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MATHEMATICAL ANALYSIS AND SIMULATIONS INVOLVING CHEMOTHERAPY AND SURGERY ON LARGE HUMAN TUMOURS UNDER A SUITABLE CELL-KILL FUNCTIONAL RESPONSE

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Abstract. Dosage and frequency of treatment schedules are important for successful chemotherapy. However, in this work we argue that cell-kill response and tumoral growth should not be seen as separate and therefore are essential in a mathematical cancer model. This paper presents a mathematical model for sequencing of cancer chemotherapy and surgery. Our purpose is to investigate treatments for large human tumours considering a suitable cell-kill dynamics. We use some biological and pharmacological data in a numerical approach, where drug administration occurs in cycles (periodic infusion) and surgery is performed instantaneously. Moreover, we also present an analysis of stability for a chemotherapeutic model with continuous drug administration. According to Norton & Simon [22], our results indicate that chemotherapy is less efficient in treating tumours that have reached a plateau level of growing and that a combination with surgical treatment can provide better outcomes.

1. **Introduction.** Cancer is considered a serious public health problem worldwide. According to data provided by the World Health Organization (WHO) [32], 7.6 million people worldwide died from cancer in 2008, approximately 70% of cancer deaths occur in low- and middle-income countries and 30% of cancers could be prevented. One of the most applied type of cancer treatment is antineoplastic chemotherapy, which utilizes various approaches in order to eliminate tumour cells: the administration of one or more cycle-nonspecific or cycle-specific drug, used in conjunction (or not) with other treatments. Said drug is usually administered periodically, that is, in cycles.

The evolution of cancer treatment and its difficulties is a very interesting part of the history of science (Mukherjee [20]), including chemotherapy. Chemotherapy uses drugs to kill tumour cells, decrease their growth rate or ameliorate the symptoms of the disease presented by the patient. Neoadjuvant chemotherapy is designed to be applied before any surgical procedure, and its aim is the reduction of the tumoral mass, as well as to facilitate the surgeon's task of distinguishing normal cells from

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tumour cells. Another form of chemotherapy is that which is known as adjuvant, which is applied after other treatments, such as radiotherapy or surgery, aiming to reduce the chance of recurrence and metastasis (the spread of a disease from one organ or part to another non-adjacent part).

One fundamental pattern in cancer development is angiogenesis, in which a neovascularization process is started by the tumour. It consists, basically, of the migration of capillary sprouts stimulated by substances known as Tumoral Angiogenic Factors (TAF). However, there are other substances that inhibit tumoral neovascularization, the Tumoral Inhibitor Factors (TIF). In our proposed model, the angiogenesis process is considered in a steady state level, that is, in equilibrium (Ferrara & Gerber [9]).

Mathematical models are very important in the understanding of the effects of drug administration in chemotherapy (Fister & Panetta [10], Martin *et al.* [15]) and cancer chemotherapy failures (Pinho *et al.* [24], Rodrigues *et al.* [25]). Because the amount of the drug administered should be minimized, many papers address the optimal control problem (de Pillis & Radunskaya [4], de Pillis *et al.* [5], d'Onofrio *et al.* [6]). Other deals with multi-scale simulation (Stamatakos *et al.* [30]), Monte Carlo models (Marcu *et al.* [14]) and ordinary differential equations (for example, Pinho *et al.* [23]). However, only a few papers have been dedicated to cell-kill dynamics, as Kohandel *et al.* [13].

Regarding the modelling of tumour cell mortality rates caused by chemotherapeutic agents, Skipper *et al.* [28] conjecture that a given dose of chemotherapy kills a fixed fraction of the remaining cells – a hypothesis known as the log-kill. Another approach by Norton & Simon [22] hypothesized that cell-kill is proportional to the growth rate of the tumour population, in a exponential, logistic or Gompertzian manner. It must be emphasized that these are different models of tumoral pharmacodynamics and that in general, one is not necessarily more effective than the other. However, in particular cases one is the more appropriate choice. For chemotherapy of large human tumours, that is, those that have reached a saturated level of growth, the log-kill model is not suitable – otherwise all solid tumours would be potentially curable, assuming the anticancer drugs utilized had a sufficiently large fractional kill rate. Therefore, we argue that the Norton-Simon hypothesis provides a better explanation in such situations, as large human tumours grow more slowly than small tumours. We refer only to human tumours because "non-human" tumours do not always show sigmoidal growth curves (see Browder *et al.* [2] for a counter-example of an exponential growth of the tumour in mice). In this way, we focus our analysis on this treatment, considering the normal and tumour cell growth behaviour given by logistic equation, which has been shown to be a more accurate choice for the purposes of modelling the growth of some human tumours (Vaidya & Alexandro-Jr. [31]).

In this paper, we present a model that is based on previous work by Rodrigues *et al.* [25], in which the fundamental difference lies in the drug functional response. In spite there existing only this difference, we have added another kind of treatment (surgery) in order to investigate treatments of large human tumours under the Norton-Simon hypothesis (Norton & Simon [22]). We performed numerical simulations using some data for the model parameters and tumour/normal cells. Moreover, we analysed the stability of the system of ordinary differential equations – only as it regarded chemotherapy involving continuous drug administration. Our

simulations provide a mathematical explanation for why chemotherapy often fails when it is used to treats large human tumours.

