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Research paper

The effect of time ordering and concurrency in a mathematical model of chemoradiotherapy

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ABSTRACT

We study the effect of switching the order of administration of cytotoxic drugs and radiation in cancer therapy by comparing a sequential and a concurrent protocol of chemoradiation. For this purpose, we derive a nonlinear ordinary differential equation model based on well-accepted knowledge of chemotherapy and radiotherapy for *in vitro* solid tumors. Using the bifurcation theory, we demonstrate that the administration of radiotherapy concurrently, once the chemotherapeutic regime has caused a considerable reduction of the tumor burden, might be more pertinent than the reverse strategy in those circumstances where bistability occurs. Consequently, our analysis suggests that an adequate time order and concurrency may have potential benefits in chemoradiation of solid tumors.

1. Introduction

It is well accepted that the combination of chemotherapy and radiotherapy is a beneficial strategy for the treatment of many solid malignancies, as for example the treatment of low grade glioma [1–3] or lung cancer [4–6]. Apart from the minimization of the toxic side effects impaired by drugs and radiation on healthy tissues, as well as the avoidance of the development of tumor resistance through clonal evolution, the particular strategy that is adopted when arranging the schedules of these protocols can be of great relevance as well [7–9].

In particular, when chemoradiation is the therapeutical choice, the dose of the drugs and radiation play a key role in the success of the therapy. Depending on their specific values, the two modalities of treatment can synergize to produce an increased overall destruction of tumor cells or, on the contrary, they can antagonize leading to an infra-additivity effect [10]. Two fundamental strategies are frequently considered in chemoradiotherapy, namely, concurrent and sequential therapy [1]. The former approach delivers chemotherapy and radiotherapy together within the same cycle of treatment, while the second strategy uses one treatment after the other. Despite the fact that there is no general consensus on which strategy is better for certain specific cancers, some recent studies point towards the former method in non-small cell lung cancer [4]. In those cases in which both sequential and concurrent therapy constitute a viable choice, it is then natural to ask if, in addition to an adequate drug dosage planning, there exists any benefit between using one setting or the other. Furthermore, hesitation

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about the most convenient time ordering also arise, which demand investigation of the conditions under which it is more beneficial to use some therapy before the other and vice versa.

Sometimes, an increased understanding of the complex dynamics of tumor growth in the presence of traditional therapies for the treatment of cancer can be achieved through the development of mathematical models [11–13]. These models allow to represent the evolution of these nonlinear dynamical systems, which can then be tested against experimental data [14] to ascertain their degree of accuracy and range of application. Then, a detailed study of the fixed points and the bifurcation phenomena that take place when some parameters of the model of empirical relevance are varied, might provide useful guidance in the development or falsification of hypotheses. These hypotheses, in addition, could turn out to be of certain usefulness concerning the arrangement of new therapy protocols.

Considering previous efforts in the mathematical modeling of chemoradiotherapy, there exists an increasing amount of recent literature dedicated to its study [15–21]. Some of these models focus on optimal radiation fractionation for specific tumors [17,18], while some others concentrate on global asymptotic stability properties [20]. However, as far as the authors are concerned, no previous mathematical study has dedicated its efforts to the issue pointed out here, which concerns any possible advantage of administering chemotherapeutic agents in advance to radiotherapy. In addition to the well-known benefits of radiosensitivization [10], dynamical phenomena arising from the nonlinear nature of the growth of solid tumors and its response to therapy (*e. g.* the Norton-Simon hypothesis) could possibly favor the use of this practice.

In the present work, we focus on the importance of the role played by the time ordering in sequential and concurrent chemoradiotherapy by studying a treatment with a single dose of radiation and continuous chemotherapy. Given the fundamental character of the model, it is not our purpose to suggest this strategy for the treatment of any specific malignancy, but rather to illustrate in simple terms and to provide insights about a dynamical effect that leads to an asymmetry concerning the time-order in the treatment. For this reason, continuous administrations are considered as an approximation of repeated cycles of chemotherapy and the effect of chemotherapy on the healthy tissue is disregarded. Apart from these approximations, we adopt the point of view of dynamical systems theory, providing a detailed description of the model in terms of attractors, basins of attraction, the separatrices and their associated zones of stability. The paper is organized as follows. In Section 2 we develop the general model and describe in detail its basic features. In Section 3 the dynamics of the model under the usage of chemotherapy alone is thoroughly described. Then, in Section 4 we develop the main topic of the present work, by studying chemoradiotherapy and how the time ordering of the schedule and its concurrency can affect the outcome of a treatment. We close this work by discussing the main findings of the present analysis.

2. Model description

In general terms, cancer chemotherapy is frequently represented using a multicompartment approach [22–25]. The usage of several compartments is very relevant because most chemotherapeutic protocols use combination of drugs, each of which destroy cells in a specific phase of the cell cycle [26,27]. This occurs because different drugs take advantage of different biomolecular mechanisms of action. Nevertheless, in the present work, we are investigating the effect of a single cytotoxic cycle non-specific drug in combination with radiotherapy. Therefore, we can reduce the population of tumor cells $P(t)$ to just one cell compartment, gathering even mitotic and quiescent cells. Following previous works [28], the differential equation governing the dynamics of the tumor in the presence of chemoradiotherapy can be written as

$$\frac{dP}{d\tau} = rP\left(1-\frac{P}{K}\right) - rb\frac{K}{K+sP}\left(1-e^{-\rho C}\right)P - \sum_{i=1}^{N} c_i\delta(t-T_i)P, \tag{1}$$

where we recall that P is the size of the cell population, while τ represents the time. The first positive term models the growth of the tumor, while the other two negative contributions represent the cell destruction mediated by cytotoxic drugs and radiation, respectively. We thoroughly describe this differential equation in the following lines.

