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ON THE MTD PARADIGM AND OPTIMAL CONTROL FOR MULTI-DRUG CANCER CHEMOTHERAPY

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Abstract. In standard chemotherapy protocols, drugs are given at maximum tolerated doses (MTD) with rest periods in between. In this paper, we briefly discuss the rationale behind this therapy approach and, using as example multi-drug cancer chemotherapy with a cytotoxic and cytostatic agent, show that these types of protocols are optimal in the sense of minimizing a weighted average of the number of tumor cells (taken both at the end of therapy and at intermediate times) and the total dose given if it is assumed that the tumor consists of a homogeneous population of chemotherapeutically sensitive cells. A 2-compartment linear model is used to model the pharmacokinetic equations for the drugs.

1. **Introduction.** In standard chemotherapy protocols, drugs are given at maximum tolerated doses (MTD) with rest periods in between. High dose chemotherapy is designed to be as toxic as possible to the cancerous cells. Typically, anti-cancer drugs interfere with one or more biochemical pathways important in cell duplication. Naturally, the more the targeted pathway is specific to cancer cells, the less severe collateral damage is. But drugs are rarely selective to the tumor cells and thus equally kill a large number of proliferating healthy cells at the same time. Especially in the first stages of chemotherapy that aim at remission of the disease, so-called *induction chemotherapy*, drugs target all or at a minimum large classes of proliferating cells with potentially severe effects on a wide range of physiologically proliferating cells important for life, like the bone marrow. Therefore an MTD approach to scheduling drugs clearly has its pitfalls. The underlying rationale for this approach is that the patient was only diagnosed late, unfortunately an all too common scenario for a disease that is widely symptomless in its early stages, and that the disease has progressed into a form where immediate action is required.

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The paradigm thus simply is that cancer cells need to killed, and that it has to be done right now and in large quantities. But because of the scarce selectivity of chemotherapeutic agents, serious side effects are related to the use of cytotoxic agents and if these side effects become too strong, chemotherapy fails.

In this paper, starting with a standard cell cycle nonspecific model of tumor growth under chemotherapy and leading over to a cell cycle specific compartmental model for combination chemotherapy with a cytotoxic and cytostatic agent, we explore the rationale for an MTD scheduling of chemotherapeutic agents. Mathematically, these regimes correspond to so-called bang-bang controls that switch between the two extreme values $u = u_{\max}$ corresponding to full dose chemotherapy and $u = 0$ corresponding to rest periods. For many optimal control problems, there still exists a natural third class of candidates, so-called singular controls, that give drugs at time-varying lower dose rates. We show that an MTD strategy indeed is optimal for the model considered here where a weighted average of the tumor cells (taken both at the end of therapy and at intermediate times) and the total dose of drugs given is minimized, even if the pharmacokinetics of a multi-drug treatment is taken into account. As initial condition we use the normalized fractions of the steady-state proportions of the numbers of cancer cells in the phases of the cell cycle. It will be shown that this steady-state is well defined (i.e., the limits exist) for a 3-compartment model with compartments G_1/G_0, S and G_2/M. As a consequence, by the time chemotherapy treatment starts, the system has settled down to have specific fractions of cycling cells in the compartments independent of the tumor size. This fact provides a simple explanation for the commonly medically observed feature of a fractional cell-kill under chemotherapy.

An MTD related structure consistently arises as optimal for a great variety of cell cycle specific and non-specific mathematical models (e.g., [8, 18, 21, 22, 24, 26]). On the other hand, in these models it is assumed that the tumor consists of a homogeneous population of chemotherapeutically sensitive cells. Once tumor heterogeneity (Norton-Simon hypothesis) and developing drug resistance are incorporated, models become more complicated, possibly even involving infinite-dimensional structures [20, 28, 29]. Simpler, finite-dimensional versions of models for drug resistance have been proposed and analyzed in [10, 11], but the full answer to how heterogeneity of a tumor effects the structure of optimal protocols is still unknown. In the other direction, incorporating elements of the tumor environment like the tumor vasculature and the immune system into the model for tumor growth and treatment may change the qualitative structure of optimal protocols. However, the answers still depend on the formulation of the objective, the therapy horizon etc. (e.g., [7, 12, 25]).

2. **The classical cell cycle non-specific model.**

We briefly review the classical framework of cell cycle nonspecific cancer chemotherapy that underlies the MTD dosing paradigm (e.g., see [4, 5, 23]). Mathematically, it can be explained with a standard phenomenological tumor growth model of the form

$$\dot{p} = pF(p) \tag{1}$$

where p denotes the tumor size (measured in terms of volume, number of cells, density of cells, etc.) and $F(\cdot)$ models its net proliferation rate, i.e., the difference between the proliferation rate of the cells and their death rate governed by apoptosis. Standard models used in this context include exponential growth, $F_E(p) \equiv \xi = \text{const}$, with ξ a tumor growth parameter, Gompertzian growth,

$F_G(p) = -\xi \ln\left(\frac{p}{q}\right)$ where q denotes a fixed carrying capacity, and logistic and generalized logistic growth, $F_L(p) = \xi\left(1 - \left(\frac{p}{q}\right)^{\nu}\right)$, with ν a positive parameter that differentiates slow from fast growing tumors. Chemotherapy lowers the tumor proliferation rate, either by slowing down the transition of cells through the cell cycle (cytostatic agents) or by preventing cell duplication in mitosis (cytotoxic agents). The latter, even if it does not induce cell death (apoptosis), generally is considered a killing action in cancer treatments since it prevents the further formation of cohorts of cancer cells.

