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LOG-KILL CHEMOTHERAPY RESPONSE VERSUS THE NORTON-SIMON HYPOTHESIS

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ABSTRACT

This article investigates how the conclusions drawn from mathematical modelling of tumour growth with chemotherapeutic treatment differ for the two choices of chemotherapy response: the Norton-Simon and the log-kill types. Both models are analysed under an assumption of constant, indefinite chemotherapy protocols. Differences between the bifurcation analysis of the two systems are presented. The dependence of the survival time on the competition coefficients between the two types of malignant cells is considered. It is shown that the survival time depends significantly on the ability of the sensitive cells to suppress the resistant population, while the impact of the resistant cells on the sensitive ones is less important. The survival time and optimal dosage is shown to be less dependent on the chemotherapy initiation threshold in the log-kill case than it is under the Norton-Simon hypothesis.

INTRODUCTION

One of the main reasons why mathematical models of tumour growth are being developed is their potential ability of testing therapeutic protocols *in silico*. Ideally, a model tightly coupled with experimental or clinical data is capable of predicting the tumour's response to therapy. Theoretically optimal therapeutic protocols can then be found in hope to provide some suggestions as for the drug dosage and scheduling or support certain hypotheses or concepts (e.g. metronomic therapy).

A modeller necessary faces a choice when selecting a particular functional form for the tumour growth equations. For example, a key aspect of the model is the growth law for the malignant cell population. One may opt for a logistic, Gompertzian, Malthusian or other. As these growth laws are purely empirical there is no real way of telling which of them is more realistic. A good test of model robustness is how strongly it depends on the particular choice of the growth law.

The problem described in the previous paragraph is quite well-studied in the literature, but the other aspect of the model is choosing how tumour responds to chemotherapy. The two common choices are the Norton-Simon hypothesis [3] and log-kill response [4] models.

The Norton-Simon hypothesis states that the effectiveness of therapy is proportional to the cancer growth rate. This is contrast to the log-kill chemotherapy response often used in mathematical models. These two hypotheses give rise to two qualitatively different types of differential equations. This work aims to highlight some of the key differences obtained when comparing these two approaches in modelling of the growth of heterogeneous tumours.

MODELLING THE CHEMOTHERAPY RESPONSE

In our investigation of the two treatment approaches we will use the work of Monro and Gaffney [2] as an example of the model incorporating the Norton-Simon hypothesis in modelling the growth of heterogeneous tumours.

The mathematical model of unperturbed tumour growth is build on the following set of assumptions, following the work of Monro and Gaffney [2]:

- Tumour consists of two types of cells: sensitive and resistant to chemotherapy. The cell numbers are denoted by N_S and N_R respectively.
- Both types of cells follow a Gompertzian growth law with the same proliferation rate and are treated as competing species. To be consistent with the experimental results, the assumption is that in the absence of therapy the sensitive cells should outcompete the resistant ones.
- The mutation between the cell types is Darwinian and happens at a rate proportional to the population growth.

These assumptions lead to the following model of unperturbed tumour growth:

$$\begin{aligned} \dot{N}_S &= -\lambda(1-\tau_1)N_S \ln\left(\tfrac{N_S+\alpha_{12}N_R}{N_\infty}\right) - \lambda\tau_2 N_R \ln\left(\tfrac{N_R+\alpha_{21}N_S}{N_\infty}\right), \\ \dot{N}_R &= -\lambda(1-\tau_2)N_R \ln\left(\tfrac{N_R+\alpha_{21}N_S}{N_\infty}\right) - \lambda\tau_1 N_S \ln\left(\tfrac{N_S+\alpha_{12}N_R}{N_\infty}\right), \end{aligned} \tag{1}$$

where β is the proliferation rate, N_∞ is the carrying capacity, τ_1, τ_2 are the mutation rates and α_{12}, α_{21} are the competition coefficients. The response to the chemotherapeutic agent may then be introduced in model (1) in two different ways as described in the following paragraphs.