As can be read from the first term in Eq. (1), we assume that tumor cells follow a sigmoid growth curve. For mathematical simplicity, but without loss of generality, we consider a logistic growth with a growth rate r and carrying capacity K [29]. For some avascular tumors, typical values of these parameters are $r = 0.8$ weeks^{-1} and $K = 10^9$ cell, for example [28].

In connection with chemotherapy, we consider the most simple model that allows to represent the Norton-Simon hypothesis. This hypothesis states that the rate of destruction of a cytotoxic agent is proportional to the rate of growth of the unperturbed tumor. The fractional cell kill impaired by cytotoxic agents can then be described by means of the Exponential Kill Model, which has been tested against experimental results [14,30]. This model describes the rate of cell kill by the mathematical function $b(1-e^{-\rho C})$, where b represents the relative maximum fractional cell kill, C is the drug concentration, and the constant ρ stands for the sensitivity of the tumor cells to the drugs [9,30]. More precisely, ρ is directly proportional to the sensitivity. To complete the description of chemotherapy, we consider a Holling type II functional response in the form $rK/(K+sP)$. This function allows to represent the Norton-Simon hypothesis in a feasible way. It has as a main effect the reduction of the fractional cell kill as the tumor cell population P gets close to its carrying capacity K. The bounded nature of this function can be justified by recalling that the action of certain cytotoxic agents resemble enzyme kinetics, suggesting a Michaelis-Menten type law. The maximum value at the carrying capacity is $r/(1+s)$, and therefore the parameter s controls in a simple way the extent to which the Norton-Simon effect is operating. As the value of s increases, such effects becomes more pronounced. Specific values of the parameters b, ρ and s can be found in previous works [28].

Finally, the administration of one or more sessions of radiotherapy can be represented by means of a sequence of Dirac delta distributions $\delta(t-T_i)$, where the index i runs from one to the total number N of radiotherapeutic fractions delivered, and T_i is a time of this deliver [31]. Just as an example, a typical treatment for low grade glioma can harbor thirty daily fractions of radiotherapy [17]. The Dirac delta approximation is acceptable if we bear in mind that the sessions of radiotherapy are short in comparison with the rates of tumor growth. Then, the intensity of each administration can be represented using the linear-quadratic model [32]. In this regard, each constant c_i appearing in Eq. (1) can be written as $c_i = \alpha D_i + \beta D_i^2$, where D_i represents the ith dose of radiation delivered, which is frequently measured in grays. The parameters α and β are called the linear and quadratic coefficients of cell damage, and describe how destructive is radiation on the affected tissues. We refer the reader to specialized literature [33] for an inspection of the particular values of these parameters in different malignancies.

In the present study we do not need to concern with the pharmacokinetics of the drug, since the drug concentration will be treated here as a parameter, which is enough to explain the fundamental phenomenon that leads to the time asymmetry and the benefits of concurrency. Given this approximation, and also because we are not modeling the effect of the drugs on the healthy tissue, our conclusions should be restricted to *in vitro* tumors. In order to study this model, we shall first examine the dynamics of chemotherapy alone in the following lines.

3. Effects of chemotherapy alone

To investigate the effects of chemotherapy in the absence of radiation ($c_i = 0$), we first nondimensionalize the model by rescaling the cell population to the value of the carrying capacity $x = P/K$ and the time scale to the typical constant rate of growth $t = r\tau$. These transformations yield the simplified model

$$\frac{dx}{dt} = x(1-x) - \frac{b}{1+sx}\left(1-e^{-\rho C}\right)x. \tag{2}$$

This model possesses three equilibrium points, which are nicely written as

$$x^* = 0, \quad x^*_{1,2} = \frac{s-1 \pm \sqrt{(s+1)^2 - 4sb(1-e^{-\rho C})}}{2s}.$$

Naturally, in absence of chemotherapy ($C = 0$), we observe the typical dynamics of the logistic or Gompertzian growth of solid tumors. The concentration of tumor cells tends to the equilibrium $x_1^* = 1$, regardless of the initial value x_0 of tumor cells. This value corresponds to a malignant attractor, representing the point above which the tumor can develop increased vascularity and metastatic potential. In the framework of this model, we refer to such equilibrium as an *active tumor* (AT) with an unacceptable level of tumor cells. Another equilibrium, $x_0 = 0$, which is unstable, represents tumor extinction. We refer to such equilibrium as a *dead tumor* (DT). Because of the instability of this equilibrium, even for an arbitrary small value x_0, the concentration of tumor cells x tends to the state of active tumor. This instability, which represents the fact that just a single residual cell might be capable of repopulating a whole tumor, constitutes one among the many difficulties encountered in the treatment of cancer.

Let us now evaluate how the chemical therapy with increasing concentration C of drugs affects the changes in the concentration x of tumor cells for various values of the parameter b, which characterizes the maximum intensity of the influence of drugs on the tumor cell kill. Since the parameter ρ can be absorbed in the dose of the drug, we settle its value equal to one, hereafter. Then, we study the system dynamics depending on the parameters b, s and C, by inspecting the parameter space.