When a drug is delivered to a human or an animal host, in an ideal situation, according to the law of mass action, the speed of the chemical reaction is proportional to the product of the active masses (concentrations) of the reactants. It has been postulated by Skipper et al. in the 1960s that cell death follows first order kinetics with anticancer drugs (e.g., [19, 31]), i.e., the number of cancer cells killed per unit time is proportional to the number of cancer cells with the rate depending on the concentration of the anti-cancer drug. Thus, if it is assumed that the density profile of the chemotherapeutic agent at an absorption site is described by a time-varying function $c = c(t)$, then the cell loss caused by this concentration is proportional to $c(t)p(t)$. In other words, the pharmacodynamic model is linear in both the concentration c and p. This hypothesis is called the linear *log-kill hypothesis* and incorporating it into the growth law (1) results in the following simple growth model under chemotherapy,

$$\dot{p} = pR(p) - \varphi cp \tag{2}$$

with φ a positive constant that describes the effectiveness of the agent.

We briefly discuss the effects of chemotherapy using the model for exponential growth,

$$\dot{p} = \xi p - \varphi cp, \qquad p(0) = p_0. \tag{3}$$

Over a short time-period, this is a realistic formulation. Suppose drugs are given in a single bolus dose, i.e., concentrated at some time instant with the time of application normalized to $t_0 = 0$. Drug clearance rates typically are fast—half-lives tend to be in the order of minutes to hours—while cell-cycle times are in the order of hours to days and even longer for some cell lines. Thus, over a short period, for many drugs it is valid to neglect pharmacokinetic effects and for simplicity of argument, let us assume that the concentration is constant, $c(t) \equiv \bar{c}$, over a small interval $[0, \Delta t]$, so that the solution to (3) is

$$p(t) = p_0 \exp\left((\xi - \varphi\bar{c})\,\Delta t\right) = p_0 e^{\xi\Delta t} \cdot \exp\left(-\varphi\bar{c}\Delta t\right). \tag{4}$$

Without treatment, the tumor grows to $p_0 e^{\xi\Delta t}$ and thus the second factor determines the reduction due to treatment. The total dose D administered is the product of the concentration and time, $D = \bar{c}\Delta t$. A bolus administration of dose D corresponds to an impulse and is the mathematical limit when this dose is given over decreasingly smaller intervals with higher concentrations in the limit as $\Delta t \to 0$. But the reduction term only depends on the constant total dose and therefore the tumor reduction achieved by a bolus injection of dose D is given by

$$r = \exp\left(-\varphi D\right)$$

with φ a positive constant dependent on the drug and the specific type of tumor. In particular, *a given bolus dose of anti-cancer drugs eliminates a specific proportion of cancer cells regardless of the size of the tumor, not a specific number of cancer*

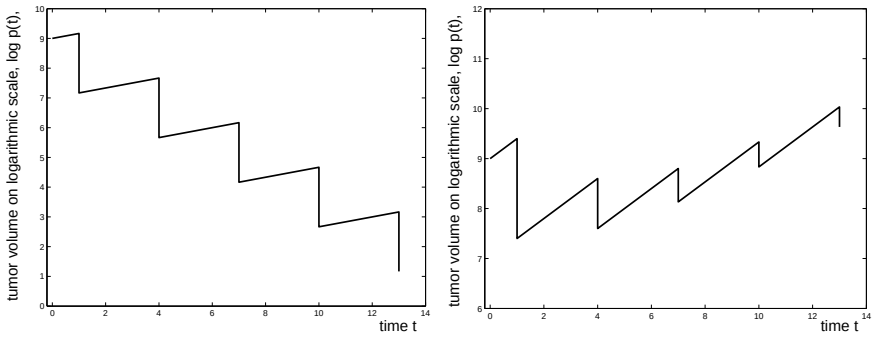

FIGURE 1. Evolution of tumor volume under bolus injection at times $t = 1, 4, 7, 10, 13$ weeks: (a, left) if cancer cells are sensitive and (b, right) if cancer cells contain a high portion of resistant cells. In case (a), therapy will be successful while it fails in case (b).

cells. Since this treatment does not only kill the cancer cells, but all other strongly proliferating cells as well (especially in the bone marrow), it needs to be followed by significant rest periods that allows the damaged healthy cells to recover. A typical length T for the time between doses in the US is three weeks. During this time the cancer will regrow and, still using the simple exponential growth model, the total effect over a therapy interval of length T is thus given by

$$\exp(-\varphi D) \cdot \exp(\xi T). \tag{5}$$

Only if this quantity is less than 1, therapy can be successful - in principle. Figure 1 depicts some typical response curves to bolus type chemotherapy with restperiods that result from this reasoning and are common in medical presentations and publications on this topic. We plot the number of cancer cells on a logarithmic scale vertically and time in weeks horizontally. In Fig. 1(a) the initial condition corresponds to 10^9 cells, probably the smallest size of tumor clinically detectable, and just for sake of numerical illustration it is assumed that 99% of the cancer cells are eliminated by the treatment with the remaining cells then regrowing slowly during the restperiod. Clearly, overall this is a very favorable scenario and this is a model for a successful chemotherapy. In reality, however, often only a much smaller ratio of cells is sensitive to the therapy and, in the course of time, as these sensitive cells are killed, the proportion of the resistant population of cancer cells increases. Unfortunately, healthy cells do not develop similar resistance properties and thus, over time, chemotherapy becomes less and less effective and eventually fails. A simple such scenario is depicted in Fig. 1(b).

