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A MATHEMATICAL MODEL OF CHEMOTHERAPY RESPONSE TO TUMOUR GROWTH

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ABSTRACT. A simple mathematical model, developed to simulate the chemotherapy response to tumour growth with stabilized vascularization, is presented as a system of three differential equations associated with the normal cells, cancer cells and chemotherapy agent. Cancer cells and normal cells compete by available resources. The response to chemotherapy killing action on both normal and cancer cells obey Michaelis-Menten saturation function on the chemotherapy agent. Our aim is to investigate the efficiency of the chemotherapy in order to eliminate the cancer cells. For that, we analyse the local stability of the equilibria and the global stability of the cure equilibrium for which there is no cancer cells. We show that there is a region of parameter space that the chemotherapy may eliminate the tumour for any initial conditions. Based on numerical simulations, we present the bifurcation diagram in terms of the infusion rate and the killing action on cancer cells, that exhibit, for which infusion conditions, the system evolves to the cure state.

1 Introduction Neoplastic diseases are considered a very severe health problem worldwide. Understanding the dynamics of cancer in the cell level is very important mainly when it is taken into account their interaction with therapy agents. Due to its complexity, building mathematical models is thought as a great challenge.

One of the most relevant phenomena for tumour growth is tumour angiogenesis that corresponds to the formation of new blood vessels (from a previous vascularization) due to the proliferation of endothelial cells that revest the blood vessels [**1**]. After the pre-vascular stage, the tumour cells induce a synthesis of several substances, generally called Tumour Angiogenic Factors (TAF) that stimulate the proliferation of new endothelial cells [**4**]; they also produce smaller amounts of inhibitors

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(TIF—Tumor Inhibitor Factors) that can regulate the density of endothelial cells. During the vascular stage, TAF dominates TIF and the quantity of endothelial cells increases as well as the vascularization. After the stabilization of that process, the tumour grows depending on its fixed carrying capacity [**6**].

In this paper, we intend to describe the tumour growth after the stabilization of vascularization. For that purpose, we analyse a simple mathematical model taking into account the cancer cells (CCs), the normal cells (NCs) and the chemotherapy agent (CA). The model is inspired by some previous works of Prof. Freedman and collaborators [**11, 15**] about mathematical modelling of tumour treatment by chemotherapy. Our focus is to investigate the response to a continuous chemotherapy infusion in terms of the the agent capacity in killing CCs (efficiency of CA) and the infusion rate.

The paper is organized as follows. In Section 1 we introduce our model as a special case of a general chemotherapy model of tumour growth. In Section 2, the local stability of equilibria is analysed. Section 3 contains some numerical examples. In Section 4, the global stability of cure state is developed. The discussion and concluding remarks are presented in Section 5.

2 The model Similar to what was done by Nani and Freedman [**13**], we model our system by means of three ordinary differential equations altogether simulating the interactions between the normal cells, cancer cells and chemotherapy agent. For $t \geq 0$, let $N_i(t)$, $i = 1, 2$, be the number of CCs and NCs, respectively; $Q(t)$, be the dose of CA. From a general point of view, we assume that:

- Both $N_1(t)$ and $N_2(t)$ exhibit saturated growth rates defined by functions $\mathcal{G}_1(N_1(t))$ and $\mathcal{G}_2(N_2(t))$, respectively, and compete for available resources (nutrients and oxygen) according to functions $\mathcal{C}_i(N_1(t), N_2(t))$, $i = 1, 2$.
- $Q(t)$ increases due to its time-dependent infusion rate given by $q(t)$ and decrease due to the washout function $\mathcal{R}(Q(t))$.
- $Q(t)$ acts killing $N_1(t)$ and $N_2(t)$ with different intensities according to the killing functions $\mathcal{P}_i(N_i(t), Q(t))$, $i = 1, 2$, with two terms: one term saturated on $N_j(t)$, $j = 1, 2$ and another one saturated on $Q(t)$.
- $Q(t)$ may also decrease due to its action on the cells according to similar functions $\mathcal{F}_i(N_i(t), Q(t))$, $i = 1, 2$, respectively.