Firstly, we consider the parameter values $b = 1$ and $s = 0.1$, when the Norton-Simon hypothesis is negligible (*e.g.* an haematological tumor). In Fig. 1(a), we show the stable equilibrium $x_1^*(C)$ (solid line) and the unstable equilibrium $x^* = 0$ (dashed line) versus the drug concentration C. As it is evident from the figure, the dynamical system appearing in Eq. (2) is monostable when the impact of the drug is small, even if such drug is administered uninterruptedly. For any C, a quantity of the tumor cells stabilizes to the equilibrium $x_1(C)$ independently of the initial data $x_0 > 0$. Therefore, the effect of the drug is to reduce the carrying capacity of the tumor, driving it close to elimination as the dose-intensity C is increased. As expected, the function $x_1^*(C)$ monotonically decreases with increasing C.

To gain insight into this situation, some details of a treatment consisting of a continuous everlasting administration of drugs is shown in Fig. 1(b). As can be seen, several treatment programs $C(t)$ affect the dynamics of tumor cells $x(t)$ by reducing the tumor size following a rather exponential decay. In this simulations, it is assumed that the initial state of the system is $x_0 = 1$ and that the treatment starts at the time $t = T_C$. For $0 < t < T_C$, the concentration of drugs is $C = 0$ and the tumor exists at its carrying capacity. In the top panel of the Fig. 1(b), three programs of the treatment with constant values $C = 0.2$ (blue), $C = 1$ (green), and $C = 5$ (brown) are shown. The evolution of the tumor cell population for such treatment is demonstrated on the bottom panel using the same colors. As can be seen, the concentration of tumor cells decreases and stabilizes to the different levels defined by $x_1^*(C)$. The greater it is the value of C, the lower the size at equilibrium $x_1^*(C)$.

Further on, we consider in the second place the behavior of the Eq. (2) for the fixed value $s = 2$ and different values of the relative maximum cell kill rate b (see Fig. 2). This represents a solid tumor where the Norton-Simon hypothesis is considerable. For $b = 1$, the Eq. (2) is monostable again (see Fig. 2(a)). We show the stable equilibrium $x_1^*(C)$ by a solid line and the unstable equilibrium $x^* = 0$ with a dashed line. For any value of C, any quantity of initial tumor cells stabilizes to the

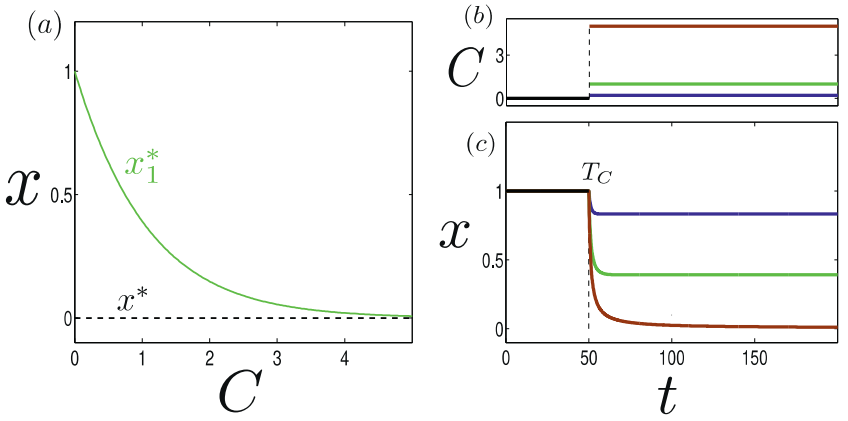

Fig. 1. Inefficient chemotherapy. (a) A bifurcation diagram showing the dependence of the size of the tumor fixed point x_1^* with the drug concentration C of a continuous protocol with parameters $s = 0.1$ and $b = 1.0$ is shown. In this case a sufficiently high dose is able to reduce the tumor considerably, but not to eliminate it. (b) Three protocols showing the drug concentration evolution as time goes by. A low dose protocol uses $C = 0.2$ (blue), a middle one considers $C = 1$ (green), and the most dose-intense delivers a dose of $C = 5$ (brown). Every continuous protocol starts at time $t = T_C$. (c) The time series of the tumor when the three continuous treatments are administered. After a brief decay, the tumor stabilizes at a size below its carrying capacity. It is evident that chemotherapy is not being effective in this regime of parameters, since a very high dose of a continuously administered drug is required to reduce the tumor sufficiently (brown).