In theory, since the terms in the basic relation (5) commute,

$$\exp(-\varphi D) \cdot \exp(\xi T) = \exp\left(-\varphi \frac{D}{2}\right) \cdot \exp\left(\xi \frac{T}{2}\right) \exp\left(-\varphi \frac{D}{2}\right) \cdot \exp\left(\xi \frac{T}{2}\right),$$

the same dose can be given at lower dose rates spread over time with the same effect. This has led to the concept of a *metronomic* scheduling of chemotherapy. In this form of therapy, drugs are administered in an essentially continuous low-dose way in the hope of avoiding limiting toxic side effects, possibly with small interruptions to increase the efficacy of the drugs. These represent the other extreme of many options for treatment schedules that are used in chemotherapy. As is obvious

from Eq. (4), if it is possible to give chemotherapy at lower doses over prolonged time intervals (e.g., if toxic side effects are absent), then the overall effect may be improved because of the greatly extended time horizon in the term $\exp(-\varphi\bar{c}\Delta t)$ [30]. For example, using a similar reasoning as above for a 2-compartment model of sensitive and partially resistant cells, Hahnfeldt, Folkman and Hlatky make a case for a metronomic scheduling of chemotherapy [5]. The optimization of treatment schedules to this day remains an active and important area of medical research.

3. **Cell cycle specific compartmental models for combination cancer chemotherapy.** Although the reasoning outlined in Section 2 is oversimplified in many aspects, it is the staple of much of the praxis of drug scheduling in chemotherapy. As one simplification, this argument does not consider the dynamics of the cell cycle. Chemotherapeutic agents act in the cycling compartments of the cell cycle (synthesis and mitosis), but quiescent cells (in the dormant stage) are generally resistant to treatment. Below we show that, in the absence of treatment, there always exist well-defined proportions of cancer cells that are in certain phases of the cell-cycle. This result accounts for the well-known *fractional kill effect* observed in chemotherapy treatments. As a consequence, slowly growing tumors with a small growth fraction of cycling cells will respond quite differently to an MTD treatment protocol than fast growing tumors when this fraction is high. In the model (2), these effects are simply subsumed in the coefficient φ that determines the cancer cell kill fraction. For some types of tumors, especially in certain types of leukemia, this fraction may represent only a small percentage, possibly less than 1%, of the total number of cancer cells. Therefore, it generally is of importance to consider cell cycle effects in the scheduling of chemotherapy.

In this section, we revisit a cell-cycle specific mathematical model for combination chemotherapy when the interactions of a cytotoxic (killing) and cytostatic (blocking) agent are considered. The basis for the model formulated below is a class of compartmental models introduced in the work of Swierniak and his coworkers (e.g., [6, 24, 27]), but different from the models considered in these publications, here we include a linear 2-compartment model for the pharmacokinetics of the drugs. We stress that these models **assume** that *the tumor consists of a homogeneous population of drug sensitive cells.*

3.1. **A cell-cycle specific compartmental model for combination cancer chemotherapy.** We briefly review a 3-compartment model for chemotherapy due to Swierniak [24] that considers the combined actions of a cytostatic (blocking) and cytotoxic (killing) agent. Cytostatic drugs slow down the growth of malignant cells in the sense that they prevent cells from reaching the phase where cell division occurs. Drugs of this type include, for example, anthracycline antibiotics like adriamycin [1] or antineoplastic agents like hydroxyurea (HU) [14] that inhibit DNA and RNA synthesis and arrest cells in the first growth phase G_1 of the cell cycle. Cytotoxic agents (e.g., spindle poisons like paclitaxel or vincristine) predominantly act during mitosis in the phase G_2/M of the cell cycle where cell division occurs. We use a 3-compartment model with the compartments given by the first growth phase G_1 (which is lumped with the dormant cells), synthesis S, and the second growth phase and mitosis, G_2/M. The state space thus is the first orthant in $\mathbb{R}^3$ and we denote the states by N_1, N_2 and N_3.

The transitions of cells through the phases of the cell cycle are described by a stochastic process with the individual cells determining the sample paths from cell

birth to cell death in cell division and the transit times following some empirical distribution. Various probabilistic models, in particular Weibull distributions, have been used to describe these transit times. Here we follow the simplest example, an exponential distribution with mean θ, i.e., the probability that a particular cell remains in a specific compartment after time t is given by

$$P(T \geq t) = \int_t^\infty \frac{1}{\theta} \exp\left(-\frac{s}{\theta}\right) ds = \exp\left(-\frac{t}{\theta}\right).$$