This leads to a general model

$$(1)\quad \begin{cases} \dot{N}_1(t) = r_1 N_1(t)\,\mathcal{G}_1(N_1(t)) \\ \qquad\qquad -\mathcal{C}_1(N_1(t), N_2(t)) - \mathcal{P}_1(N_1(t), Q(t)), \\ \dot{N}_2(t) = r_2 N_2(t)\,\mathcal{G}_2(N_2(t)) \\ \qquad\qquad -\mathcal{C}_2(N_1(t), N_2(t)) - \mathcal{P}_2(N_2(t), Q(t)), \\ \dot{Q}(t) = \mathcal{A}(t) - \mathcal{R}(Q(t)) - \mathcal{F}_1(N_1(t), Q(t)) - \mathcal{F}_2(N_2(t), Q(t)), \end{cases}$$

with $\cdot = d/dt$.

As in our previous work [**16**], we assume the following specific functions of the general model (1):

a) Logistic growth functions: $\mathcal{G}_i(N_i) = r_i\,(1 - N_i/K_i)\,,\ i = 1, 2;$
b) Competition functions: $\mathcal{C}_i(N_1, N_2) = r_i \alpha_i N_1 N_2 / K_i,\ i = 1, 2;$
c) Holling type 2 killing functions: $\mathcal{P}_i(N_i, Q) = N_i Q \left(\frac{p_i}{d_i + Q} + \frac{s_i}{c_i + N_i}\right),$ $i = 1, 2,$ with $s_1 = s_2 = 0,\ p_1 = \mu,\ p_2 = \nu,\ d_1 = a,\ d_2 = b;$
d) Linear life-time drug function: $\mathcal{R}(Q) = \lambda Q;$
e) Negligible consumption of drug: $\mathcal{F}_i(N_i, Q) = 0,\ i = 1, 2;$
f) Continuous infusion functions: $\mathcal{A}(t) = q,\ \forall\ t \geq 0.$

Summarizing the meaning of parameters:

- r_i and K_i are the proliferation rates and carrying capacities of N_i, $i = 1, 2;$
- α_i, $i = 1, 2$, are the competition coefficients between N_1 and N_2;
- μ and ν are the killing rate of CA on N_i, $i = 1, 2$, respectively.
- a and b are the Holling type 2 constant for $\mathcal{P}_1$ and $\mathcal{P}_2$, respectively;
- q is the infusion rate of CA;
- λ is the per unit washout rate of CA from the system.

For $t \geq 0$, let $N_i(t)$, $i = 1, 2$ be the number of NCs, CCs, respectively; $Q(t)$ the concentration of CA. Therefore, we have the following model [**16**]:

$$(2)\quad \begin{cases} \dot{N}_1(t) = r_1 N_1(t) \left[1 - \dfrac{N_1(t)}{K_1} - \dfrac{\alpha_1 N_2(t)}{K_1}\right] - \dfrac{\mu N_1(t) Q(t)}{a + Q(t)}, \\ \dot{N}_2(t) = r_2 N_2(t) \left[1 - \frac{N_2(t)}{K_2} - \dfrac{\alpha_2 N_1(t)}{K_2}\right] - \dfrac{\nu N_2(t) Q(t)}{b + Q(t)}, \\ \dot{Q}(t) = q - \lambda Q(t), \end{cases}$$

with $N_i(t=0) = N_{i0} \geq 0$, $i = 1, 2$, $Q(t=0) = Q_0 \geq 0$. We assume positive values for all parameters.

Beside the fact that we are taking into account only one site (no metastasis), the main differences of some previous model developed by Freedman, Nani and Pinho [**15**] are:

i) Based on pharmacodynamics arguments, Michaelis-Menten saturation of killing functions is applied on the agent as in [**9**]. Therefore we neglect the saturation on the cells in comparison with the saturation on the agent assuming $\mathcal{P}_i(N_i, Q) = p_i N_i Q/(d_i + Q)$; meanwhile in [**15**], $\mathcal{P}_i(N_i, Q) = p_i N_i Q/(c_i + N_i)$ due to the saturation on the cells.
ii) The reduction of the agent due to consumption is neglected in relation to its natural elimination: $\mathcal{F}_i(N_i, Q) = 0$, $i = 1, 2$. We consider the chemotherapy as a forcing action on the cells in order to analyse their response to the treatment. Its time evolution, for a fixed infusion q, is given by

$$Q(t) = \frac{q}{\lambda} + \left[Q_0 - \frac{q}{\lambda}\right] \exp(-\lambda t).$$

Let us establish two important properties of the system (2): invariance and dissipativity.