This paper has the following structure: In section 2, we present the proposed model. In section 3, we analyse the local stability of equilibrium. Section 4 contains simulations of treatment involving chemotherapy and surgery. In section 5, the conclusions are presented.

2. **Model.** We consider a mathematical model formed by 3 ordinary differential equations whose compartments are tumour cells, normal cells and chemotherapeutic agent. For chemotherapy, we reference just one cycle-nonspecific drug.

Denoting the number of tumour and normal cells by $N_i\,(i=1,2)$ and the dose of chemotherapeutic agent by Q, we propose the following model based on Rodrigues *et al.* [25, 26]:

$$\begin{cases} \dfrac{dN_1}{dt} &= r_1\,N_1\left(1-\dfrac{N_1}{k_1}-\dfrac{\alpha_{12}}{k_1}N_2\right)-\mu\,r_1\,N_1\left(1-\dfrac{N_1}{k_1}\right)Q \\ \dfrac{dN_2}{dt} &= r_2\,N_2\left(1-\dfrac{N_2}{k_2}-\dfrac{\alpha_{21}}{k_2}N_1\right)-\nu\,r_2\,N_2\left(1-\dfrac{N_2}{k_2}\right)Q \\ \dfrac{dQ}{dt} &= q-\lambda\,Q \end{cases}, \tag{1}$$

where the index $i=1$ is associated with the tumour cell population and $i=2$ with the normal cell population, $r_i>0$ denotes the rate of growth of the tumour and normal populations; the flux of infusion of the chemotherapeutic agent is modelled by the function q defined in $[\,0,\infty)$ and satisfying $q(\cdot)\geq 0$; α_{ij} is the competition coefficient on the population N_i due to N_j (adimensional); k_1 is the carrying capacity of tumour cells and k_2 is the carrying capacity of the normal cells; $\mu=\frac{1}{m}$ and $\nu=\frac{1}{n}$, where m and n are the numbers of molecules (or unit of drugs) uptaken by, respectively, tumour and normal cells, to effectively kill them, and it is supposed to be $n>m$; $\lambda>0$ is the washout rate of a given agent cycle-nonspecific chemotherapy.

Although it is important to analyse the stability of the tumour-free equilibrium in the absence of chemotherapy, we do not do this because $Q(0)=0$ and $q(\cdot)\equiv 0$ represent no treatment and system (1) becomes a Lotka-Volterra model, which has been proposed and analysed by Gatenby [11].

In order to focus on the connection between drug effect and tumour growth, we use the simplest pharmacokinetic and pharmacodynamic models. For pharmacokinetics, we consider the decay of the drug plasma concentration to be exponential (see Bellman [1], Martin [17]). Regarding pharmacodynamics, we use a much simpler functional response than the Michaelis-Menten response: linear in Q, in order to focus on the saturation of tumour growing we neglect additional non-linearities in the amount of the drug. We use only one chemotherapic drug, since polychemotherapy includes drug-drug interactions and synergy/antagonism relations are difficult to model.

Due to previous research (Rodrigues *et al.* [26]) we do not consider angiogenesis explicitly in the proposed model (1), since we suppose that: a) In $t=t_0$, the neovascularization process is in a stable steady-state; TAF and TIF have reached equilibrium, and b) there is no significant antiangiogenic effect of chemotherapeutic

drug on endothelial vascular cells. With regard to a), we know that tumoral angiogenesis occurs firstly, and that after this neovascularization the tumour growth is more pronounced (Ferrara & Gerber [9]). Related to item b), we consider only conventional schedules in which antiangiogenic effects are inexistent or negligible, and therefore metronomic schedules cannot be considered (see Browder *et al.* [2] for both cases).

3. **Equilibrium solutions: Local stability.** Considering that $q(t)$ is constant (autonomous system), the equilibrium points of (1) are given by the following expressions, where $Q = \frac{q}{\lambda}$:

- $P_1 = (0, 0, Q)$;
- $P_2 = (0, k_2, Q)$;
- $P_3 = (k_1, 0, Q)$;
- $P_4 = (N_1, N_2, Q)$.

We now define both ν_c and μ_c, which can assume positive or negative values, but are bounded by $\nu_c < 1$ and $\mu_c < 1$. Assuming that $\alpha_{12} > 0$ and $\alpha_{21} > 0$, we have

$$\nu_c = 1 - \frac{k_1}{k_2}\alpha_{21}, \tag{2}$$

$$\mu_c = 1 - \frac{k_2}{k_1}\alpha_{12}. \tag{3}$$

We write N_1 and N_2 as

$$N_1 = \frac{\mu\,\nu\,k_1\left(\frac{1}{\nu} - Q\right)\left(\frac{\mu_c}{\mu} - Q\right)}{b}, \tag{4}$$

$$N_2 = \frac{\mu\,\nu\,k_2\left(\frac{\nu_c}{\nu} - Q\right)\left(\frac{1}{\mu} - Q\right)}{b}, \tag{5}$$

where

$$b = \mu\,\nu\,Q^2 - (\mu + \nu)\,Q + (1 - \alpha_{12}\,\alpha_{21})\,. \tag{6}$$

We now analyse the local stability of the equilibrium points (from the Jacobian matrix).