Taking the average over all cells, the outflow from the compartment then is governed by the linear ordinary differential equation $\dot{M} = -\frac{1}{\theta} M$ with the coefficient the inverse average transit time. Applying this to the 3-compartment model, and assuming that no external stimuli are present, the balance equations for the second and third compartments then take the form

$$\dot{N}_2(t) = -a_2 N_2(t) + a_1 N_1(t), \tag{6}$$

$$\dot{N}_3(t) = -a_3 N_3(t) + a_2 N_2(t), \tag{7}$$

with a_i the inverse mean transit time through the ith compartment. Here the outflows of the first and second compartments equal the inflows into the second and third compartment. But in the third compartment cell division needs to be taken into account and thus, while the outflow is still given by $a_3 N_3(t)$, the inflow into the first compartment doubles giving

$$\dot{N}_1(t) = -a_1 N_1(t) + 2a_3 N_3(t). \tag{8}$$

We now incorporate drug actions [3]. In accordance with the log-kill hypothesis, the number of cells killed or blocked is proportional to both the tumor volume and the drug's concentration. Pharmacokinetic equations model the time evolution of a drug's concentration in the plasma. If a drug is given at a time-varying dose rate $u = u(t)$, let $c = c(t)$ denote the concentration in the plasma that builds up in response. The standard mathematical model is one of exponential growth and decay,

$$\dot{c} = -\gamma c + u, \qquad c(0) = 0, \tag{9}$$

with γ the clearance rate of the drug, a constant. Once no more drugs are administered, $u \equiv 0$, this concentration simply dissipates at an exponential rate determined by the body's abilities to clear the drug. In this simplest 1-compartment model for PK, the drug dose rate u is related to the drug's concentration and its elimination in one part of the body, e.g., the blood plasma. More generally, in 2-compartmental models for PK, the drug's concentration and its elimination are considered at a central (e.g., plasma) and a peripheral compartment (e.g., at an absorption site) with their interactions. Here drug concentrations are modeled by a 2-dimensional vector $c(t) = (c_1(t), c_2(t))^T$ with the components describing the concentrations in the central and peripheral compartments. The model still is one of exponential growth and decay described by a linear system $\dot{c}(t) = Fc(t) + bu(t)$ of the form

$$\dot{c}(t) = \begin{pmatrix} -\gamma - \alpha & \beta \\ \alpha & -\beta \end{pmatrix} c + \begin{pmatrix} b_1 \\ b_2 \end{pmatrix} u(t)$$

where γ again denotes the clearance rate, α and β are nonnegative rates that describe the interactions between the central and peripheral compartments and the coefficients b_i ($b_i \geq 0$, $b_1 + b_2 = 1$) describe the influx of the drug into the compartments. The eigenvalues of the matrix F are always negative reals and the general

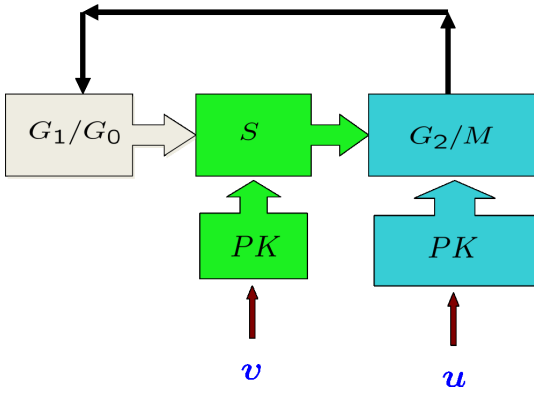

FIGURE 2. A 3-compartment model with cytostatic and cytotoxic agent and pharmacokinetic models

solution takes the form

$$c_1(t) = ae^{-\lambda_1 t} + be^{-\lambda_2 t}$$

with $0 < \lambda_1 < \lambda_2$ the absolute values of the eigenvalues. This modeling with $\alpha = 0$ is typical when one of the compartments describes the concentration in the plasma and the other one the drug concentration at an absorption site. Here we add such models for both the cytotoxic and cytostatic agents.

The control set for the cytotoxic agent u is a compact interval $[0, u_{\max}]$ with $u_{\max}$ the maximum dose rate and $u = 0$ again denoting the case when no drugs are administered. We denote the vector describing the concentrations in the 2-compartment model for PK by $c = (c_1, c_2)$ with c_1 the concentration at the absorption site and the dynamics given by

$$\dot{c}(t) = \begin{pmatrix} -\gamma_u & \beta_u \\ 0 & -\beta_u \end{pmatrix} c + \begin{pmatrix} 0 \\ 1 \end{pmatrix} u(t) = Fc + bu.$$

Similarly, the control set for the cytotoxic agent v is a compact interval $[0, v_{\max}]$ with $v_{\max}$ the maximum dose rate and $v = 0$ again denoting the case when no drugs are administered. Here we denote the vector describing the concentrations in the 2-compartment model for PK by $d = (d_1, d_2)$ with d_1 the concentration at the absorption site and the dynamics given by

$$\dot{d}(t) = \begin{pmatrix} -\gamma_v & \beta_v \\ 0 & -\beta_v \end{pmatrix} d + \begin{pmatrix} 0 \\ 1 \end{pmatrix} v(t) = Gd + bv.$$

The cytostatic agent is applied to slow down the transit times of cancer cells during the synthesis phase S and, as a result, the flow of cancer cells from the second into the third compartment is reduced by a factor of $d_1(t)$ percent from its original flow $a_2 N_2(t)$ to $(1 - d_1(t))a_2 N_2(t)$, $0 \le d_1(t) \le d_{1,\max} < 1$. We illustrate the general structure of the model in Fig. 2.