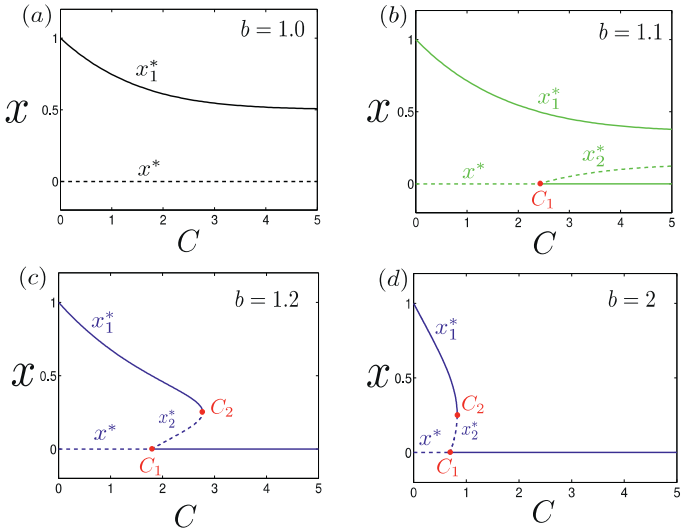

Fig. 2. Bifurcation diagrams. Several bifurcation diagrams showing the different fixed points for a value of $s = 2$ are shown. (a) An inefficient scenario with $b = 1.0$. In the present case there is one fixed point attractor representing the tumor size x_1^*. (b) A more efficient drug is here represented with $b = 1.1$. As the drug concentration increases above a critical value, a transcritical bifurcation (C_1) turns the system bistable. In this region the tumor can be eliminated depending on its size at the onset of the treatment. (c) When the drug is more cytotoxic, for $b = 1.2$, there exists a new region of monostability, which is reached by a saddle-node bifurcation (C_2), forming a hysteresis region. For values of the dose higher that this threshold, the tumor free equilibrium becomes stable. (d) A further increase in efficiency with $b = 2.0$ leads to a reduction of the region of bistability.

equilibrium $x_1^*(C)$ irrespective of such initial data $x_0 > 0$. It should be noted that even an essential increase of C decreases the value of x only in two times. Mathematically, we can write that $x_1(C) \to 0.5$ as $C \to \infty$. Therefore, beyond some point, the concentration of tumor cells remains high (active tumor) no matter how much we increase the dose of drug. This is a consequence of the nature of the cell kill dependence with C. The tumor size plateaus at some point, what means that the increase in the dose of drug has no relevant effects [28]. Thus, as a consequence of the nonlinearity in the Exponential Kill Model, even if we disregard the toxicity impaired to the healthy tissues, the paradigm that states the more dose the better, is not here attained. This means that for $b = 1$ the drug therapy can not be very effective when the Norton-Simon effect is considerable.

As we further increase b, the situation changes dramatically. Indeed, for $b > 1$ the trivial equilibrium $x^* = 0$ is unstable only in the interval $0 < C < C_1 = \ln(b/(b-1))$. However, for $C > C_1$ this equilibrium becomes stable through a transcritical bifurcation and bistability can be observed. In this configuration the tumor is metastable and a transition from an active tumor to an extincted cell population can be furnished. In Fig. 2(b) we show a bifurcation diagram for $b = 1.1$. Along with

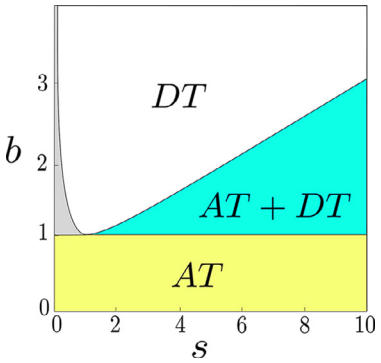

Fig. 3. Parameter space. The parameter space (s, b) for very high doses of drug $C \to \infty$. Below the value $b = 1$ we see that the tumor is always active (AT) and can not be eliminated, since the drug is inefficient. In the gray and white regions the tumor is always asymptotically dead (DT), since the drug is effective and the Norton-Simon effect is comparably small. Finally, in the green zone bistability can occur. The tumor might be eradicated or not depending on its original size. Here the drug is efficient, but the Norton-Simon effect is important and can lead to ineffective therapy.

the zone of monostability $0 < C < C_1 = 2.40$, one can also see the bistability zone $C > C_1$. The basins of attraction of the two coexisting stable equilibria x^* and x_1^* are separated by the unstable equilibrium x_2^* (dashed line).

When the drugs are more destructive b, as for example when $b = 1.2$, the bistability interval becomes limited to a region $C_1 < C < C_2$, which progressively shrinks as b increases. Indeed, for $b = (s+1)^2/4s$ its right border is $C_2 = \ln\left(4bs/(4bs - (s+1)^2)\right)$. The equilibrium x_1^* is stable on the interval $0 < C < C_2$. At the saddle-node bifurcation point C_2, the equilibrium x_1^* merges with an unstable equilibrium x_2^* and disappears. This scenario is illustrated in Fig. 2(c) for $b = 1.2$ and in Fig. 2(d) for $b = 2.0$. These two figures show a qualitative change in the behavior of the system represented by Eq. (2) by increasing C. In this scenario, increasing the dose-intensity up to the critical value is certainly beneficial. One can see a sharp jump from the equilibrium $x_1^*(C)$ to $x^* = 0$ at the point C_2. If further, after this jump, we decrease the drug concentration C, then the system will stay at $x^* = 0$ if the tumor extincts when a sufficient low value of x has been achieved. However, it is important in this regard to avoid a rapid decay of the drug concentration below C_1 before the tumor is extincted. Otherwise, the hysteresis loop could not be completed, leading to the regrow of the tumor to its original size.

A general parametric description of zones of mono and bistability of the dynamical system in the (s, b)-plane is presented in Fig. 3. In the former case we can see that, in the limit of very high drug concentration $C \to \infty$, the parameter set (s, b) shows four different regions. For $b < 1$, the chemotherapeutic treatment is not efficient enough to destroy the active tumor (AT), but it can only reduce its carrying capacity. However, when the drugs are effective ($b > 1$), a richer scenario appears. If the Norton-Simon effect is small and the effectiveness of the cytotoxic agents is considerable ($b > 1 + (s-1)^2/4s$), then the tumor can be driven to extinction (DT) independently of its size at the beginning of the treatment (white zone in Fig. 3). In this case, and at the expense of delivering very high doses, it would not be needed to reduce the size of the tumor before applying the chemotherapeutic agents, as it is usually done in the clinical practice. This situation seldom occurs in real situations, since adjuvant chemotherapy is frequently used to destroy residual tumor cells, rather than to treat the tumor alone at intolerable doses. The remaining region (green zone in Fig. 3) is a region of bistability, where the tumor can be destroyed or not depending on its size at the beginning of the treatment.

