{z}+a_3)^2] + (1 - 2\,\check{z}/K_3)\,\alpha_3 & -p_3\check{z}/(a_3+\check{z}) \\ -d_3\check{w}a_3/(a_3+\check{z})^2 & -\eta - d_3\check{z}/(a_3+\check{z}) \end{pmatrix},$$

Using the Routh-Hurwitz criterion again, it is easy to prove that if $\check{z} > K_3/2$ then $Tr(\mathcal{D}_{CA}) < 0$ and $\det(\mathcal{D}_{CA}) > 0$. So the real part of $\lambda_3^{(1)}$ and $\lambda_5^{(1)}$ are negative.

Table 4
Parameters of combined model.

saturation rate on the cells of AA drug on the agent	b_2	100
saturation rate on the agent of AA drug on the agent	c_2	100
rate of the AA on chemo agent, due to interaction with NC's	d_{12}	0.05
rate of the AA on chemo agent, due to interaction with CC's	d_{22}	0.1
rate of the AA helpful on chemo action on NC's	p_{12}	0.005
rate of the AA helpful on chemo action on CC's	p_{22}	1

Let us focus our analysis in the comparison between the stability of the cure state CA_1 for the CA-model with the stability of the cure state C_1 for the C-model (the other cure state C_{10} is locally unstable). As discussed in the previous section, the cure state A_1 for the A-model is locally unstable due to the the cancer hypothesis.

Comparing the eigenvalues for C_1 and CA_1, it is enough to observe the second line of the Jacobian matrices (16) and (24) for the respective cure states C_1 and CA_1:

$$(0, -\frac{\hat{\hat{y}}}{a_2}\left(p_{20} + \frac{K_3\,p_{21}}{K_3 + b_1}\right) - q_2\,\hat{\hat{x}}_1 + \alpha_2, 0, 0, 0) \tag{28}$$

$$(0, -\frac{\check{y}}{a_2}\left(p_{20} + \frac{\check{z}\,p_{21}}{\check{z} + b_1} + \frac{\check{w}\,p_{22}}{\check{w} + b_2}\right) - q_2\,\check{x}_1 + \alpha_2, 0, 0, 0). \tag{29}$$

In (28) and (29), it is shown that, for a choice of parameter values such that C_1 is a hyperbolic saddle point according to Theorem 2, it is always possible to increase the value of the parameter p_{22} until the cure state CA_1 of the CA-model becomes locally stable, i.e., the real part of the eigenvalues of CA_1 are negative. Hence there exists a region of parameter set such that C_1 is locally unstable and CA_1 is locally stable.

Therefore the following theorem can be stated.

Theorem 4 *Suppose that $\alpha_2 > q_2\hat{\hat{x}}_1 - a_2^{-1}\hat{\hat{y}}\left[p_{20} + K_3p_{21}/(b_1 + K_3)\right]$. The cure*

state CA_1 of the CA-model is asymptotically stable if and only if

(i) $\alpha_2 < q_2 \check{x}_1 + \check{y} \{p_{20} + [\check{z} p_{21}/(\check{z} + b_1)] + [\check{w} p_{22}/(\check{w} + b_2)]\}/a_2$
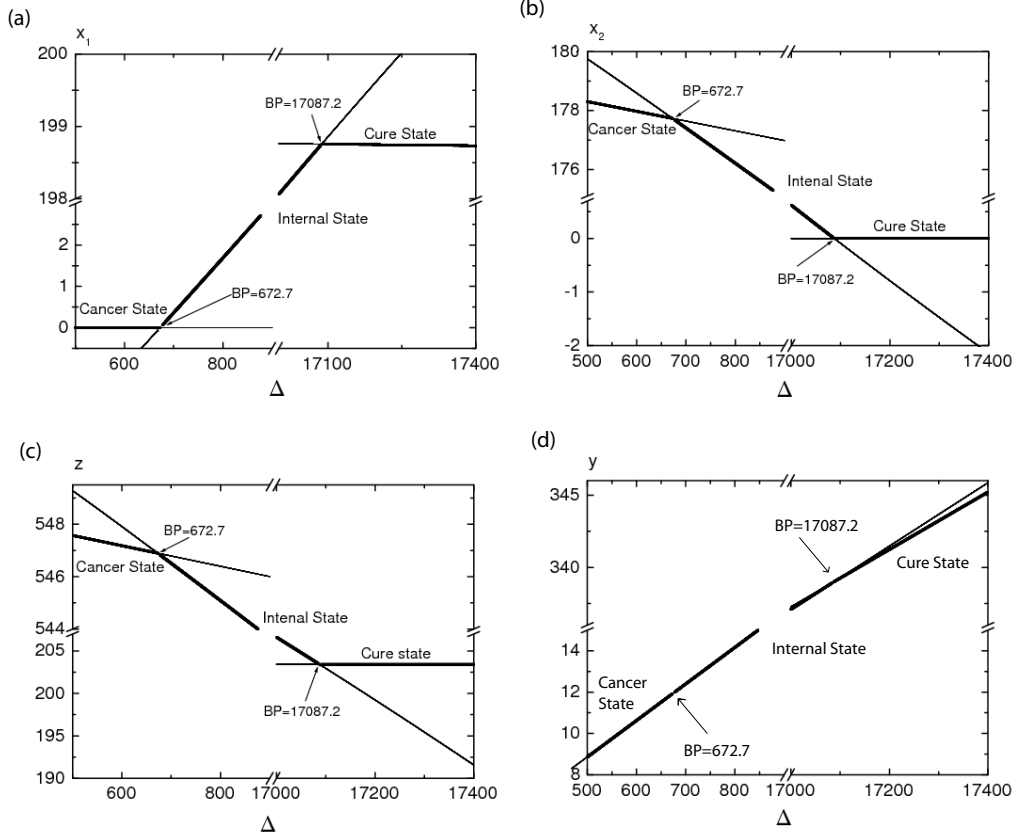*(ii) $\check{z} > K_3/2$*
(iii) the inequalities (26) and (27) hold.