The equilibrium point $P_1 = (0, 0, Q)$ is stable if $Q > \frac{1}{\nu}$ and $Q > \frac{1}{\mu}$. This situation implies that the amount of the drug administered is greater than the amount of the drug uptaken by both normal and tumour cells. As our goal is the survival of the patient, P_1 must be unstable.

The second point $P_2 = (0, k_2, Q)$ is stable if $Q < \frac{1}{\nu}$ and $Q > \frac{\mu_c}{\mu}$ (or, $\frac{\mu_c}{\mu} < Q < \frac{1}{\nu}$). Therefore, in successful treatment, the amount of the drug administered is less than the amount of drug uptaken by normal cells and greater than a threshold value for tumour cells elimination. We note that for $\mu_c < 0$ only $Q < \frac{1}{\nu}$ results in the stability of P_2.

The third point $P_3 = (k_1, 0, Q)$ is stable if $Q > \frac{\nu_c}{\nu}$ and $Q < \frac{1}{\mu}$ (or, $\frac{\nu_c}{\nu} < Q < \frac{1}{\mu}$). Therefore, this situation implies that the amount of the drug administered is less than the amount of drug uptaken by tumour cells and greater than a threshold value above which normals cells are destroyed. Again, we expect the survival of the patient, rendering P_3 biologically unfeasible. For $\nu_c < 0$, only $Q < \frac{1}{\mu}$ allows for the stability of P_3.

The local stability analysis for $P_4 = (N_1, N_2, Q)$ is now presented. The Jacobian matrix corresponding to P_4 is given by

$$J = \begin{bmatrix} \frac{r_1 N_1}{k_1} \mu \left(Q - \frac{1}{\mu} \right) & \frac{r_1 N_1}{k_1} \alpha_{12} \\ \frac{r_2 N_2}{k_2} \alpha_{21} & \frac{r_2 N_2}{k_2} \nu \left(Q - \frac{1}{\nu} \right) \end{bmatrix}$$

and its stability is given by $\mathrm{tr}(J) < 0$ and $\det(J) > 0$.

The trace is

$$\mathrm{tr}(J) = \frac{r_1 N_1}{k_1} \mu \left(Q - \frac{1}{\mu} \right) + \frac{r_2 N_2}{k_2} \nu \left(Q - \frac{1}{\nu} \right). \tag{7}$$

We have $\mathrm{tr}(J) < 0$ if $Q < \frac{1}{\mu}$ and $Q < \frac{1}{\nu}$.

The determinant is given by

$$\det(J) = \frac{r_1 N_1}{k_1} \frac{r_2 N_2}{k_2} b. \tag{8}$$

Let us analyze the sign of b. We observe that N_1 and N_2 contains the term b, but it does not influence in the sign of $\det(J)$ because it appears as a square. We obtain two positive roots, since the discriminant of the second degree polinomial is positive, and the minor is

$$Q_< = \frac{\mu_c^<}{\mu} = \frac{\nu_c^<}{\nu}, \tag{9}$$

where

$$\mu_c^< = \frac{(\mu + \nu) - \sqrt{(\mu - \nu)^2 + 4\mu\,\nu\,\alpha_{12}\,\alpha_{21}}}{2\nu} \tag{10}$$

and

$$\nu_c^< = \frac{(\mu + \nu) - \sqrt{(\mu - \nu)^2 + 4\mu\,\nu\,\alpha_{12}\,\alpha_{21}}}{2\mu}. \tag{11}$$

It is not difficulty to show that $\mu_c^< < 1$ and $\nu_c^< < 1$.

The greater value is

$$Q_> = \frac{\mu_c^>}{\mu} = \frac{\nu_c^>}{\nu}, \tag{12}$$

where

$$\mu_c^> = \frac{(\mu + \nu) + \sqrt{(\mu - \nu)^2 + 4\mu\,\nu\,\alpha_{12}\,\alpha_{21}}}{2\nu} \tag{13}$$

and

$$\nu_c^> = \frac{(\mu + \nu) + \sqrt{(\mu - \nu)^2 + 4\mu\,\nu\,\alpha_{12}\,\alpha_{21}}}{2\mu}. \tag{14}$$

It is easy to show that $\mu_c^> > 1$ and $\nu_c^> > 1$.

Hence, if $Q < Q_<$ or $Q > Q_>$, we have $b > 0$; otherwise $Q_< < Q < Q_>$, and $b < 0$. If $b > 0$, then $\det(J) > 0$, which is true if $Q < Q_<$. The other possibility $Q > Q_>$, when $b > 0$, results in $\mathrm{tr}(J) > 0$.

Let us compare μ_c and $\mu_c^<$ (also ν_c and $\nu_c^<$), by defining, for $\mu > \nu$,

$$\begin{aligned} k_1^c &= \frac{k_2}{\alpha_{21}}\frac{\mu-\nu}{2\mu}\left[\sqrt{1+\frac{4\mu\,\nu\,\alpha_{12}\,\alpha_{21}}{(\mu-\nu)^2}}+1\right] \\ &= k_2\,\alpha_{12}\frac{2\nu}{\mu-\nu}\frac{1}{\left[\sqrt{1+\frac{4\mu\,\nu\,\alpha_{12}\,\alpha_{21}}{(\mu-\nu)^2}}-1\right]}. \end{aligned} \tag{15}$$

- For a low carrying capacity of tumour cells, that is, if $k_1 < k_1^c$ then we have $\mu_c < \mu_c^<$ and $\nu_c > \nu_c^<$.
- For a high carrying capacity of tumour cells, that is, if $k_1 > k_1^c$ then we have $\mu_c > \mu_c^<$ and $\nu_c < \nu_c^<$.