We now study the parameter space (C, b) to gain insight into the dependence on the dose of drug. We consider a moderate Norton-Simon effect by setting $s = 2$. In the bottom, a monostability zone (lime green color in Fig. 4) where the system has a stable equilibrium x_1^* corresponding to a rather big active tumor (AT) can be identified. In the upper monostability zone (white color), the system has the stable equilibrium $x^* = 0$ corresponding to a dead tumor (DT). In the middle zone (blue color), we find that it is bistable and possesses both stable equilibria x_1^* and x^* (AT+DT). The boundary between these zones can be computed as follows. The lower curve is defined as $C = \ln(b/(b-1))$, and the upper curve is defined as $C = \ln\left(4bs/(4bs - (s+1)^2)\right)$. These curves have horizontal asymptotes $b_1 \equiv 1$ and $b_2 \equiv (s+1)^2/4s$.

Consider now the effectiveness of the drug therapy in dependence on the parameter b that characterizes the maximum rate of tumor cell kill by the drugs. For $0 < b \le b_1$, even large doses of drugs only slightly decrease the level of tumor cells. This means that drug therapy with such value of the parameter b is not able to push the system out of the active tumor state (see again Fig. 2(a)). For $b_1 < b < b_2$, the equilibrium $x^* = 0$ becomes stable for $C > C_1$. However, the drug therapy, even with large doses of C, can not throw the system across the unstable equilibrium x_2^* and stabilize to the dead state $x^* = 0$ (see, e.g. Fig. 2(b) for $b = 1.1$). Such a jump can be achieved by radiotherapy and, as shown below, it is precisely in this region where the benefits of time ordering are mostly achieved.

When the relation $b > b_2$ holds, we have a region where the tumor can be destroyed. A schematic program and the effect of the drug therapy is shown in Fig. 5 for $b = 1.2, s = 2$. In Fig. 5(b) the evolution of chemotherapy is clearly appreciated. First of all, it is needed a considerable dose of drug ($C > C_2$) to transfer the system from the zone where the equilibrium x_1^* is stable to the zone of monostability of equilibrium $x^* = 0$. For $b = 1.2$ and $s = 2$ we have $C_2 = 2.77$, so $C = 3$ will be sufficient therefore. As a result of this transition, a sharp decrease in x occurs. Next, the drug dose C can be relaxed, but

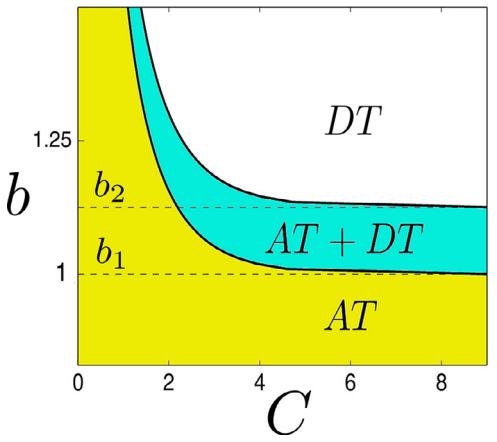

Fig. 4. Parameter set. The parameter set (C, b) for a value of $s = 2$ is shown. Again, three regions can be distinguished. For $b < b_1 = 1$ the therapy can not destroy the active tumor (AT). When the drug concentration is enough destructive $b > b_2 = 1.125$ and the dose of a continuously administered drug is sufficiently high, the tumor can be driven to a dead state (DT). An intermediate region of bistability subsists. Our simulations show that this region enlarges when s increases. Importantly, we note the saturation effect of the curves separating the different regions to the values b_1 and b_2. This critical values represent the relative maximum fractional cell kill limits separating the three regions when high values of the drug concentration C are delivered. This saturation is a consequence of the nonlinear dependence between the survival fraction and the drug impact.

