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# Anti-angiogenic and chemotherapy scheduling optimisation using mathematical modelling

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**Abstract:** One of the main obstacles in chemotherapy planning is acquired drug resistance. It causes that even though the initial response to a drug may show promising results, re-administration of the drug may have no effect. Based on the Hahnfeldt et al. model, we formulate a new model of tumour growth under angiogenic signalling that is adapted to heterogeneous tumours and accounts for the Norton-Simon hypothesis. Using mathematical modelling and applying optimal control framework we show that lower doses of chemotherapy may be beneficial for patients by reducing resistance. Our analysis offers insights into the effects of combined anti-angiogenic agent and chemotherapy. By numerical simulations we show the longest survival time is achieved for intermediate doses. It supports the concept of metronomic therapy.

**Keywords:** tumour growth, resistance, chemotherapy, anti-angiogenic treatment, optimal control

## 1. Introduction

The most frequently used therapy strategy in cancer treatment is chemotherapy. However, chemotherapy is not selective and affects not only tumour cells but also healthy cells. Genetic instability of tumour cells, coupled with high proliferation rates may lead to acquired drug resistance (ADR), which is one of the biggest obstacles in chemotherapy scheduling. Using mathematical modelling we would like to make insights into the hypothesis: delaying the onset of drug resistance by appropriate chemotherapy scheduling may maintain tumour size at low level and prolong patient survival time.

In 1999 Hahnfeldt et al. proposed a model of tumour growth under angiogenic signalling assuming that the tumour population is homogeneous. In order to model ADR, we propose an extension of the Hahnfeldt et al. model, which takes into account heterogeneity of tumour cells in the context of resistance. In [1] we proposed another version of such model accounting for log-kill hypothesis.

Minimizing tumour volume together with some constraints on the drug dosage is the standard therapeutic goal. However, it does not ensure that tumour does not switch to the resistant phenotype. Such tumours do not respond properly to treatment, which may result in therapy failure. In [2] we formulated a new objective functional that penalizes drug resistance and presented mathematical analysis of the relevant optimal control problem. Optimization of chemotherapy scheduling using a three-dimensional model with varying carrying capacity can be found in [3]. Here our aim is to find optimal chemotherapy scheduling when a small constant supply of anti-angiogenic agent is applied during the therapy. We assume that the tumour population is divided into two sub-populations: sensitive and resistant to chemotherapy. We include constant flow between compartments caused by mutations and assume that sensitive cells are killed by the drug according to the Norton-Simon hypothesis, i.e. the rate of cancer cell death in response to treatment is proportional to the tumour growth rate.

## 2. Results and Discussion

Under the above assumptions, we consider the following system of differential equations

$$\begin{aligned} \frac{dN_1}{dt} &= -\big(\lambda_1 - \beta_1 u(t)\big) N_1 ln\frac{N_1+N_2}{K} - \tau_1 N_2 + \tau_2 N_2, \\ \frac{dN_2}{dt} &= -\lambda_2 N_2 ln\frac{N_1+N_2}{K} + \tau_1 N_2 - \tau_2 N_2, \\ \frac{dK}{dt} &= -\mu K + b(N_1+N_2) - d(N_1+N_2)^{2/3} - \beta K u(t) - \gamma K v(t), \end{aligned} \tag{1}$$

where $N_1$ and $N_2$ denote sizes of sensitive and resistant sub-populations, $K$ is the carrying capacity related to the size of the vasculature, $\lambda_1$ and $\lambda_2$ are proliferation rates, $\tau_1$ and $\tau_2$ are mutation rates, $\mu$ is natural death rate of endothelial cells, $b$ is vascular growth rate stimulated by cancer cells, $d$ is vascular inhibition rate by cancer cells, $\beta_1$ is sensitivity rate of sensitive cells to the chemotherapy agent, $\beta$ and $\gamma$ are sensitivity rates of the vasculature to the chemotherapy and anti-angiogenic agent, respectively, while $u(t)$ and $v(t)$ are concentration of chemotherapy and anti-angiogenic agent, respectively.

We formulate the optimal control problem for System (1) as follows: find a measurable function $u: [0, T] \to [0,1]$ for a given fixed terminal time $T$, which minimizes the functional

$$J(u) = \omega_1 N_1(T) + \omega_2 N_2(T) + \int_0^T \eta_1 N_1(t) + \eta_2 N_2(t) + \frac{\xi}{2}\left(1 + tanh\left(\frac{N_2(t) - N_1(t)}{\epsilon}\right)\right) + \theta u(t) dt.$$

Here, $\omega_i$, $\eta_i$ and $\xi$ are non-negative weights, while $\epsilon$ is positive parameter. Terms involving $\omega_i$ and $\eta_i$ penalize the size of the whole cell population at the end and during therapy, respectively, while the term $\theta u(t)$ minimizes side-effects. We include the term $\frac{\xi}{2}\left(1 + tanh\left(\frac{N_2(t)-N_1(t)}{\epsilon}\right)\right)$ in order to penalize time period during which the tumour is resistant (i.e. consists of more resistant than sensitive cells).

We consider two therapeutic protocols. First one is a long-time horizon protocol, where our aim is to prolong the patient survival time the most. We show that the longest survival time occurs for intermediate chemotherapy doses. The second protocol consists of two 14-day therapy windows. We show that the optimal therapy scheduling is consisted of two short MTD protocols at the beginning and at the end of therapy and a singular dosage in between. To solve the optimal control problem we choose the numerical approach "First Discretize then Optimize". To examine how the solution depends on the model parameters, we perform a sensitivity analysis with respect to those parameters.

## 3. Concluding Remarks

We consider a mathematical model of tumour growth that encompass heterogeneity of cell population and incorporates for the Norton-Simon hypothesis. Using optimal control theory, we obtain numerically optimal combined chemotherapy and anti-angiogenic protocols. As optimal dosages are time-varying, they may not be practically realizable. We provide a tool that can be used to design piecewise-constant intermediate or average-optimal dose protocols and precisely indicate switching points. Derivation of such suboptimal protocols without theoretical analysis would be extremely difficult.

## References


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