For $\mu < \nu$,

$$\begin{aligned} k_1^d &= \frac{k_2}{\alpha_{21}}\frac{\nu-\mu}{2\mu}\left[\sqrt{1+\frac{4\mu\,\nu\,\alpha_{12}\,\alpha_{21}}{(\nu-\mu)^2}}-1\right] \\ &= k_2\,\alpha_{12}\frac{2\nu}{\nu-\mu}\frac{1}{\left[\sqrt{1+\frac{4\mu\,\nu\,\alpha_{12}\,\alpha_{21}}{(\nu-\mu)^2}}+1\right]}. \end{aligned} \tag{16}$$

- For a low carrying capacity of tumour cells, that is, if $k_1 < k_1^d$ then $\mu_c < \mu_c^<$ and $\nu_c > \nu_c^<$.
- For a high carrying capacity of tumour cells, that is, if $k_1 > k_1^d$ then $\mu_c > \mu_c^<$ and $\nu_c < \nu_c^<$.

Summarizing the stability of $P_4 = (N_1, N_2, Q)$, for the case $\mu > \nu$ (biologically relevant):

- Low carrying capacity of tumour cells (decreased N_2), $k_1 < k_1^c$: We have $\mu_c < \mu_c^<$ and $\nu_c > \nu_c^<$. P_4 is stable if $Q < \frac{\mu_c}{\mu} = \min\left\{\frac{\mu_c}{\mu}, \frac{\nu_c^<}{\nu}\right\}$, the minimum value between $\frac{\mu_c}{\mu}$ and $\frac{\nu_c^<}{\nu}$. However, for $\mu_c < 0$, P_4 is unstable.
- High carrying capacity of tumour cells (increased N_2), $k_1 > k_1^c$: We have $\mu_c > \mu_c^<$ and $\nu_c < \nu_c^<$. P_4 is stable if $Q < \frac{\nu_c}{\nu} = \min\left\{\frac{\nu_c}{\nu}, \frac{\mu_c^<}{\mu}\right\}$. However, for $\nu_c < 0$, P_4 is unstable.

For $\mu < \nu$ (biologically irrelevant), the only change is k_1^d, instead of k_1^c. In the Appendix we present further results related to the stability of P_4.

3.1. **Stability analysis with varying Q.** The situation $\mu > \nu$ or $\frac{1}{\nu} > \frac{1}{\mu}$ represents a biologically relevant phenomenon, because the drug kills more tumour cells than normal cells. For example, according to Buick [3], the drug effect in lymphomas is up to 10^4 times higher than in bone marrow cells. Again we note that $\frac{\mu_c}{\mu} = \frac{\nu_c}{\nu} = Q_<$.

Varying Q, the stable equilibrium point(s) are presented:

1. Strong interaction between normal and tumour cells: $k_2\alpha_{12} > k_1$ ($\mu_c < 0$) and $k_1\alpha_{21} > k_2$ ($\nu_c < 0$), or, equivalently, $\alpha_{12}\alpha_{21} > 1$.
   (a) For $\mu > \nu$ (biologically relevant) we have:
      - If $Q > \frac{1}{\nu}$, then P_1 is stable;
      - If $\frac{1}{\mu} < Q < \frac{1}{\nu}$, then P_2 is stable;
      - If $Q < \frac{1}{\mu}$, then P_2 and P_3 are stable.
   (b) For $\mu < \nu$ (biologically irrelevant) we have:
      - If $Q > \frac{1}{\mu}$, then P_1 is stable;

- If $\frac{1}{\nu} < Q < \frac{1}{\mu}$, then P_3 is stable;
- If $Q < \frac{1}{\nu}$, P_2 and P_3 are stable.

2. Normal cells strongly inhibiting tumour cells: $k_2\alpha_{12} > k_1$ ($\mu_c < 0$) and $k_1\alpha_{21} < k_2$ ($\nu_c > 0$).
   (a) For $\mu > \nu$ (biologically relevant) we have:
   - If $Q > \frac{1}{\nu}$, then P_1 is stable;
   - If $\frac{1}{\mu} < Q < \frac{1}{\nu}$, then P_2 is stable;
   - If $\frac{\nu_c}{\nu} < Q < \frac{1}{\mu}$, then P_2 and P_3 are stable;
   - If $Q < \frac{\nu_c}{\nu}$, then P_2 is stable.

   (b) For $\mu < \nu$ (biologically irrelevant) we have:
   - If $Q > \frac{1}{\mu}$, then P_1 is stable;
   - If $\frac{1}{\nu} < Q < \frac{1}{\mu}$, then P_3 is stable;
   - If $\frac{\nu_c}{\nu} < Q < \frac{1}{\nu}$, then P_2 and P_3 are stable;
   - If $Q < \frac{\nu_c}{\nu}$, then P_2 is stable

3. Tumour cells strongly inhibiting normal cells: $k_2\alpha_{12} < k_1$ ($\mu_c > 0$) and $k_1\alpha_{21} > k_2$ ($\nu_c < 0$).
   (a) For $\mu > \nu$ (biologically relevant) we have:
   - If $Q > \frac{1}{\nu}$, then P_1 is stable;
   - If $\frac{1}{\mu} < Q < \frac{1}{\nu}$, then P_2 is stable;
   - If $\frac{\mu_c}{\mu} < Q < \frac{1}{\mu}$, then P_2 and P_3 are stable;
   - If $Q < \frac{\mu_c}{\mu}$, then P_3 is stable.