1. *Invariance: all solutions with positive values remain positive.*

By uniqueness of solutions, since $N_1 \equiv 0$ is a solution of the first equation of (2), no solution with $N_1(t) > 0$ at any time $t \geq 0$ can become zero in finite time. Similarly, the same is true for $N_2(t)$. Since $\dot{Q}(0) = q - \lambda Q_0$, no solution $Q(t)$ of (2) with $Q(t) > 0$ can become zero.

2. *Dissipativity: the trajectories evolve to an attracting region of* $\mathbb{R}^3_+$.

Since the initial conditions are nonnegative, so are the solutions. From (2),

$$\dot{N}_1(t) \leq r_1 N_1(t) \left[1 - \frac{N_1(t)}{K_1}\right].$$

From standard comparison theory, we get

$$\limsup_{t\to\infty} N_1(t) \leq K_1.$$

Similarly,

$$\limsup_{t\to\infty} N_2(t) \leq K_2.$$

We also have $\dot{Q}(t) \leq q - \lambda Q(t)$ giving

$$\limsup_{t\to\infty} Q(t) \leq \lambda^{-1} q.$$

Hence, the region $\mathbf{R} = \{(N_1, N_2, Q) \in \mathbb{R}^3_+ \,|\, 0 \leq N_1 \leq K_1,\ 0 \leq N_2 \leq K_2,\ 0 \leq Q \leq \lambda^{-1}q\}$ is an attracting invariant region proving the property.

The last, but not least, important property was introduced in [**14**] but also used in [**15**]:

3. *Cancer Hypothesis: In the absence of any treatment, CCs always win the competition with NCs.*

In this case, the system (2) is simplified as

$$\begin{cases} \dot{N}_1(t) = r_1 N_1(t)\left[1 - \dfrac{N_1(t)}{K_1} - \alpha_1 \dfrac{N_2(t)}{K_1}\right], \\ \dot{N}_1(t) = r_2 N_2(t)\left[1 - \dfrac{N_2(t)}{K_2} - \alpha_2 \dfrac{N_1(t)}{K_2}\right], \end{cases} \tag{3}$$

in which we must have, if $N_2(0) > 0$, $N_1(0) \geq 0$, then

$$\lim_{t\to\infty} (N_1(t), N_2(t)) = (K_1, 0).$$

From [**7**] this implies that

$$\alpha_1 < \frac{K_1}{K_2} \quad \text{and} \quad \alpha_2 > \frac{K_2}{K_1}, \tag{4}$$

which we assume throughout this paper. The no-treated particular model given by (3) was discussed in [**8**].

3 Existence and local stability of equilibria We denote the equilibria of system (2) by $G(N_1^*, N_2^*, Q^*)$. The equilibria are given by

- $G_1(0, 0, q/\lambda)$ (no cells state);
- $G_2(0, \overline{N}_2, q/\lambda)$ (cure state - no CCs);
- $G_3(\overline{N}_1, 0, q/\lambda)$ (cancer state - no NCs);
- $G_4(\overline{N}_1, \overline{N}_2, q/\lambda)$ (interior state);

where

$$\breve{N}_1 = \frac{K_1\,[r_1\,a\,\lambda - q(\mu - r_1)]}{r_1\,(a\,\lambda + q)}, \quad \breve{N}_2 = \frac{K_2\,[r_2\,b\,\lambda - q(\nu - r_2)]}{r_2\,(b\,\lambda + q)},$$

(5)
$$\overline{N}_1 = \frac{(q+b\lambda)K_1 r_2\,[q\mu - (q+a\lambda)r_1] - (q+a\lambda)K_2 r_1\,[q\nu - (q+b\lambda)r_2]\,\alpha_1}{(q+a\lambda)(q+b\lambda)r_1 r_2\,(\alpha_1\alpha_2 - 1)},$$

and
(6)
$$\overline{N}_2 = \frac{(q+a\lambda)K_2 r_1\,[q\nu - (q+b\lambda)r_2] - (q+b\lambda)K_1 r_2\,[q\mu - (q+a\lambda)r_1]\,\alpha_2}{(q+a\lambda)(q+b\lambda)r_1 r_2\,(\alpha_1\alpha_2 - 1)}.$$