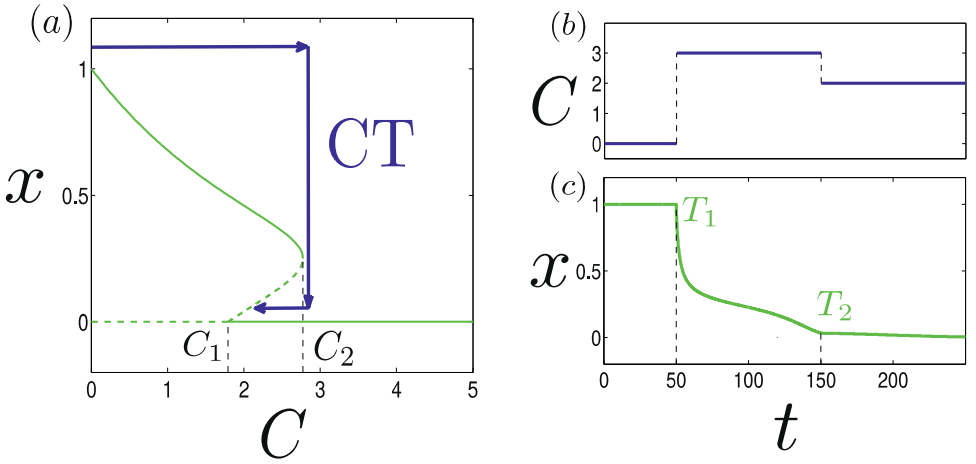

Fig. 5. Successful chemotherapy. A chemotherapeutic protocol consisting on two continuous administrations of a drug for the parameter region $s = 2$ and $b = 1.2$. (a) The drug initially increases beyond C_2 driving the tumor from a region of tumor dominance, through a region of bistability and finally to a region of tumor elimination (blue arrows). (b) The chemotherapeutic protocol starting at T_1 with a reduction of dose administration at T_2. (c) The decrease of the tumor cell population as the times goes by. For these parameter values the treatment is successful and the drug administration can be stopped when x goes below a certain nadir. However, the reduction of the drug dose should not occur too quickly to avoid going below C_1 before the tumor extincts.

the reduction should not be done to a value lower than C_1. Here, we have approximately $C_1 = 1.79$, so a value $C = 2$ is admissible.

A temporal program of the treatment can be represented as a dynamics in the bifurcation diagram, by regarding C as a parameter. The blue arrows in Fig. 5(a) show the evolution of the treatment through the bifurcation diagram. The tumor cell population corresponding to such evolution is shown in Fig. 5(c). We suppose that in the interval $0 < t < T_1$ the concentration of drugs is $C = 0$. Later on the treatment starts with high drug intensity $C = 3$ at time $t = T_1$ and continues up to T_2. Finally, we progressively reduce the drug concentration to a value $C = 2$. Note that this reduction must be performed with care, since if the transition is done too quickly we might cross the separatrix and arrive back to the original point. This fact reveals the importance of adjusting timing properly when transient phenomena are taking place. In the right panels, we show the drug schedule and the time series for this chemotherapy regime. As can be seen, this program gradually reduces the concentration of tumor cells and allows to transfer the tumor from the active state to a dead state.

4. Effects of combination therapy

Now we will return to the case $b_1 < b < b_2$, where b_1 and b_2 represented the values of the maximum drug efficiency delimiting the region of bistability when the drug concentration is high (see again Fig. 4). Then, we consider a treatment that

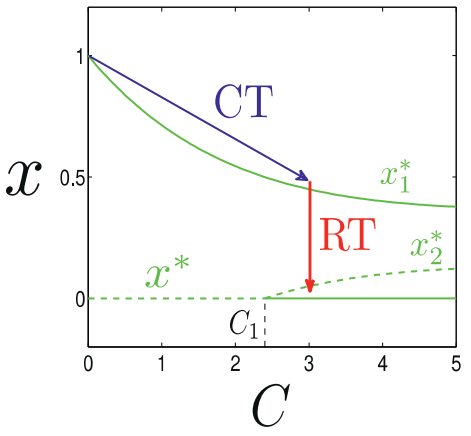

Fig. 6. Combined therapy. A concurrent administration of radiotherapy for a tumor with parameter values $s = 2$ and $b = 1.1$. Note that radiotherapy (red arrow) is given once chemotherapy (blue arrow) has caused a considerable reduction of the tumor, allowing it to drift from the region where x_1^* is monostable ($C < C_1$) to the region ($C > C_1$) where it is metastable. Once this transition has taken place, an impulse of radiotherapy permits to cross the boundary between the two basins of attraction of the active tumor and dead tumor states.

combines chemotherapy and radiotherapy. We recall that the effects of radiotherapy are very localized, while chemotherapy has a systemic effect on the organism. Then, radiotherapy allows to decrease more or less sharply the concentration of tumor cells at a specific location, depending on the dose administered. The addition of radiation therapy together with chemotherapy can be useful given this complementary role, but also due to the capacity of some drugs to radiosensitize. Here we show that when chemotherapy alone is already ineffective, radiotherapy can be incorporated to increase the efficiency of the whole treatment. As shown above, for $b_1 < b < b_2$ the chemotherapy can not provide the positive desired result. Let us consider the following nondimensionalized model

$$\frac{dx}{dt} = x(1-x) - \frac{b}{1+sx}\left(1 - e^{-\rho C}\right)x - c\delta(t-T)x. \tag{3}$$

In our conceptual study, we restrict ourselves by a case of a single administration of radiation therapy at time T. In the mathematical model appearing in Eq. (3), we use an impulse δ-function, where the intensity c of the radiotherapy satisfies the mathematical restriction $0 \le c < \infty$. In practice, typical values can be computed from the experimental data [33], which frequently give small values of c. Here we use rather high values of c, since we approximate a coarse-grained dose of radiotherapy to represent a series of daily doses. This δ-term in the Eq. (3) causes the following fall down of the concentration of tumor cells at the time T, since $x(T_+) = S(c)x(T_-)$, where T_+ and T_- are the limits of T when approached from above and from below in time, which are different due to the effect of the Dirac delta distribution. We note that the survival fraction $S(c) = e^{-c}$ has been introduced here. This factor represents the fraction of cells that survive the treatment of radiotherapy.