   (b) For $\mu < \nu$ (biologically irrelevant) we have:
   - If $Q > \frac{1}{\mu}$, then P_1 is stable;
   - If $\frac{1}{\nu} < Q < \frac{1}{\mu}$, then P_3 is stable;
   - If $\frac{\mu_c}{\mu} < Q < \frac{1}{\nu}$, then P_2 and P_3 are stable;
   - If $Q < \frac{\mu_c}{\mu}$, then P_3 is stable.

4. Weak interaction between normal and tumour cells: $k_2\alpha_{12} < k_1$ ($\mu_c > 0$) and $k_1\alpha_{21} < k_2$ ($\nu_c > 0$), or, equivalently, $\alpha_{12}\alpha_{21} < 1$, with $Q_< = \frac{\mu_c}{\mu} = \frac{\nu_c}{\nu}$.
   (a) For $\mu > \nu$ (biologically relevant) we have:
   - If $Q > \frac{1}{\nu}$, then P_1 is stable;
   - If $\frac{1}{\mu} < Q < \frac{1}{\nu}$, then P_2 is stable;
   - If $Q_< < Q < \frac{1}{\mu}$, then P_2 and P_3 are stable;
   - If $Q < Q_<$, then P_4 is stable.

   (b) For $\mu < \nu$ (biologically irrelevant) we have:
   - If $Q > \frac{1}{\mu}$, then P_1 is stable;
   - If $\frac{1}{\nu} < Q < \frac{1}{\mu}$, then P_3 is stable;
   - If $Q_< < Q < \frac{1}{\nu}$, then P_2 and P_3 are stable;
   - If $Q < Q_<$, then P_4 is stable.

In this subsection, we have shown the necessary and sufficient conditions to guarantee the stability of the equilibrium points, and that they are obtained imposing constraints upon Q, the amount of the drug value.

4. **Treatment: Numerical simulations.** The purpose of the simulations is to improve the understanding of cell-kill dynamics in tumour cells that are less affected by some drug and tumours that are sensitive to some drug. Additionaly, we also discuss the survival time of patients with large tumours under chemotherapy or

chemotherapy–surgery. By survival time we mean the time interval between the beginning of treatment and the instant for which the tumour reached 10^{12} cells.

For chemotherapy, following Martin & Theo [16], we define the infusion as

$$q(t) = \begin{cases} q > 0, & n \leq t < n + \tau, \\ 0, & n + \tau \leq t < n + T, \end{cases} \tag{17}$$

where T is the cycle time interval, $n = 0, T, 2T, ...$ and τ is the infusion time with $T \gg \tau$ (administration in *bolus* doses).

At the implementation of surgery, we assume instantaneous surgical performance only on the tumour cell population, the death of a proportion a of those cells. Then

$$N_1 \leftarrow aN_1, \quad \text{in} \quad t = t_s, \tag{18}$$

where t_s is the time of surgery and a is the fraction of the removed tumour cells population. Since a is a fraction, mathematically we have $0 \leq a \leq 1$, but in practice there is a lower limit below which the tumour cannot be seen or detected, which implies that $a > 0$. For example, a solid tumour is clinically palpable in humans from 10^9 cells ($\approx$ 1g) and visible in X-rays from 10^8 cells (Weinberg *et al.* [33]). For the plateau level of tumoral growth, we know that people with neoplastic disease usually do not survive for a long time after the tumour reaches around 10^{12} cells ($\approx$ 1 kg) (Spratt et al. [29], Weinberg *et al.* [33]). Therefore, we assumed that the carrying capacity of tumour cells k_1 is equal to 10^{12} cells.

An oncologic protocol established for breast cancer treatment is FEC100 [8] (fluorouracil, epirubicin and cyclophosphamide) and requires among other drugs, the intravenous application of cyclophosphamide in *bolus* at a dose of 500 mg/m^2 of the body surface of the patient, every 21 days. We adopt this oncologic protocol, but considering that the treatment only with cyclophosphamide. From a formula given by Mosteller [19], we estimate that the body surface of a patient's weight of 70 kg and height 1.70m is 1.8m^2, thus establishing dose of 900 mg per cycle. In fact, the administration time of cyclophosphamide is much less than 3 hours. However, we admit that this dose is infused into 3 hours because we assume that the drug interacts immediately with the tumour and also because the peak of plasma concentration of cyclophosphamide is approximately 3 hours after infusion (MeadJohnson [18]). An infusion of 3 hours (1/8 day) implies a infusion rate of $8 \times 900 = 7200$ mg/day.

All the calculations were carried out with consideration for the parameters given by Rodrigues et al. [26], but $\mu = 1.0$ and $\nu = 8.0 \times 10^{-2}$, and are summarized and reproduced in Table 1. At the instant of surgery $t = t_s$, we consider the removal of a fixed tumoral mass of 99,9%, that is, $a = 0.001$ in (18). In all simulations, we adopt $Q(0) = 0$ and $N_1(0) = N_2(0) = 10^{12}$ cells. The conventional schedule considered has a cycle T of 21 days (4 infusions).