Fig. 4. Bifurcation analysis of the CA-model with respect to infusion rate Δ. The set of parameter values are shown in Tables 1, 2, 3 and 4, except the value of Δ. There are two transcritical bifurcations: the first one between cancer state and internal state at $\Delta_1 = 672.7$ and, the second one between the internal state and cure state at $\Delta_2 = 17087.2$. The bifurcation diagram for NC's, CC's, EC's, chemotherapy agent are represented by (a), (b), (c) and (d) respectively.

We have found numerical evidences of the advantageous effect of combining both therapies. In the combined model, we still have the same stable states, but now the presence of anti-angiogenic treatment displaces the bifurcation to the left side of the Δ axis. Thus, for the purpose of comparison with the C-model, the bifurcation analysis is done with respect to the chemotherapy infusion parameter, Δ. The cure stable state occurs for a smaller value of chemotherapy doses Δ (see Figure 4).

Since the value of p_{22} is responsible for changing the stability of the cure state, we perform a two parameter analysis ($\Delta \times p_{22}$) shown in Figure 5 and
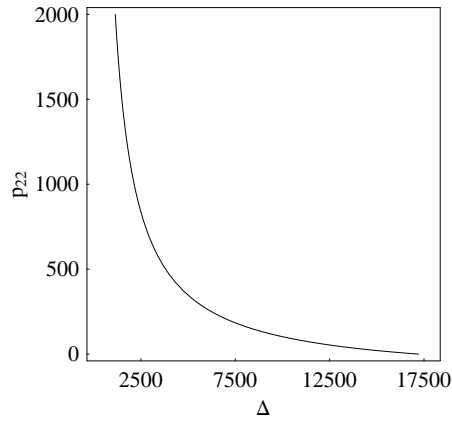
27

Fig. 5. Two-parameter bifurcation analysis: $p_{22} \times \Delta$. The two parameter bifurcation diagram in a restricted region of p_{22} and Δ values where the transcritical bifurcation between intenal and cure states. The same set of parameters of figure (4) is considered.
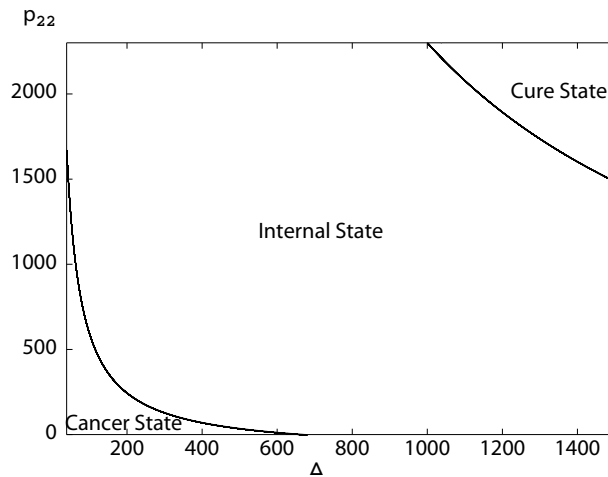

Fig. 6. Two parameter bifurcation analysis: $p_{22} \times \Delta$. The black line indicates the two transcritical bifurcations. The stable state is indicated in each region. The same set of parameters of figure (4) is considered.