Overall, the controlled dynamics is a 7-dimensional bilinear system of the form

$$\dot{N} = (A + \varphi_1 c_1 B_1 + \varphi_2 d_1 B_2)\, N, \qquad N(0) = N_0, \tag{10}$$

$$\dot{c} = Fc + bu, \qquad c(0) = 0, \tag{11}$$

$$\dot{d} = Gd + bv, \qquad d(0) = 0, \tag{12}$$

with the matrices A, B_1 and B_2 given by

$$A = \begin{pmatrix} -a_1 & 0 & 2a_3 \\ a_1 & -a_2 & 0 \\ 0 & a_2 & -a_3 \end{pmatrix}, \quad B_1 = \begin{pmatrix} 0 & 0 & -2a_3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad B_2 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & a_2 & 0 \\ 0 & -a_2 & 0 \end{pmatrix},$$

the matrices F, G and b as specified above, and the constants φ_1 and φ_2 defining the effectiveness of the drugs. It is clear that the concentrations are nonnegative and, once drugs are given, become positive and remain so for all time. It follows from the form of the matrices F and G that these values are bounded: $c_1^{\max} \leq \frac{u_{\max}}{\gamma_u}$ and $c_2^{\max} \leq \frac{u_{\max}}{\beta_u}$. Thus, since the flows cannot be negative, we must have that $\varphi_1 \frac{u_{\max}}{\gamma_u} \leq 1$ and, similarly, $\varphi_2 \frac{v_{\max}}{\gamma_v} \leq 1$. This implies that the matrix

$$A + \varphi_1 c_1 B_1 + \varphi_2 d_1 B_2 = \begin{pmatrix} -a_1 & 0 & 2(1-\varphi_1 c_1)a_3 \\ a_1 & -(1-\varphi_2 d_1)a_2 & 0 \\ 0 & (1-\varphi_2 d_1)\, a_2 & -a_3 \end{pmatrix}$$

has negative diagonal and nonnegative off-diagonal entries, i.e., is an M-matrix. It therefore follows from standard arguments about linear differential equations that the positive octant $\mathbb{P} = \mathbb{R}^3_+ = \{N \in \mathbb{R}^3 : N_i > 0 \text{ for } i = 1,2,3\}$ is positively invariant, i.e., we have the following result:

Proposition 1. [9] *Given arbitrary Lebesgue measurable functions $u : [0,T] \to [0, u_{\max}]$ and $v : [0,T] \to [0, v_{\max}]$, the solution to the system (10)-(12) exists over the full interval $[0,T]$ and the values of N are positive.*

3.2. **Steady-state behavior of proportions in the compartments.** An important consequence of this model is that there exists a well-defined steady state for the proportions of cells in the individual compartments for the uncontrolled model. If no drugs are given, the concentrations are zero and the dynamics for N simply becomes $\dot{N} = AN$. Let $C(t) = N_1(t) + N_2(t) + N_3(t)$ denote the total number of cancer cells and denote the proportions of cancer cells in the three compartments by x, y and z, respectively,

$$x(t) = \frac{N_1(t)}{C(t)}, \qquad y(t) = \frac{N_2(t)}{C(t)} \qquad \text{and} \qquad z(t) = \frac{N_3(t)}{C(t)}.$$

We then have that

$$\dot{x} = -a_1 x + 2a_3 z - a_3 xz, \tag{13}$$

$$\dot{y} = a_1 x - a_2 y - a_3 yz, \tag{14}$$

$$\dot{z} = a_2 y - a_3 z - a_3 z^2. \tag{15}$$

One of these equations is redundant because of the trivial relation $x(t)+y(t)+z(t) \equiv 1$ and we use it to eliminate the variable y from the system. We thus are left with the planar system,

$$\dot{x} = -a_1 x + 2a_3 z - a_3 xz, \tag{16}$$

$$\dot{z} = a_2 (1 - x - z) - a_3 z - a_3 z^2. \tag{17}$$

Theorem 3.1. *The unit simplex*

$$\Sigma = \{(x,y,z) :\ 0 \leq x,\ 0 \leq y,\ 0 \leq z,\ x + y + z = 1\}$$

is positively invariant under the dynamical system given by Eqs. (13)-(15) and has a unique, asymptotically stable equilibrium point (x_*, y_*, z_*) inside of Σ that contains the entire simplex Σ in its region of attraction. Given an arbitrary initial condition

$(x_0, y_0, z_0) \in \Sigma$, the solution of Eqs. (13)-(15) exists for all times $t \geq 0$, lies in Σ, and converges to (x_*, y_*, z_*) as $t \to \infty$.

Proof. Because of the relation $x(t) + y(t) + z(t) \equiv 1$, we can identify Σ with the planar simplex $\tilde{\Sigma} = \{(x, z) : \ 0 \leq x, \ 0 \leq z, \ x + z \leq 1\}$ and it suffices to show that $\tilde{\Sigma}$ is positively invariant under the equations for $\dot{x}$ and $\dot{z}$. This is guaranteed if for every initial point (x_0, z_0) in the boundary of $\tilde{\Sigma}$, $(x_0, z_0) \in \partial\tilde{\Sigma}$, the local solution $(x(t; x_0, z_0), z(t; x_0, z_0))$ to the corresponding initial value problem enters the interior of $\tilde{\Sigma}$. For then, by the uniqueness of solutions to ordinary differential equations, no trajectory of the system that starts in $\tilde{\Sigma}$ can ever leave $\tilde{\Sigma}$ and thus this region is positively invariant. It is a standard argument from the theory of ODEs, using the local existence of solutions, to show that solutions then must exist over all of $[0, \infty)$.