Now, we present the numerical simulations performed with Runge-Kutta 4th order method. In all figures, we omitted the normal cells curve as its amount remains almost constant over time, i.e., $N_2(t) \sim 10^{12} = N_2(0)$.

In order to simulate tumour cells that are less affected by chemotherapy we decrease the μ value from 1.0 to 0.3. In Figures 1 and 2 we exhibit the temporal evolution of the conventional schedule. We obtained an ineffective tumoral response for $\mu = 0.3$ when compared to $\mu = 1.0$. It is crucial to note the behaviour in the beginning of the treatment, where the therapy has no effect, implying almost no tumoral response to the first two infusions ($t = 0$ and $t = 21$) even for drug-sensitive tumours (thick solid line in Figure 1, a close-up of the Figure 2 from 0 to

TABLE 1. Parameters values for model.

Parameter	Value	Unity	Reference/Comments
r_1	10^{-2}	day^{-1}	Spratt et al. [29]
r_2	10^{-3}	day^{-1}	$r_2 < r_1$
k_1	10^8	cell	estimated value†
k_2	10^{12}	cell	Weinberg [33], Spratt et al. [29]‡
α_{12}	9×10^{-5}	-	assumed value§
α_{21}	9×10^{-2}	-	assumed value§
λ	4.16	day^{-1}	MeadJohnson [18]♮
μ	1.0 or 0.3	mg^{-1}	-
ν	0.08	mg^{-1}	$\nu < \mu$ (biologically relevant), Buick [3]

‡k_2 can also be estimated considering that 10^9 cells equals 1g and an human adult has about 5×10^{13} cells Schaebel [27].

†Following Spratt *et al.* [29], a 6mm-diameter tumour has 1.13×10^8 cells, and Kerbel [12] afirms that an avascular tumour has a diameter less or equal to 2mm.

§We assumed values with the same magnitude of cell-cell interactions and cell-drug interactions.

♮The value of λ is calculated from equation dQ/dt with $q(t) \equiv 0$ (see system (1)) considering cyclophosphamide has as elimination half-life $t_{1/2}$ of 4 hours (MeadJohnson [18]), where $\lambda = \ln 2/t_{1/2}$.

100 days). Nevertheless, we stress that the novelty here is that large human tumours are more difficult to treat than the small human tumours due to Norton-Simon cell-kill dynamics, specially if the tumour is not so affected by chemotherapeutic drug (see thin solid line in Figure 1). In the log-kill hypothesis large or small tumours exhibit the same behaviour: each infusion of the drug kills a fixed fraction of cells that is proportional to the tumour size, but not to its growth dynamics. On the contrary, in the Norton-Simon hypothesis tumoral growth dynamics are completely relevant, and the cell-kill is not constant in a log-scale (see Figure 1).

Also regarding pharmacodynamic response, we note that the tumour as so affected by chemotherapy as by its aggressiveness, because the treatment term is given by $-\mu r_1 N_1(1 - N_1/k_1)Q$ and r_1 can be interpreted as a measure of aggressiveness, but on the other hand, dynamics are also governed by $r_1 N_1(1 - N_1/k_1)$. Therefore, although an aggressive tumour is more sensitive to chemotherapy, it grows faster than a non-agressive tumour when chemotherapy has already been completed. On the topic of the untreated tumour dynamics, we show a simulation in Figures 1 and 2 where in the absence of chemotherapy, the coexistence equilibrium point is stable (dashed line). In this way, we hold that in all our simulations we deal with a tumour is not cured spontaneously – otherwise the use of chemotherapy would not make sense.

Regarding the surgery simulation, Figure 3 shows the effect of surgery after the application of the conventional schedule at $t_s = 100$, exhibiting an increasing survival time as it was expect. Surgery does not remove all tumour cells because in practice there is a lower limit below which the tumour cannot be seen or detected (again, we note that a solid tumour is clinically palpable in humans from 10^9 cells (Weinberg *et al.* [33])) and then the tumour grows up again. However, surgery provides a further increase in the survival time of the patient. In a similar way given by Kohandel *et al.* [13], but with numerical simulation instead of a theoretical approach, this result ilustrates a real surgical oncology procedure of large human tumour.