In order to analyse the local stability of equilibria, the Jacobian matrix $\mathbb{J}(N_1, N_2, Q)$ of system (2) is given by

$$\mathbb{J}(N_1, N_2, Q) = \begin{bmatrix} j_{11} & j_{12} & j_{13} \\ j_{21} & j_{22} & j_{23} \\ 0 & 0 & -\lambda \end{bmatrix}, \tag{7}$$

where

$$j_{11} = \frac{r_1(K_1 - 2N_1 - \alpha_1 N_2)}{K_1} - \frac{\mu Q}{a+Q},$$
$$j_{22} = \frac{r_2(K_2 - 2N_2 - \alpha_2 N_1)}{K_2} - \frac{\nu Q}{b+Q},$$
$$j_{12} = -\frac{r_1 N_1 \alpha_1}{K_1}, \qquad j_{21} = -\frac{r_2 N_2 \alpha_2}{K_2},$$
$$j_{13} = -\frac{\mu N_1}{a+Q} + \frac{\mu N_1 Q}{(a+Q)^2}, \qquad j_{23} = -\frac{\nu N_2}{b+Q} + \frac{\nu N_2 Q}{(b+Q)^2}.$$

The no cells state G_1 always exists in $\mathbb{R}^3_+$. Based on (7), its eigenvalues are

$$\Theta_1 = \frac{r_1\,a\,\lambda - q(\mu - r_1)}{a\,\lambda + q}, \quad \Theta_2 = \frac{r_2\,b\lambda - q(\nu - r_2)}{b\,\lambda + q}, \quad \Theta_3 = -\lambda. \tag{8}$$

Since $\lambda > 0$, $\Theta_3 < 0$. However, G_1 must be unstable because there is no biological meaning for no cells state. Therefore, we have to impose $\Theta_1 > 0$ or $\Theta_2 > 0$, that correspond to the conditions for which G_2 and G_3, respectively, exist in the positive cone.

Lemma 1. *Assuming $\nu > r_2$, G_2 exists in $\mathbb{R}^3_+$ and G_1 is locally unstable when $\nu < r_2\,(q + b\,\lambda)/q$.*

Lemma 2. *Assuming $\mu > r_1$, G_3 exists in $\mathbb{R}^3_+$ and G_1 is locally unstable when $\mu < r_1\,(q + a\,\lambda)/q$.*

The eigenvalues of cure state G_2 are:

$$\begin{aligned} &\Gamma_1 = -\frac{[r_2 b\lambda - q(\nu - r_2)]}{q + b\lambda}, \qquad \Gamma_3 = -\lambda, \\ &\Gamma_2 = r_1 \left\{ \frac{1 - K_2\alpha_1\,[r_2 b\lambda - q(\nu - r_2)]}{(q + b\lambda)K_1 r_2} \right\} - \frac{q\mu}{q + a\lambda}. \end{aligned} \tag{9}$$

According to Lemma 2, which sets up the condition for existence of G_2, we have $\Gamma_1 < 0$. Therefore, since $\Gamma_3 < 0$, that is enough $\Gamma_2 < 0$ to guarantee asymptotical stability of G_2. Using the condition $\Gamma_2 < 0$ we can enunciate the following theorem.

Theorem 1. *Suppose that $r_2 < \nu < r_2\,(q + b\,\lambda)/q$. Then G_2 is locally asymptotically stable if and only if*

$$\mu > r_1 \frac{(q + a\lambda)}{q} \left\{ 1 - \frac{\alpha_1 K_2}{K_1} \left[1 - \frac{q\nu}{(q + b\lambda)r_2} \right] \right\}. \tag{10}$$

Otherwise it is a hyperbolic saddle point.

Since μ represents how much efficient the chemotherapy agent is to kill CCs, Theorem 1 sets up the threshold condition to guarantee the elimination of CCs when the chemotherapy acts, for initial conditions, such that the tumour is not too large. Using one of the conditions ($K_2 < K_1\alpha_2$) of cancer hypothesis (4), Theorem 1 leads to the following corollary.

Corollary 1. *Suppose that $r_2 < \nu < r_2\,(q + b\,\lambda)/q$. Then G_2 is a hyperbolic saddle point when*

$$\mu < r_1 \frac{(q + a\lambda)}{q} \left\{ 1 - \alpha_1\alpha_2 \left[1 - \frac{q\nu}{(q + b\lambda)r_2} \right] \right\}.$$

Note that the above condition does not depend on the carrying capacities of the cells.