According to the Norton-Simon hypothesis, the rate of cell death is proportional to their proliferation rate. This leads to the following system of equations:

$$\begin{aligned} \dot{N}_S &= -\lambda\big(1-\tau_1-\beta u(t)\big)N_S \ln\left(\tfrac{N_S+\alpha_{12}N_R}{N_\infty}\right) - \lambda\tau_2 N_R \ln\left(\tfrac{N_R+\alpha_{21}N_S}{N_\infty}\right), \\ \dot{N}_R &= -\lambda(1-\tau_2)N_R \ln\left(\tfrac{N_R+\alpha_{21}N_S}{N_\infty}\right) - \lambda\tau_1 N_S \ln\left(\tfrac{N_S+\alpha_{12}N_R}{N_\infty}\right), \end{aligned} \tag{2}$$

where β is a parameter describing the sensitivity of the tumour to the chemotherapeutic agent and $u(t)$ is the concentration of the agent in blood at time t. Note that in case $\alpha_{12} = \alpha_{21} = 1$ this model reduces to the one proposed in [2].

The log-kill-death hypothesis on the other hand leads to a qualitatively different mathematical model of the form

$$\begin{aligned} \dot{N}_S &= -\lambda(1-\tau_1)N_S \ln\left(\tfrac{N_S+\alpha_{12}N_R}{N_\infty}\right) - \lambda\tau_2 N_R \ln\left(\tfrac{N_R+\alpha_{21}N_S}{N_\infty}\right) - \gamma N_S v(t), \\ \dot{N}_R &= -\lambda(1-\tau_2)N_R \ln\left(\tfrac{N_R+\alpha_{21}N_S}{N_\infty}\right) - \lambda\tau_1 N_S \ln\left(\tfrac{N_S+\alpha_{12}N_R}{N_\infty}\right), \end{aligned} \tag{3}$$

where γ controls the effectiveness of the chemotherapeutic agent and $v(t)$ is the concentration of the agent at time t.

The rest of this work is devoted to the investigation of Eqs. (2) and (3).

The evidence in the literature suggests that prior to the treatment the tumour consists of mainly chemotherapy-sensitive cells with a small sub-population of chemotherapy-resistant ones. Following the methodology used by Monro and Gaffney [2], Eqs. (1) are simulated from initial conditions $(N_S(0), N_R(0)) = (1, 0)$ until the number of cells reaches a critical size N_{ch}, which corresponds to the tumour detection and the onset of therapy. For the exact parameters used in the model the reader is referred to [2]. We generalised the original model by allowing different mutation rates in different directions. Theoretical results (i.e. steady states) are obtained for general τ_1, τ_2 with an assumption that τ_1, $\tau_2 \ll 1$. All the simulations, however, are conducted with $\tau_1 = \tau_2 = 10^{-6}$. Values of the parameters not listed in [2] are quoted either in the text or in relevant figure captions.

RESULTS

As a first and simplest approximation of the treatment, which nevertheless highlights some of the differences between the two approaches, we will consider a continuous, indefinite chemotherapy. Namely, for the remaining of this subsection, we set $u(t) = u = const$ and $v(t) = v = const$.

We are in particular interested in how the dosage and timing of the therapy influences the survival time, i.e. the time between the onset of therapy and the moment the total number of malignant cells reaches a critical volume N_{crit} which is considered lethal. Monro and Gaffney found that the maximum survival time is obtained for intermediate drug dose and that delaying the therapy while increasing the dosage may in fact increase the survival time. The former result, in particular, is consistent with a hypothesis that lower doses of drug applied and more frequent intervals (or continuously) may be more effective treatment than the maximum tolerated dose therapy as it may prevent drug resistance. In particular our intention was to check whether these results are true regardless of how the tumour responds to chemotherapy.

Steady States

We begin our analysis by considering the steady states of Eqs. (2) and (3).