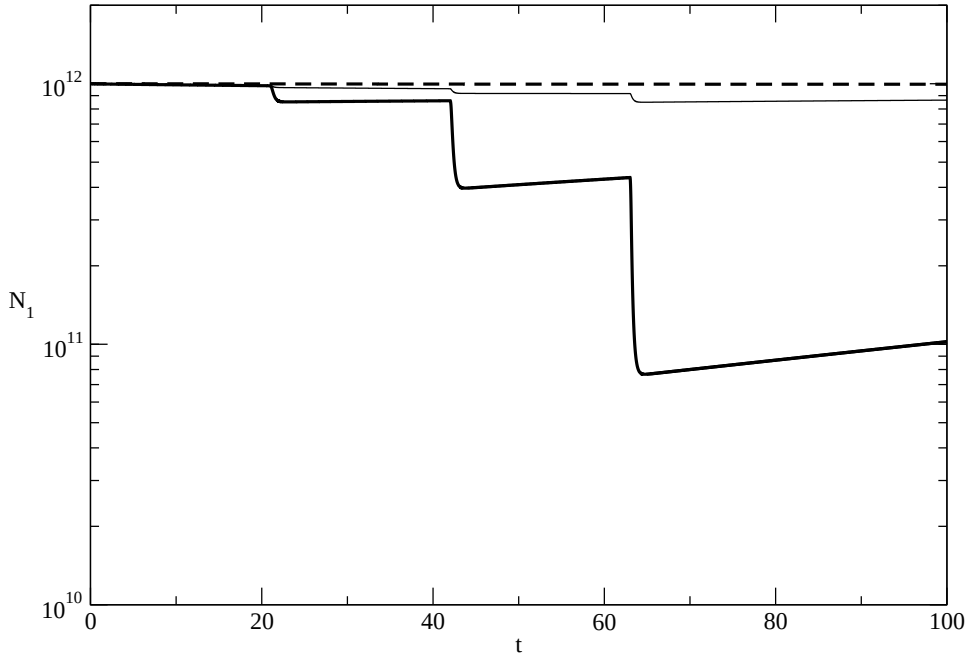

FIGURE 1. Tumoral dynamics: antineoplastic chemotherapy for $\mu = 1.0$ (thick solid line) – drug sensitive tumour, $\mu = 0.3$ (thin solid line) – drug "less sensitive" tumour and without any treatment (dashed line). For $\mu = 1.0$ (sensitive tumour) or $\mu = 0.3$ there is no response at the first infusion of the drug at $t = 0$. This occurs for both because if $N_1 \approx k_1$ the treatment term $-\mu r_1 N_1(1 - N_1/k_1)Q \approx 0$ (see system (1)).

5. **Conclusions.** We proposed and analysed a mathematical model of ordinary differential equations for cancer treatment, where the growth equation for the tumoral cell population is given by the logistic equation and the cell-kill response by the Norton-Simon hypothesis. As we have declared, it is essential to understand the relationship between cell-kill response and tumour growth dynamics, and theferore a thorough understanding of tumoral pharmacodynamics is as important as optimizing anticancer drug schedules.

From the analysis of equilibrium stability, we find the lower and upper bounds for the amount of the drug administered in order to cure the disease via chemotherapy. Above a certain upper dose, the chemotherapy is so strong that it eliminates even normal cells. On the other hand, doses under a given lower bound cannot eliminate the tumoral cells completely.

The coexistence of both tumour and normal cells, for a low carrying capacity of tumour cells, is guaranted by a drug infusion lower than tumour cells' absorption of the drug. For a higher carrying capacity, coexistence occurs at a drug infusion level lower than normal cells' absorption of the drug. If the amount of the drug administered is increased, one of the cells types (tumoral or normal) will prevail.

Numerical simulations for the sequencing of chemotherapy and surgery are presented, assuming drug administration in cycles. When surgery is performed after

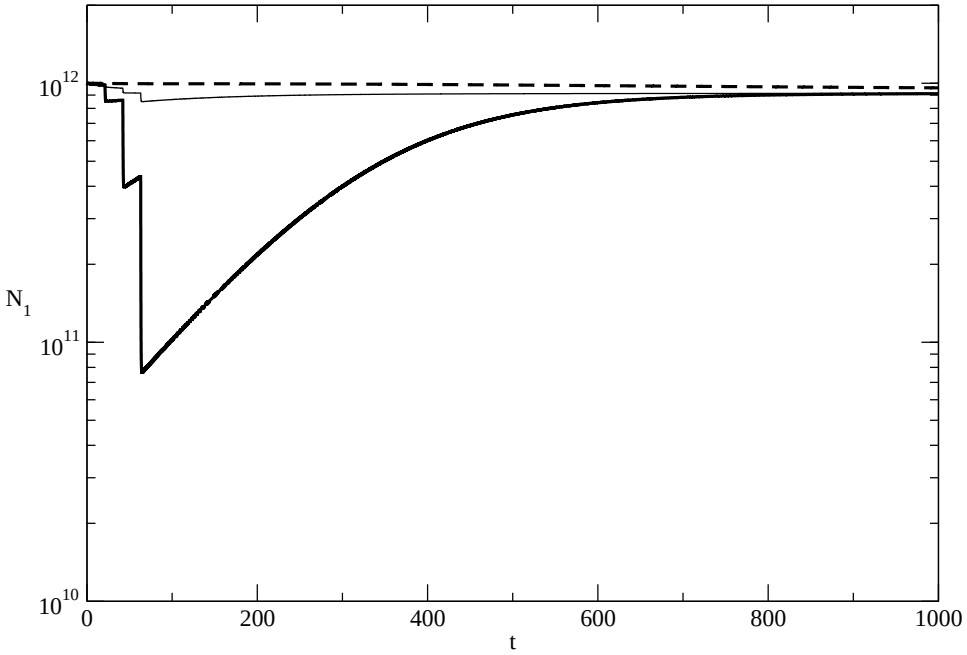

FIGURE 2. Tumoral dynamics: antineoplastic chemotherapy for $\mu = 1.0$ (thick solid line) – drug sensitive tumour, $\mu = 0.3$ (thin solid line) – drug "less sensitive" tumour and without any treatment (dashed line). After the last infusion at $t = 64$, no treatment is applied and then the tumour grows until reaching about 10^{12} cells.

chemotherapy, we observed a further increase in the survival time of the patient. According to our results, large human tumours are less responsive than those of intermediate (or small) size and therefore their clinical regression is probably best explained by the Norton-Simon hypothesis.