Analogously, the eigenvalues of cancer state G_3 are

$$\begin{aligned}
&\Psi_2 = -\frac{[r_1 a\lambda - q(\mu - r_1)]}{q + a\lambda}, \qquad \Psi_3 = -\lambda, \\
&\Psi_1 = r_2 \left\{ \frac{1 - K_1\alpha_2\,[r_1 a\lambda - q(\mu - r_1)]}{(q + a\lambda)K_2 r_1} \right\} - \frac{q\nu}{q + b\lambda}.
\end{aligned} \tag{11}$$

According to Lemma 1, which sets up the condition for existence of G_3, we have $\Psi_2 < 0$. Since the cancer state G_3 has no biological meaning, if it exists, we have to impose $\Psi_1 > 0$; in this case, we enunciate the following theorem.

Theorem 2. *Suppose that $r_1 < \mu < r_1(q + a\,\lambda)/q$. G_3 is a hyperbolic saddle point if and only if*

$$\mu > r_1 \frac{(q + a\lambda)}{q} \left\{ 1 - \frac{K_2}{K_1\alpha_2} \left[1 - \frac{q\nu}{(q + b\lambda)r_2} \right] \right\}. \tag{12}$$

Otherwise it is locally asymptotically stable.

The existence of the interior equilibrium G_4 is related to the unstable character of G_2 and G_3. Comparing the expressions (5) and (6) with Theorems 1 and 2, we obtain the following theorem.

Theorem 3. *Suppose that $r_1 < \mu < r_1\,(q + a\,\lambda)/q$, $r_2 < \nu < r_2\,(q + b\,\lambda)/q$ and $\alpha_1\alpha_2 < 1$. G_4 exists when G_2 and G_3 are hyperbolic saddle points.*

The characteristic polynomial of the interior state G_4 is given by

$$(-\lambda - \Theta)(\Theta^2 + A_1\Theta + A_0) = 0, \tag{13}$$

with

$$\begin{aligned}
A_1 = &-\frac{K_2\,[q\nu - (q + b\lambda)r_2]\,\alpha_1 r_1}{K_1 r_2(q + b\lambda)\,(\alpha_1\alpha_2 - 1)} - \frac{K_1\,[q\mu - (q + a\lambda)r_1]\,\alpha_2 r_2}{K_2 r_1(q + a\lambda)\,(\alpha_1\alpha_2 - 1)} \\
&- \frac{(r_1 + r_2)}{(\alpha_1\alpha_2 - 1)} + \frac{[q(q(\mu + \nu) + \lambda(b\mu + a\nu))]}{(q + a\lambda)(q + b\lambda)\,(\alpha_1\alpha_2 - 1)}, \\
A_0 = &\frac{[q\mu - (q + a\lambda)r_1]\,(1 + \alpha_2)}{(q + a\lambda)^2(q + b\lambda)K_2 r_1\,(\alpha_1\alpha_2 - 1)} \\
&- \frac{[q\nu - (q + b\lambda)r_2]\,(1 - \alpha_1)}{(q + a\lambda)(q + b\lambda)^2 K_1 r_2\,(\alpha_1\alpha_2 - 1)}.
\end{aligned}$$

The local stability of G_4 depends on the signals of A_0 and A_1. If $A_0 > 0$ and $A_1 > 0$, then G_4 is locally asymptotically stable.

Note that the above analytical results were presented in terms of the threshold of μ and ν for fixed value of q. A similar analysis can be performed, based on the eigenvalues, for fixed values of μ and ν, varying the value of q, leading to more complicated inequalities.

4 Numerical simulations In this section, we present some numerical simulations of the model (2) such that the system may evolve to the cure state G_2 or to the interior state G_4.

The parameter values, presented on Table 1, are based on some biological information and on the conditions imposed by Lemmas 1 and 2. Moreover, we assume G_3 is a hyperbolic saddle point according to Theorem 2.

Parameter	Value	Unit	Reference/Comment
r_1	10^{-2}	day^{-1}	[**17**]
r_2	10^{-3}	day^{-1}	$r_2 < r_1$
K_1	10^{12}	cells	[**17**]
K_2	10^{12}	cells	$K_2 \sim K_1$
α_1	9×10^{-2}	-	$\alpha_1 < K_1/K_2$ (*cancer hypothesis*)
α_2	1.5	-	$\alpha_2 > K_1/K_2$ (*cancer hypothesis*)
μ	8	day^{-1}	$\mu > r_1$ (Lemma 2)
ν	8×10^{-2}	day^{-1}	$\nu > r_2$ (Lemma 1) and $\nu \ll \mu$ [**3**]
q	5	mg day^{-1}	continuous infusion [**5**]
λ	4.16	day^{-1}	[**12**]
a	2×10^3	mg	assumed value
b	5×10^6	mg	assumed value

TABLE 1: A list of parameter values for the model (2).