Equations (2) have at most three steady states, whose stability is summarised in a table below:

Coordinates	Stability conditions
$(N_\infty, 0)$	$\beta u < \frac{1-\tau_1-\tau_2}{1-\tau_2}$ if $\alpha_{21} > 1$, $\frac{1-\tau_1-\tau_2}{1-\tau_2} < \beta u < 1-\tau_1+\tau_1\alpha_{12}+(1-\tau_2)\ln\alpha_{21}$ if $\alpha_{21} < 1$.
$(0, N_\infty)$	$\beta u < \frac{1-\tau_1-\tau_2}{1-\tau_2}$ if $\alpha_{12} > 1$, $\beta u > \max\left(\frac{1-\tau_1-\tau_2}{1-\tau_2}, \frac{1-\tau_2+\tau_2\alpha_{21}}{\ln\alpha_{12}} + 1 - \tau_1\right)$ if $\alpha_{12} < 1$.
$\frac{N_\infty}{1-\alpha_{12}\alpha_{21}}(1-\alpha_{12}, 1-\alpha_{21})$ if $(1-\alpha_{12})(1-\alpha_{21}) > 0$	$\beta u < \frac{1-\tau_1-\tau_2}{1-\tau_2}$ if $\alpha_{12}, \alpha_{21} < 1$, $\frac{1-\tau_1-\tau_2}{1-\tau_2} < \beta u < 1-\tau_1+\tau_1\alpha_{12}+\frac{(\alpha_{21}-1)(1-\tau_2+\tau_2\alpha_{21})}{\alpha_{12}-1}$ if $\alpha_{12}, \alpha_{21} > 1$.

Not all steady states of Eqs. (3) can be found analytically. It can be nevertheless shown that two non-negative steady states exist, namely

$$(0, N_\infty), \text{ and } (N_\infty \mathrm{e}^{-\delta} - \alpha_{12} N_R^*, N_R^*),$$

where N_R^* is a unique positive solution of

$$\alpha_{21}\mathrm{e}^{-\delta} + \tfrac{1-\alpha_{12}\alpha_{21}}{N_\infty} N_R^* = \exp\left(\tfrac{\tau_1\delta}{1-\tau_2}\tfrac{\mathrm{e}^{-\delta}N_\infty - \alpha_{12}N_R^*}{N_R^*}\right), \tag{4}$$

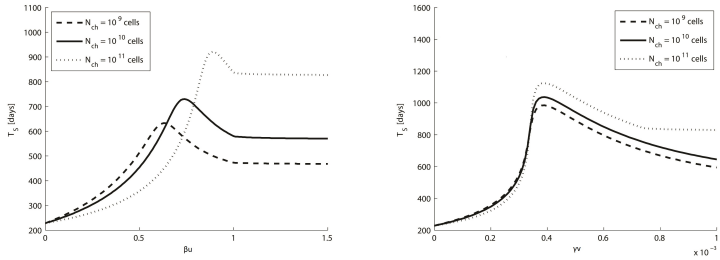
where $\delta = \frac{\gamma v(1-\tau_2)}{\lambda(1-\tau_1-\tau_2)}$. Note that the solution exists uniquely, as the left hand side of Eq. (4) is a strictly increasing function of N_R^* (as $\alpha_{12}\alpha_{21} < 1$), while the right hand side is a strictly decreasing function of N_R^* for $N_R^* > 0$. This, and the fact that the limit of the right hand side as N_R^* tends to 0 is $+\infty$, is enough to guarantee a unique, positive solution.

If $\alpha_{12} > 1$, then the steady state $(0, N_\infty)$ is stable. For $\alpha_{12} < 1$, the steady state is stable only if $\gamma v > \frac{-\lambda(1-\tau_1-\tau_2)\ln\alpha_{12}}{1-\tau_2}$. Note that the purely sensitive steady state with $(N_\infty, 0)$ exists only if $\gamma v = 0$, i.e. there is no therapy.