We consider the three line segments in $\partial\tilde{\Sigma}$ separately starting with $x = 0$ and $0 \leq z \leq 1$. On this interval, we have that $\dot{z} = a_2 (1 - z) - a_3 z - a_3 z^2$ and this 1-dimensional system has a unique equilibrium $\tilde{z}$ in $(0, 1)$ that is asymptotically stable. Thus $\dot{z}$ is positive for points below $\tilde{z}$ and negative for points above it. Since $\dot{x} = 2a_3 z > 0$ if $x = 0$, it follows that the vector field

$$F(x, z) = \begin{pmatrix} -a_1 x + 2a_3 z - a_3 xz \\ a_2 (1 - x - z) - a_3 z - a_3 z^2 \end{pmatrix}$$

points inside of $\tilde{\Sigma}$ at all boundary points of the form $(0, z)$ with $0 < z < 1$. But at the vertices $(0, 0)$ and $(0, 1)$ the dynamics is tangent to the boundary of the unit simplex $\tilde{\Sigma}$ and we need to determine the next derivative. As an illustration of the argument, consider the origin. By the implicit function theorem, we can express the solution curve starting at the origin as a function $x = h(z)$ and the derivative $h'(z)$ is given by

$$h'(z) = \frac{dx}{dz} = \frac{-a_1 x + 2a_3 z - a_3 xz}{a_2 (1 - x - z) - a_3 z - a_3 z^2}.$$

Differentiating the relation $\dot{x} = h'(z)\dot{z}$ once more with respect to t gives that $\ddot{x} = h''(z)\dot{z}^2 + h'(z)\ddot{z}$ and evaluating this expression at the origin, and using that $h'(0) = 0$, gives

$$h''(0) = \frac{\ddot{x}}{\dot{z}^2} = \frac{2a_3 a_2}{a_2^2} = 2\frac{a_3}{a_2} > 0.$$

Thus the curve $x = h(z)$ has a local minimum at $z = 0$ with order 1 contact implying that it lies inside the region $\tilde{\Sigma}$ for small positive times. This shows that solutions starting at points in the vertical boundary segment of $\tilde{\Sigma}$ enter the interior of $\tilde{\Sigma}$ forward in time. Similar computations apply to each vertex and show that trajectories enter the unit simplex. On the horizontal boundary segment $0 \leq x \leq 1$ and $z = 0$, we have that $\dot{z} = a_2 (1 - x) > 0$ for $x < 1$ and thus again $F(x, 0)$ points inside $\tilde{\Sigma}$ at those points. Finally, along the line $x + z = 1$, we have that $\frac{d}{dt}(x + z) = -a_1 x < 0$ and thus also here all trajectories starting on this line enter the interior of Σ. This verifies that the simplex $\tilde{\Sigma}$ is positive invariant for the system (16) and (17).

The system has a unique equilibrium point (x_*, z_*) in $\tilde{\Sigma}$: Solving the equation $\dot{z} = 0$ for x gives

$$x_* = 1 - \left(1 + \frac{a_3}{a_2}\right) z_* - \frac{a_3}{a_2} z_*^2$$

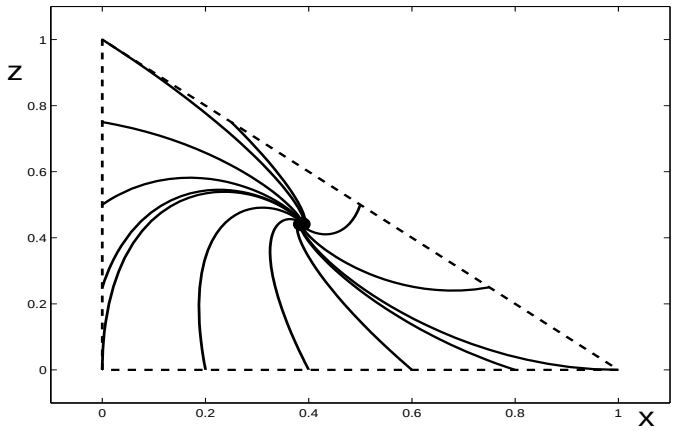

FIGURE 3. Positive invariance of the unit simplex Σ under the flow for the proportions (diagram drawn for the values $a_1 = 0.197$, $a_2 = 0.395$ and $a_3 = 0.107$ [24]).

and substituting this relation into the equation $\dot{x} = 0$ leads to the following cubic polynomial in z whose solutions define the equilibria (x_*, z_*):

$$a_3^2 z^3 + (a_1 + a_2 + a_3)\, a_3 z^2 + ((a_2 + a_3)\, a_1 + a_2 a_3)\, z - a_1 a_2 = 0.$$

Dividing by a_3^2 and setting $\alpha_1 = \frac{a_1}{a_3}$ and $\alpha_2 = \frac{a_2}{a_3}$, we get the simpler expression

$$Q(y) = z^3 + (1 + \alpha_1 + \alpha_2)\, z^2 + (\alpha_1 + \alpha_2 + \alpha_1\alpha_2)\, z - \alpha_1\alpha_2 = 0.$$

This cubic polynomial has exactly one change of sign in its coefficients and since $Q(0) = -\alpha_1\alpha_2 < 0$, it follows from Descartes' sign rule that it has exactly one positive root. But $Q(1) = 2\,(1 + \alpha_1 + \alpha_2) > 0$ and thus this root lies in the open interval $(0, 1)$. It then follows that

$$x_* + z_* = 1 - \frac{1}{\alpha_2} z_*(1 + z_*) < 1$$

and from $\dot{x} = 0$ we obtain that

$$x_* = \frac{2z_*}{\alpha_1 + z_*} > 0.$$

Hence the equilibrium (x_*, y_*) lies in the interior of $\tilde{\Sigma}$ and it is unique.