In relation to the biological restrictions, it is important to emphasize that

i) $r_1 > r_2$ means that CCs grows faster than NCs due to the fact that CCs postpone apoptosis;

ii) $\mu \gg \nu$ because the chemotherapy action on CCs is more intense than on NCs [**3**].

Concerning the chemotherapy infusion, we assume a situation for which the CA is applied continuously [**5**] or as a limit case of the periodic infusion such that the time interval between the infusions goes to zero [**2**]. As a chemotherapy agent, we consider, for example, cyclophosphamide whose elimination half-life $t_{1/2}$ of 4 hours [**12**] leads to $\lambda = \ln 2/t_{1/2} \approx 4.16$ day^{-1}.

In Figure 1, we illustrate the effect of infusion rate q of CA on the steady state, for fixed value of killing rate μ of CA on CCs in case of a detectable tumour at $t = 0$. In Figure 1(a), the model (2) evolves to the cure state. Meanwhile in Figure 1(b), for smaller value of q, it evolves to the interior equilibrium.

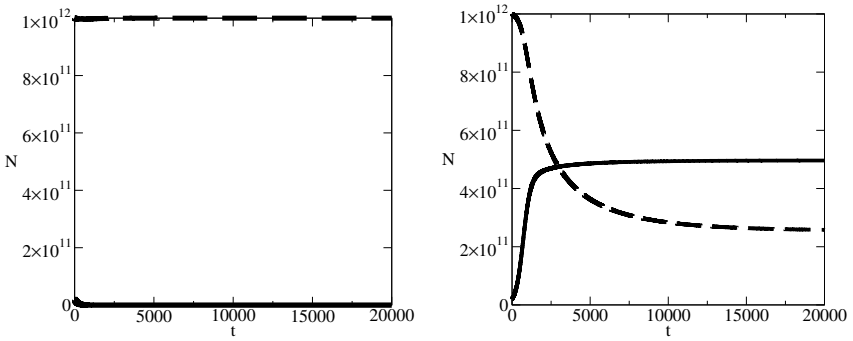

FIGURE 1: Constant infusion of CA (N_1 (CCs): solid line and N_2 (NCs): dashed line). Initial conditions: $N_1(0) = 2 \times 10^{10}$ cells, $N_2(0) = 10^{12}$ cells and $Q(0) = 0$; parameter values are listed on Table 4, except for q. (a) Cure state is reached for $q = 15$ mg day^{-1}; (b) interior equilibrium, for $q = 5$ mg day^{-1}.

Figure 2 shows the effect of CA efficiency in killing CCs (μ) assuming fixed value of infusion rate q in case of a detectable tumour at $t = 0$. It illustrates the conditions of Theorems 1 and 2. In Figure 2(a), when CA is more efficient in killing CCs, the model (2) evolves to the cure state that is asymptotically stable according to Theorem 1. For smaller

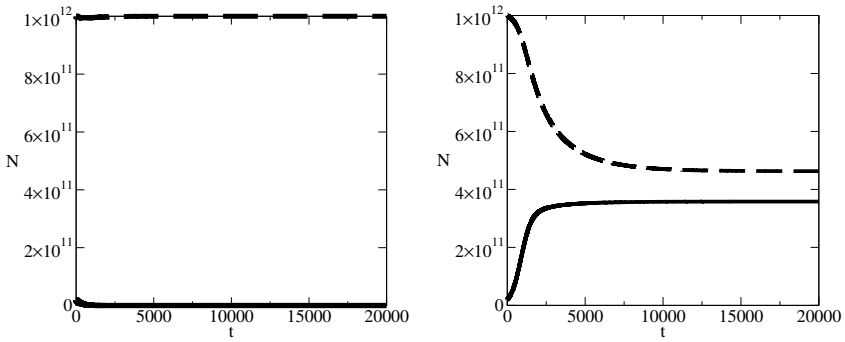

FIGURE 2: Constant infusion of CA (N_1 (CCs): solid line and N_2 (NCs): dashed line). Initial conditions: $N_1(0) = 2 \times 10^{10}$ cells, $N_2(0) = 10^{12}$ cells and $Q(0) = 0$. Parameter values are listed on Table 4, except for μ and q ($q = 10$ mg day^{-1} in both cases). (a) Cure equilibrium is reached for $\mu = 10$ day^{-1}. (b) Interior equilibrium, for $\mu = 5$ day^{-1}.