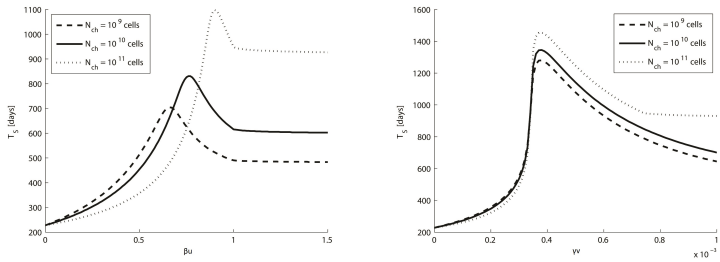
Numerical Results

Figure 1 shows a survival time versus dose plots for Eqs. (2) and (3). The simulations were performed for three different detection thresholds N_{ch}. The plots in the top row were conducted with competition coefficients α_{12}, α_{21} both equal to 1. A set of simulations were performed for different chemotherapy dose and the time needed for the tumour to reach a critical size N_{crit} was recorder. In order to assess the influence of the competition coefficients on this survival time the same simulations were performed but with the competition coefficients set to $\alpha_{12} = 0.8$ and $\alpha_{21} = 1.4$.

In our previous work [1] we postulated that explicit competition between the sensitive and resistant cells significantly contributes to the acquired drug resistance effect. We investigate this



(a) (b)

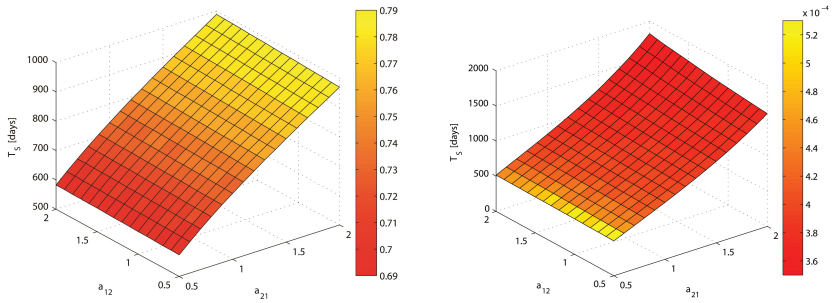


(c) (d)

Figure 1. Survival times for different chemotherapy dose for Eqs. (2) (left) and (3) (right). Three curves in each plot represent different tumour detection thresholds. The plots are constructed for two pairs of competition coefficients: $\alpha_{12} = \alpha_{21} = 1$ (top), and $\alpha_{12} = 0.8, \alpha_{21} = 1.4$ (bottom).

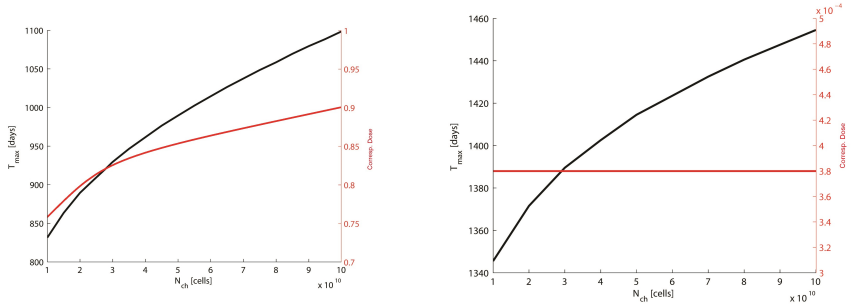
assertion further by computing the maximum survival time depending on the parameters α_{12} and α_{21}. Figure 2 shows the results of these calculations.

Monro and Gaffney observed also that delaying the moment of chemotherapy initiation and at the same time increasing the dosage increases the survival time. In order to check whether this property of the system is conserved when altering the way chemotherapy response is modelled, we constructed an analogous plot of a dose yielding maximum survival time depending on the chemotherapy initialisation moment for Eqs. (3). The results are shown in Fig. 3.



(a) (b)

Figure 2. Dependence of maximum survival time for (a) Eqs. (2), and (b) Eqs. (3) on the competition coefficients. Colour represents the chemotherapy dose which yields the maximum survival time.



(a) (b)

Figure 3. Maximum survival time (black) and corresponding chemotherapy dose (red) plotted versus the tumour detection thresholds for (a) Eqs. (2), and (b) Eqs. (3).