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Appendix. Let us compare μ_c and $\mu_c^<$ (also ν_c and $\nu_c^<$), by defining, for $\mu > \nu$,

$$\begin{aligned} k_2^c &= \frac{k_1}{\alpha_{12}} \frac{\mu - \nu}{2\nu} \left[\sqrt{1 + \frac{4\mu\nu\alpha_{12}\alpha_{21}}{(\mu-\nu)^2}} - 1 \right] \\ &= k_1 \alpha_{21} \frac{2\mu}{\mu - \nu} \frac{1}{\left[\sqrt{1 + \frac{4\mu\nu\alpha_{12}\alpha_{21}}{(\mu-\nu)^2}} + 1 \right]} \end{aligned} \tag{19}$$

1. For a low carrying capacity of normal cells, that is, if $k_2 < k_2^c$, we have $\mu_c > \mu_c^<$ and $\nu_c < \nu_c^<$.
2. For a high carrying capacity of normal cells, that is, if $k_2 > k_2^c$, we have $\mu_c < \mu_c^<$ and $\nu_c > \nu_c^<$.

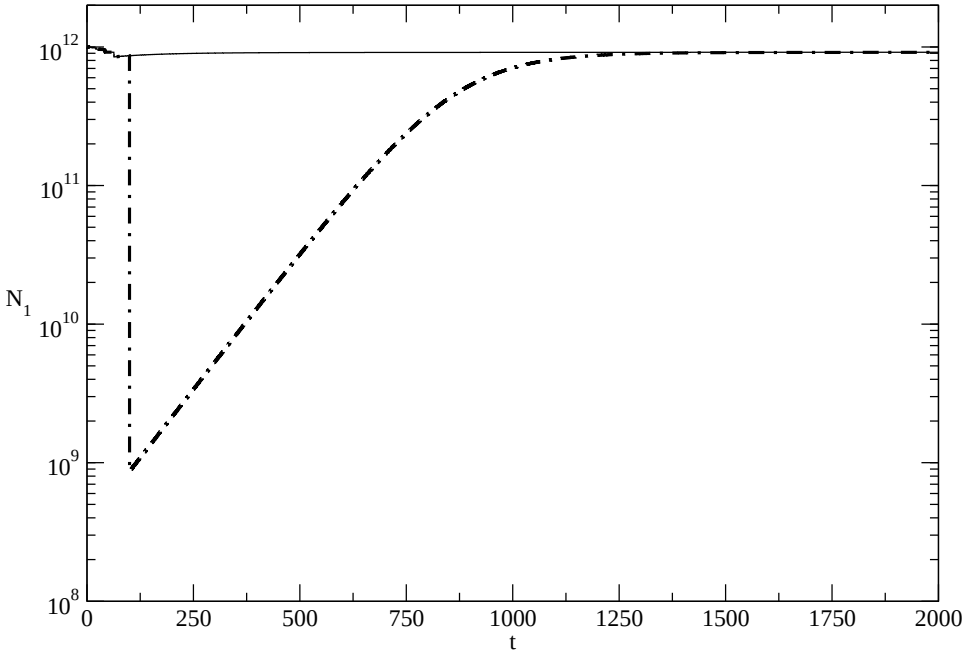

FIGURE 3. Tumoral dynamics: antineoplastic chemotherapy of a tumour ($\mu = 0.3$) with surgery at $t_s = 100$ (dashed-dot line) and without surgery (thin solid line).

For $\mu < \nu$, we define

$$\begin{aligned} k_2^d &= \frac{k_1}{\alpha_{12}} \frac{\nu - \mu}{2\nu} \left[\sqrt{1 + \frac{4\mu\nu\alpha_{12}\alpha_{21}}{(\nu - \mu)^2}} + 1 \right] \\ &= k_1 \alpha_{21} \frac{2\mu}{\nu - \mu} \frac{1}{\left[\sqrt{1 + \frac{4\mu\nu\alpha_{12}\alpha_{21}}{(\nu-\mu)^2}} - 1 \right]} \end{aligned} \tag{20}$$

1. For a low carrying capacity of normal cells, that is, if $k_2 < k_2^d$ then $\mu_c > \mu_c^<$ and $\nu_c < \nu_c^<$.
2. For a high carrying capacity of normal cells, that is, if $k_2 > k_2^d$ then $\mu_c < \mu_c^<$ and $\nu_c > \nu_c^<$.

Summarizing the stability of $P_4 = (N_1, N_2, Q)$, for the case of $\mu > \nu$ (biologically relevant), we have:

1. Low carrying capacity of normal cells (decreased N_1), $k_2 < k_2^c$: We have $\mu_c > \mu_c^<$ and $\nu_c < \nu_c^<$. P_4 is stable if $Q < \frac{\nu_c}{\nu}$. However, for $\nu_c < 0$, P_4 is unstable.
2. High carrying capacity of normal cells (increased N_1), $k_2 > k_2^c$: We have $\mu_c < \mu_c^<$ and $\nu_c > \nu_c^<$. P_4 is stable if $Q < \frac{\mu_c}{\mu}$. However, for $\mu_c < 0$, P_4 is unstable.

For $\mu < \nu$ (biologically irrelevant), the only change is k_2^d, instead of k_2^c.

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