value of μ, shown in Figure 2(b), it evolves to the equilibrium state when G_2 is a hyperbolic saddle point according to Theorem 1. In both cases, condition (12) of Theorem 2 holds and G_3 is a hyperbolic saddle point.

Finally, the bifurcation diagrams in relation to q and to μ are shown, respectively, in Figures 3(a) and 3(b). They show the transitions between the cancer state G_3 and the interior equilibrium G_4 as well as between G_4 and the cure state G_2. We can observe that both the infusion rate of CA and the efficiency of CA in killing CCs are relevant to reach the cure state. The transitions values of μ shown in Figure 3(b), μ_{t1} and μ_{t2}, correspond, respectively, to the threshold values of μ that result from $\Psi_1 > 0$ and $\Gamma_2 < 0$, leading to Theorems 1 and 2. Therefore, the threshold values are also consistent with Corollary 1 presented in Section 3.

In the next section, we will show that, for some region of parameter space, the cure state is globally stable for any initial size of tumour.

5 Global stability of cure state In this section, we find a suitable Liapunov function [**10**] for the cure state $G_2(0, \breve{N}_2, q/\lambda)$. We set up a

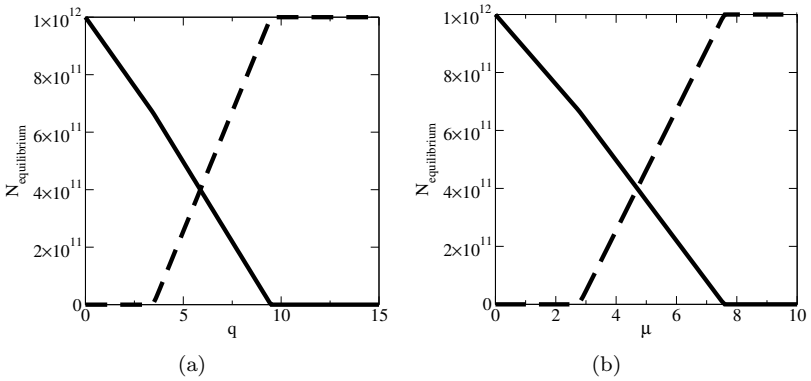

FIGURE 3: Bifurcation diagram of parameters q and μ: N_1 (CCs): solid line and N_2 (NCs): dashed line. Parameter values (except μ and q) are listed on Table 4; initial conditions: $N_1(0) = 2\times10^{10}$ cells, $N_2(0) = 10^{12}$ cells and $Q(0) = 0$. (a) q is the control parameter ($\mu = 8$ day^{-1}). (b) μ is the control parameter ($q = 10$ mg day^{-1}). The threshold values of μ are $\mu_{t1} = 2.77$ day^{-1} and $\mu_{t2} = 7.58$ day^{-1}.

positive definite functional $V : \mathcal{F}([0,\infty], \mathbb{R}^3_+) \to \mathbb{R}$ of the form

$$V[N_1(t), N_2(t), Q(t)] = N_2(t) - \breve{N}_2 - \breve{N}_2 \ln \frac{N_2(t)}{\breve{N}_2} + AN_1(t) + \frac{B}{2}\left[Q(t) - \frac{q}{\lambda}\right]^2, \tag{14}$$

for which the arbitrary constants A and B are positive. Then the derivative of V ($\dot{V} = dV/dt$) can be written as

$$\dot{V} = \frac{\dot{N}_2}{N_2}(N_2 - \breve{N})^2 + A\dot{N}_1 + B\left(Q - \frac{q}{\lambda}\right)\dot{Q}$$

that leads to

$$\begin{aligned}\dot{V}[N_1(t),N_2(t), Q(t)] &= (N_2 - \breve{N}_2)r_2\left(1 - \frac{N_2}{K_2} - \alpha_2\frac{N_1}{K_2}\right) - \frac{\nu Q}{b+Q}(N_2 - \breve{N}_2) \\ &\quad + Ar_1N_1\left(1 - \frac{N_1}{K_1} - \frac{\alpha_1 N_2}{K_1}\right) - \frac{A\mu N_1 Q}{a+Q} + B\left(Q - \frac{q}{\lambda}\right).\end{aligned}$$