The rest of the argument is a direct application of Poincaré-Bendixson theory: the divergence of the vector field F is negative on the first orthant,

$$\text{div } F = \frac{\partial F_1}{\partial x}(x, z) + \frac{\partial F_2}{\partial z}(x, z) = -a_1 - a_3 z - a_2 - a_3 - 2a_3 z$$

and thus it follows from Bendixson's theorem that there do not exist periodic orbits for the system (16) and (17). On the other hand, since $\tilde{\Sigma}$ is positive invariant, the ω-limit sets of all trajectories are nonempty and thus consist of a unique equilibrium point. Since there is only one such point and since ω-limit sets are attractive, all trajectories converge to (x_*, z_*) in the interior of $\tilde{\Sigma}$. □

Figure 3 illustrates the corresponding phase portrait in the (x, z)-plane.

This result states that, by the time chemotherapy treatment starts, the system has settled down to have specific fractions of cycling cells in the compartments independent of the tumor size. Theorem 3.1 provides a simple explanation for this medically observed feature. Even after chemotherapy is stopped, if the restperiods are long enough, cells will redistribute in the same fractions for the beginning of the next session. Naturally, in the transient phase, proportions of cells in specific compartments may be different. Mathematically, since the dynamics is linear, we can scale the initial condition so that $C(0) = 1$ (e.g., times 10^9 cells) and thus the limiting fractions define the initial condition for the computation of optimal protocols. This is not only true at the beginning of therapy, but after every prolonged rest period.

The limiting fractions are determined by the coefficients that define the cell cycle kinetics and vice versa. It is possible to give explicit formulas for the equilibrium point (x_*, y_*, z_*) in terms of the coefficients a_i using Cardano's formula for the roots of a cubic polynomial, but these expressions are unwieldy and not very informative. It is easy to compute these fractions numerically. More interestingly, the cell cycle parameters a_i, $i = 1, 2, 3$ can be determined from these steady-state proportions and the tumor doubling time, data that can be determined experimentally. For the total number of cancer cells (for the uncontrolled system) we have that

$$\dot{C}(t) = a_3 N_3(t) = a_3 z(t) C(t) \approx a_3 z_* C(t) \tag{18}$$

where, in steady-state, we assume that $z(t)$ is approximated by its steady-state value z_*. Thus, if T denotes the tumor doubling time, then $a_3 z_* = \frac{\ln 2}{T}$ and the other kinetic parameters a_1 and a_2 directly follow from the equilibrium relations.

Corollary 1. *If T denotes the tumor doubling time and x_*, y_* and z_* are the steady-state proportions of cells in the cell cycle compartments G_0/G_1, S and G_2/M, respectively, then we have that*

$$a_3 = \frac{\ln 2}{T}\frac{1}{z_*}, \qquad a_2 = \frac{\ln 2}{T}\frac{1+z_*}{y_*} \qquad \text{and} \qquad a_1 = \frac{\ln 2}{T}\left(\frac{2}{x_*} - 1\right).$$

These arguments are generally valid and can easily be adapted to other compartmental models for cancer chemotherapy.

3.3. **The structure of optimal protocols.** We now consider the optimal control problem to minimize the cancer volume. For the optimization, we choose the performance index or objective as

$$J = rN(T) + \int_0^T qN(t) + s_1 u(t) + s_2 v(t) dt \to \min \tag{19}$$

where T is an a priori specified therapy horizon and $r = (r_1, r_2, r_3)$ and $q = (q_1, q_2, q_3)$ are row vectors of positive weights. The penalty term $rN(T) = r_1 N_1(T) + r_2 N_2(T) + r_3 N_3(T)$ represents a weighted average of the total number of cancer cells at the end of an assumed fixed therapy interval $[0, T]$ and the Lagrangian term $qN(t) = q_1 N_1(t) + q_2 N_2(t) + q_3 N_3(t)$ is a running cost that measures the tumor volume during treatment. Side effects of the treatment are only included indirectly in the model through minimization of the total overall doses of the drugs given, $\int_0^T u(t)dt$ and $\int_0^T v(t)dt$, and the positive coefficients s_1 and s_2 at these integrals provide relative weights for the severity of their side effects. These terms are motivated by the fact that the number of cells that do not undergo cell division at time

t is proportional to the concentrations of the cytotoxic drug. We thus consider the following optimal control problem:

[CC]: for a fixed therapy horizon $[0,T]$, minimize the objective (19) over all Lebesgue-measurable functions $u:[0,T]\to[0,u_{\max}]$ and $v:[0,T]\to[0,v_{\max}]$ subject to the dynamics (10)-(12) with initial condition $N(0)=C_0(\bar{x},\bar{y},\bar{z})^T$ and C_0 an estimate for the overall initial tumor size.