We now consider details of the combined treatment for $b = 1.1$ (see Fig. 2(b)). In this case, monostability and bistability zones are detached by the point $C_1 = 2.40$. For $C < C_1$ the system is monostable and independently of the initial value x_0, it stabilizes in the state x_1^* representing an active tumor. For $C > C_1$ the system is bistable, and two stable states x_1^* and x^* corresponding to the active and dead tumor coexist. In absence of chemotherapy ($C = 0$), the concentration of tumor cells is high. As can be seen in Fig. 6 (upper solid curve), a significant increase of the drug concentration C decreases the concentration of tumor cells x only in two times. As previously discussed, it means that even intensive chemotherapy can not remove the system from the unwanted regime of the active tumor state. In these circumstances, the treatment that combines the chemotherapy and the impulse radiation therapy may provide a positive result.

Note that the impulse radiation therapy for $C < C_1$ is meaningless. In this zone of monostability, even after a sharp decrease of the concentration x, the tumor returns back to the active state after some time. In this situation, the following constructive strategy of treatment can be suggested. First, we transfer the system from the monostability zone to the bistability zone using chemotherapeutic drugs with a certain drug concentration, for example, $C = 3 > C_1$ (see blue arrow in Fig. 6). Later on, we apply an intensive impulse of radiotherapy, which allows to decrease sharply the concentration of tumor cells (see the red arrow in Fig. 6). The intensity of the impulse therapy should be chosen so as to obtain $x < x_2^*$, where x_2^* is the unstable equilibrium (green dashed line). Certainly, this can be achieved by the application of several fractions of daily repeated radiotherapy. Then, being in the basin of attraction of the stable equilibrium x^* corresponding to the dead tumor, we continue to provide the drug therapy with $C = 3$, for example. This allows us to keep the system in the state of the dead tumor. Once the tumor has approached a very low number of cells, chemotherapy can be canceled.

It is illustrative to compare the treatment described right above to the reverse situation, where radiotherapy is given right before the chemotherapeutic treatment begins. We refer to these two programs of the treatment as plan A and plan B. They are shown in Fig. 7(a) and (b), respectively. In the top panel, the temporal programs of the treatment are shown in blue. We

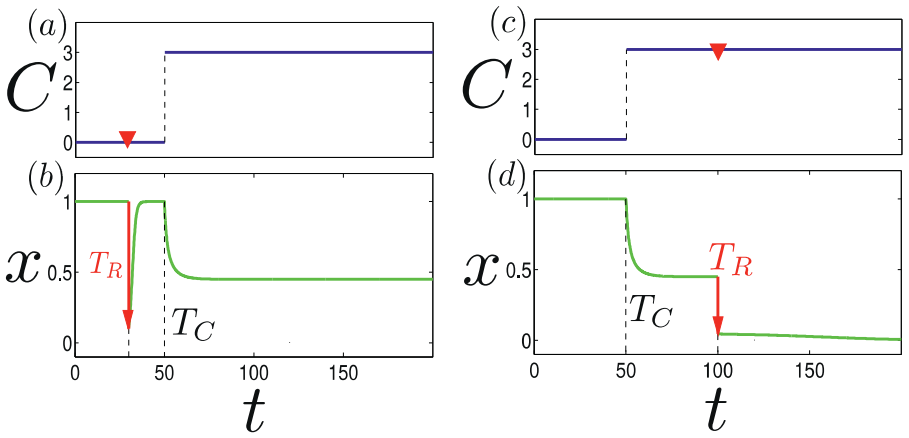

Fig. 7. Sequential versus concurrent chemoradiotherapy. Comparison of two programs of treatment for the system in Eq. (2) with $s = 2$ and $b = 1.1$. (a) The sequential arm delivers an initial session of radiotherapy before chemotherapy starts. As can be seen, the tumor regrows after radiotherapy and makes the subsequent chemotherapeutic doses irrelevant. (b) Now chemotherapy precedes radiotherapy, and the chemotherapeutic treatment is continued after it. This concurrent setting is better, due to both a correct time ordering and a more intense combined effect.

suppose that in the interval $0 < t < T_C$ the concentration of drugs is $C = 0$, and the treatment starts at a time $t = T_C$. During the interval $t > T_C$, the concentration of drugs is kept at a high value of $C = 3$. These two programs of chemotherapy are the same in Fig. 7(a) and (b). The difference between the strategies consists in the moment of administration of radiotherapy T_R. In the first plan A, an impulse of radiotherapy with $c = 2.3$ is applied sequentially before the chemotherapeutic treatment (marked by red triangles). This produces a survival fraction of the 10% of the cells. Therefore we have that ($T_R < T_C$), while in the plan B the impulse therapy is applied after the chemotherapy starts ($T_R > T_C$). In the two bottom panels (Fig. 7(c) and (d)), the results of these two treatment programs are shown (result A and result B). It is supposed again that the initial state of the system is $x_0 = 1$.

On the one hand, the result of plan A (see Fig. 7(a)) shows that the impulse therapy gives a sharp decrease of the tumor cells, however in the absence of subsequent "immediate" chemotherapy (concurrency), the population of tumor cells is quickly restored to its original active state. In these circumstances, the subsequent cycle of chemotherapy can not remove the system from this active state. Note that such program of the combined treatment gives the same result as the treatment without radiotherapy. In this regard, radiotherapy is useless, or even counterproductive, if we bear in mind its toxic effects. The result of plan B with a concurrent impulse point in time is much more positive (see Fig. 7(b)) in comparison. At first glance, a continuous protocol of chemotherapy with concentration $C = 3$ applied at T_C is ineffective, since the concentration of tumor cells decreases only to half its initial value and, therefore, the tumor is still active. However, after the application of the impulse radiotherapy with the same intensity as in the plan A, the same level $C = 3$ of chemotherapeutic agent leads the system progressively to the dead state.