After some further calculations, we obtain

$$
\begin{aligned}
(15)\qquad \dot{V} = {} & r_2(N_2-\breve{N}_2)\left[-\frac{(N_2-\breve{N}_2)}{K_2}+\frac{(K_2-\breve{N}_2)}{K_2}\right] \\
& -\frac{r_2\alpha_2}{K_2}N_1(N_2-\breve{N}_2)-\frac{Ar_1}{K_1}N_1^2 \\
& +\frac{Ar_1}{K_1}N_1\left[K_1-\alpha_1\breve{N}_2-\alpha_1(N_2-\breve{N}_2)\right] \\
& -\frac{\nu}{b+Q}Q(N_2-\breve{N}_2)-\frac{A\mu}{a+Q}N_1Q-\frac{B}{\lambda}(q-\lambda Q)^2.
\end{aligned}
$$

Since $G_2(0,\breve{N}_2,q/\lambda)$ is a steady state, we have

$$
(16)\qquad \frac{\mu q}{a\lambda+q}=\frac{r_2}{K_1}(K_1-\alpha_1\breve{N}_2)\quad\text{and}\quad\frac{\nu q}{b\lambda+q}=\frac{r_2}{K_2}(N_2-\breve{N}_2).
$$

Replacing (16) in (15) leads to

$$
\begin{aligned}
(17)\qquad & \frac{dV}{dt}[N_1,N_2,Q] \\
& =-\frac{r_2}{K_2}(N_2-\breve{N}_2)^2+\frac{\nu q}{b\lambda+q}(N_2-\breve{N}_2) \\
& \quad -\frac{r_2\alpha_2}{K_2}N_1(N_2-\breve{N}_2)-\frac{A\mu}{a+Q}N_1Q \\
& \quad -\frac{Ar_1\alpha_1}{K_1}N_1(N_2-\breve{N}_2)+\frac{A\mu q}{a\lambda+q}N_1 \\
& \quad -\frac{Ar_1}{K_1}N_1^2-\frac{\nu}{b+Q}Q(N_2-\breve{N}_2)-\frac{B}{\lambda}(q-\lambda Q)^2.
\end{aligned}
$$

Finally, we obtain that, for any value of $t>0$, the derivative of the

Liapunov function is negative according to the following expression:

$$\begin{aligned}(18)\qquad \frac{dV}{dt}[N_1,N_2,Q] &= -\frac{r_2}{K_2}(N_2-\breve{N}_2)^2 - \frac{b\nu}{(b\lambda+q)(b+Q)} \\ &\quad \times (N_2-\breve{N}_2)(\lambda Q-q) - \frac{Ar_1}{K_1}N_1^2 \\ &\quad - \left(\frac{r_2\alpha_2}{K_2}+\frac{Ar_1\alpha_1}{K_1}\right)N_1(N_2-\breve{N}_2) \\ &\quad - \frac{Aa\mu}{(a\lambda+q)(b+Q)}N_1(\lambda Q-q) - \frac{B}{\lambda}(q-\lambda Q)^2.\end{aligned}$$

Therefore, there is a region of parameter space for which the cure state G_2 is globally stable, i.e., G_2 is an attractor of the system for any initial conditions.

6 Concluding remarks Inspired by some previous works of Prof. Freedman and collaborators, we present, in this work, a simple mathematical model to simulate the chemotherapy response to tumour growth in the case that the vascularization has stabilized. Considering the interaction between the CCs, NCs and CA, we obtain the local stability conditions of cure state, cancer state and interior equilibrium.

The threshold conditions for infusion rate and efficiency of CA are set up in order to reach the cure state and some numerical simulations are performed. The diagram bifurcations, associated to infusion rate and efficiency of CA, exhibit the transitions between cancer state, interior equilibrium and cure state. Moreover, we obtain a Liapunov function for the cure state showing its the global stability. It is important to call the attention of the relevance of cancer hypothesis in our analysis.

In our future work, we intend to take into account the endothelial cells in order to consider the tumour angiogenesis as a dynamical process. Besides we analyse the periodic infusion of chemotherapy agent.

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