DISCUSSION

Two models of heterogeneous tumour growth differing in the functional form of tumour's response to chemotherapy were investigated in this work. The first model based on a work by Monro and Gaffney [2] and included a Norton-Simon type chemotherapy response, while the second one assumed chemotherapy results in a log-kill death rate of malignant cells. The main objective of this work is to identify and explain differences between the two models and assess the impact of explicitly modelling the competition between resistant and sensitive malignant cells.

Major differences were identified when the stability of the steady states was performed in a case of continuous, indefinite chemotherapy. It was shown that if the therapy is introduced, then Eqs. (3) lose a purely sensitive steady state. Therefore even small amounts of treatment allows growth of a resistant population. This is in contrast to Eqs. (2), where provided $\alpha_{21} > 1$, the desirable, sensitive equilibrium may exist for positive doses of therapy.

What is more, the Norton-Simon-based Eqs. (2) have steady states whose coordinates do not depend on the chemotherapy dose. The coordinates of the positive steady state of Eqs. (3) with linear response, however, do depend on the chemotherapy dose. This shows that in the log-kill case the chemotherapy is able to quantitatively affect the long-term behaviour of the system.

As seen in Fig. 1, both systems share a property that the maximum survival time is achieved for intermediate chemotherapy dose. It can be seen, however, that the slope of the survival time curves for chemotherapy doses lower than the optimal one is much steeper in case of the log-kill response. This suggests that in case of log-kill response, the optimal dose is not much higher than the minimal effective dose.

What is more, the same figure shows that for a Norton-Simon response there exists a maximal dose above which the survival time dose note improve. This dose is approximately equal to $\beta u = 1$. If $\beta u > 1$, the effective growth rate for the sensitive cells becomes negative. The resistant population is then free to grow and their growth is not affected by any increase in the dosage. In log-kill case, however, no such critical value is visible and increasing the dose far beyond the optimal one decreases the survival time.

Finally, Fig. 1 shows that in the log-kill case the survival time is less dependent on the chemotherapy initiation threshold. A more detailed analysis is shown in Fig. 3. In fact delaying the onset of therapy in each case extends the survival time. This may be explained by the fact that the later the treatment is started, the more the resistant cells are suppressed by the sensitive ones. The model, however, does not take into account other events associated with tumour growth, such as organ failure or metastasis, which is likely to distort the results. Interestingly, the optimal dosage in the log-kill case is independent of the detection threshold, as seen in Fig. 3(d).

Figure 2 shows how the maximum survival time and dose depend on the competition coefficients. It can be seen that the coefficient α_{21}, which measures how effectively the sensitive cells suppress the resistant population, has a significant effect on the results. The better the sensitive cells are adapted to the environment in the absence of therapy, the more they dominate over the intrinsic resistant population, which increases the survival time. The impact of the resistant cells on the sensitive ones can be seen to be far less significant. This is because if the resistant population is large enough to actually affect the sensitive one, it means that the chemotherapy is effective enough in killing the sensitive cells, that the additional competition effects are negligible.

A major difference between the two modelling approaches is also visible in Fig. 2. Namely, when Norton-Simon hypothesis is used, an increase in α_{21} results in an increase of the optimal dose. In the log-kill case, however, the result is exactly opposite. This shows that the optimal dosage is very much dependent on the model choice when cell competition is explicitly taken into account.

The way in which chemotherapy response is incorporated in the model has therefore significant impact on the results. Although some properties are shared between the two approaches (e.g. maximum survival for intermediate doses), other depend on the functional form of the response.

The long-term behaviour differs between the two systems. The log-kill response does not allow for the existence of purely sensitive steady state for positive therapy doses. Differences are also visible between the survival times versus drug dose curves for the two systems. The survival time in a Norton-Simon case smoothly approaches its peak, while in the log-kill case the survival time exhibits a more threshold-like phenomenon, i.e. a steep jump from low to high survival times.

Finally, the optimal dosage calculated using the models changes in opposite directions when competition coefficient α_{21} is varied. As the conclusions drawn from both models differ, it is important to decide which model is more appropriate to which chemotherapeutic agent. Both models, however, highlight the importance of careful chemotherapy scheduling.

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