Figure 6. The bifurcation diagram of the transcritical bifurcation between the internal and the cure state is shown in Figure 5: under this curve, the internal state is stable whereas above this curve the cure state is stable. The cure state dependence on these two parameters seems to have a hyperbolical behavior. For low values of chemotherapy infusion rate, the values of p_{22} are higher, but the dependence on p_{22} is relaxed when infusion rate is increased. In Figure 6, the bifurcation diagram is enlarged to show both transcritical bifurcations: cancer-internal states and internal-cure states.

5 DISCUSSION AND CONCLUDING REMARKS

In this paper we presented a comparative analysis between chemotherapy and combined (chemo+anti-angiogenic) therapy based on systems of ordinary differential equations taking into account the assumptions of an angiogenic process. The models (chemotherapy, anti-angiogenic and combined therapy models) are based on the main features of the dynamics of the therapy action on normal and cancer cells. We prove that the combined model is bounded and dissipative. We impose the main assumption "cancer hypothesis": with no therapy, i.e., the system goes to a cancer state as in a previous paper of two of us (Pinho et al, 2002).

The cancer hypothesis restricts the range of parameter values that we may use to analyze to the response to the therapy actions. Based on the local stability of the stationary states, Theorem 1 presents the restricted conditions that are imposed in our analysis. Figure (1) shows the bifurcation analysis for the no-treatment case based on the parameter K_3, making evident the conditions for existence and stability of the internal state.

Theorem 2 guarantees that there is a region of the parameter space such that the cure state C_1, for the C-model, is asymptotically stable. In other words, the cure state may be reached under the chemotherapy action for large values of chemotherapy infusion Δ. This is also evident in the diagram bifurcation of the C-model as shown in Figure (2).

According to Theorem 3, the cure states for the A-model are locally unstable. In other words, the isolated application of the anti-angiogenic therapy is not able to eliminate the tumor. The control of EC's has the important role of avoiding the tumor growth. Further, it reduces the cytotoxic effect over NC's. Hence the system may evolve to the internal state or to the cancer state depending on the parameter values. The behavior is shown in Figure (3).

The most important issue that we considered is as follows: Are there regions in the parameter space such that the cure state can be reached only under the effect of the combined therapy? In other words, is it possible to reduce the chemotherapy infusion (Δ) and increase the anti-angiogenic helpful effect to the conventional chemotherapy action (p_{22}) in order to get a better response in the treatment of cancer?

Our results indicate positive answers to these questions which stems from both a comparative study of local stability analysis of the cure states for the C-model and the CA-model as well as the analysis of their bifurcation diagrams. Theorem 4 guarantees that the cure state CA_1 of the CA-model is asymptotically stable in a larger region of parameter space than C_1. This is also shown by comparing Figures (2) and (4), which correspond to the bifur-

cation analysis for the C-model and the CA-model. It reveals that the addition of anti-angiogenic therapy may provide more efficiency to the traditional chemotherapy. Besides this is possible to apply smaller rates of chemotherapy agents, reducing the cytotoxic effect on normal cells.

It is also important to discuss what is the better strategy to combine the therapies. According to some numerical integrations of the A-model followed by the C-model, we can conclude that it is better to apply them simultaneously (Browder et al., 2001) instead of sequentially. We have observed that the previous action of the anti-angiogenic therapy does not modify the effect of the individual action of the chemotherapy.

Summarizing, the results of our models have shown relevant clinical features of the therapies as follows:

  a) For a sufficiently high dose of infusion, the tumor may be eliminated or reduced by continuous chemotherapy.
  b) It is not possible to eliminate the tumor by continuous anti-angiogenic therapy.
  c) The best strategy is to combine chemotherapy and anti-angiogenic therapy in order to eliminate the tumor and to reduce the cytotoxic effect on NC's.

In a generalized model, we intend to consider the time delay between the tumor growth and the neo-vascularization of the tumor observed in some experiments with mice that show that the tumor angiogenic process is triggered with a time delay after the tumor starts producing TAF and TIF (Arakelian et al, 2003). Thus a change in vascularization does not immediately affect the tumor growth. Some events take place from the time that TAF in released from the solid tumor to the instant that vascularization takes place (Maggelakis, 1996). Other time delayed differential equations models are also proposed in the context of growth tumor (Moxnes et al., 2004) and cancer treatment initiation (Sidorov et al., 2003).

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