One more important circumstance of the treatment strategy in conditions of bistability should be noted. Here there is a natural desire to keep the system in a state of the dead tumor, using minimal doses of drugs (the closest as possible to the threshold value C_1, where the transcritical bifurcation takes place). However, in the system with the parameter C close to the critical point C_1, inevitable disturbances can transfer the system to the active tumor state. Therefore, and as previously discussed, it is important that the drug dose is not decreased too quickly after the administration of radiotherapy, since otherwise the active tumor could regrow due to a transition to the monostability zone below C_1.

5. Conclusions and discussion

In the present work we have shown that solid tumor growth in the presence of cytotoxic chemotherapy can exhibit multistability and hysteresis. To our knowledge, the importance of hysteresis had been noticed in the study of tumor-immune interactions [34], but not sufficiently in the study of chemotherapy. In light of this phenomenon, we have tried to illuminate the effect of switching the time order in a combination therapy consisting of sequential chemotherapy and radiotherapy, and a concurrent schedule as well. The main conclusion is that a concurrent strategy with chemotherapy first is a much better strategy. Although this is partly in accordance with some clinical trials on lung small cell carcinoma, which favor the concurrent strategy [6], an unequivocal conclusion cannot be drawn in the absence of a careful study of the toxicity effects of the drugs. In that direction a similar analysis may be done in order to investigate *in vivo* solid tumors, including the healthy cells compartment in the model. By this way, there will be possible to check the extension of our conclusions for situations with low or even high citotoxity.

We also note that, from the point of view of our model, the sequential use of chemotherapy before radiotherapy would not be a good strategy, because the only situation in which a positive effect can be achieved is when chemotherapy alone is

already effective, but in such a case there would be no point in adding radiation to the therapy, since in this approach we have not represented radiosensitivization.

In our model, chemotherapy is used to transfer the tumor from a region of monostable active tumor dominance to a bistable region, where a concurrent session of intense radiotherapy can lead to a point close to the dead tumor attractor. This effect can be explained as follows. In those situations where monostability of an active tumor occurs, chemotherapeutic drugs alone are incapable of providing a sufficiently small nadir of the tumor. This is due to the combined effect of the saturation of cell kill as the dose of drug increases and to the Norton-Simon effect, as well. On the one hand, the nonlinear relation between drug dose and survival fraction limits the potential of increasing doses. On the other hand, when the tumor is big enough, a different nonlinearity comes into play, since the effect of the drug decreases due to the limited cycling activity of the cells.

We note that in this study, since our main purpose was to show the mechanism in a clear way, the drug concentration C has been maintained constant whenever applied, which is certainly very toxic. The dose of radiotherapy is very aggressive compared to normal dosages of drugs as well. Moreover, we also recall that in the plan B the chemotherapeutic agent has been kept at a high dose all the time, while a strict alternate regime should suspend chemotherapy briefly during radiotherapy, since they are too toxic to be given in a complete simultaneous way. As is well known, chemotherapeutic drugs are frequently delivered in cycles to avoid excessive toxicity and bone marrow depletion [28]. However, the same result can be also achieved in our model by using cycles of efficient chemotherapy and also by fractioning daily doses of radiotherapy. Therefore, we have used the simplest modeling approach as possible, since in this study we are not concerned with the modeling of toxicity, which was not necessary to illustrate the phenomenon at investigation. Again, the results are not conclusive, since as it has been pointed out in recent works [35], toxicity effects might turn sequential treatment beneficial over the concurrent schedule, without a clear distinction between the time ordering of the therapy. Thus, it is evident that further research is deserved by using a more accurate simulation of protocols, time dosages and the tumor environment.

To conclude, we suggest that the present model can be used as a basic model for theoretical chemoradiotherapy, since it incorporates typical nonlinear effects (bistability, separatrices, basins of attraction and hysteresis) that appear when studying the chemotherapy of solid tumors, as a consequence of nonlinear growth and response to therapy. As is well known, when a tumor does not grow exponentially, the log-kill hypothesis does not hold in conformity, and the Norton-Simon nonlinear effect becomes relevant. As we have shown, these nonlinearities can produce unexpected results when considering combined therapies at a very fundamental dynamical level. Furthermore, the incorporation of complex pharmacokinetics, the usage of multiple compartments that allow to study combination of drugs [9], or the evolution towards tumor resistance to drugs and the influence of radiotherapy in this evolution, represent straightforward extensions of the present model. Finally, the impact of chemotherapy impaired to the healthy tissue and the dynamical evolution of cell clones under the administration of drugs, together with the presence of the humoral and the cell-mediated immune response, are of the greatest importance for the development of *in vivo* tumors and clinical strategies. Certainly, from a mathematical point of view, all these very complex processes can suggest counterintuitive therapeutical combination strategies, by using simple principles derived from the nonlinear nature of the growth of solid tumors and its response to cytotoxic substances.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Irina Bashkirtseva: Software, Visualization, Writing - original draft. **Lev Ryashko:** Investigation, Formal analysis, Writing - original draft. **Álvaro G. López:** Investigation, Formal analysis, Writing - original draft. **Jesús M. Seoane:** Investigation, Formal analysis, Writing - original draft. **Miguel A.F. Sanjuán:** Supervision, Conceptualization, Investigation, Writing - review & editing.

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