First order necessary conditions for optimality are given by the Pontryagin maximum principle (e.g., see [16, 2, 17]). For this model, all extremals are normal and we already define the Hamiltonian function in the form

$$H = qN+s_1u+s_2v+\lambda\left(A+\varphi_1c_1B_1+\varphi_2d_1B_2\right)N+\mu\left(Fc+bu\right)+\eta\left(Gd+bv\right) \quad (20)$$

with λ, μ and η the multipliers corresponding to the dynamics and pharmacokinetic models, respectively. If (u_*,v_*) are optimal controls, then it follows that there exist absolutely continuous functions λ, μ and η which we write as row-vectors, $\lambda:[0,T]\to(\mathbb{R}^3)^*$, $\mu:[0,T]\to(\mathbb{R}^2)^*$, and $\eta:[0,T]\to(\mathbb{R}^2)^*$, that satisfy the adjoint equations

$$\dot{\lambda} = -\frac{\partial H}{\partial N} = -\lambda\left(A+\varphi_1c_1^*B_1+\varphi_2d_1^*B_2\right)-q, \qquad \lambda(T)=r, \quad (21)$$

$$\dot{\mu}_1 = -\frac{\partial H}{\partial c_1} = -\varphi_1\lambda B_1N+\gamma_u\mu_1, \qquad \mu_1(T)=0, \quad (22)$$

$$\dot{\mu}_2 = -\frac{\partial H}{\partial c_2} = \beta_u\left(\mu_2-\mu_1\right), \qquad \mu_2(T)=0, \quad (23)$$

$$\dot{\eta}_1 = -\frac{\partial H}{\partial d_1} = -\varphi_2\lambda B_2N+\gamma_v\eta_1, \qquad \eta_1(T)=0, \quad (24)$$

$$\dot{\eta}_2 = -\frac{\partial H}{\partial d_2} = \beta_v\left(\eta_2-\eta_1\right), \qquad \eta_2(T)=0, \quad (25)$$

such that along $(\lambda(t),\mu(t),\eta(t),N_*(t),c_*(t),d_*(t))$ the optimal controls minimize the Hamiltonian H pointwise over the control set $U=[0,u_{\max}]\times[0,v_{\max}]$ and the minimum value is constant over the interval $[0,T]$,

$$H(\lambda(t),\mu(t),\eta(t),N_*(t),c_*(t),d_*(t),u_*(t),v_*(t)) = \text{const.}$$

Since the Hamiltonian H is linear in the controls and since the control set is a product of intervals, this minimization problem splits into separate 1-dimensional problems of minimizing a linear function over an interval. If the coefficient multiplying the control is nonzero, the minimum is attained at the boundary points (bang controls), but intermediate values (singular controls) can be optimal if this function vanishes over some interval. This leads to the following definition of the *switching functions* for the controls u and v,

$$\Phi_1(t) = s_1+\mu(t)b \qquad \text{and} \qquad \Phi_2(t) = s_2+\eta(t)b \quad (26)$$

and optimal controls satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi_1(t)>0, \\ u_{\max} & \text{if } \Phi_1(t)<0, \end{cases} \quad \text{and } v_*(t) = \begin{cases} 0 & \text{if } \Phi_2(t)>0, \\ v_{\max} & \text{if } \Phi_2(t)<0, \end{cases} \quad (27)$$

with singular controls possible if the corresponding switching function vanishes over an open interval.

In the language of control systems, the 2-compartment linear pharmacokinetic models simply represent a chain of 'integrators' through which the control acts on

the actual system, the dynamics for the state N. Such a structure does not alter the optimality of singular controls (e.g., see [13]).

Theorem 3.2. *The generalized Legendre-Clebsch condition for optimality of singular controls for problems [CC] is equivalent to the one for the optimal control problem without pharmacokinetic model, i.e., when the dynamics is simply given by* $\dot{N} = (A + B_1 u + B_2 v)\, N$ *and drug dose rates and concentrations are identified.*

Proof. For the 2-compartment models employed in this paper, this is a somewhat lengthy, but more or less straightforward computation and we only indicate the main steps at the example of the control u. If u is singular on an open interval I, then the switching function and all its derivatives vanish on I. In particular $\dot{\Phi}(t) = \dot{\mu}(t)b = \dot{\mu}_2(t) \equiv 0$ and thus μ_2 is constant; in fact, it follows from $\Phi = 0$ that $\mu_2 = -s_1$. Formally differentiating μ_2 according to the dynamics imposes additional restrictions on the other variables and multipliers. For example,

$$0 = \ddot{\mu}_2(t) = \beta_u \left(\dot{\mu}_2(t) - \dot{\mu}_1(t)\right) = -\beta_u \dot{\mu}_1(t)$$

and thus μ_1 is constant as well. But then

$$0 = \dot{\mu}_1(t) = -\varphi_1 \lambda(t) B_1 N(t) + \gamma_u \mu_1$$

and hence the function $\lambda(t)B_1N(t)$ is constant over the singular interval I. This, however, is exactly the quantity that would arise in the switching function $\Psi(t) = s_1 + \lambda(t)B_1N(t)$ for the system without pharmacokinetic models. It is a matter of verification that the generalized Legendre-Clebsch condition for optimality of a singular control for this reduced model is the determining term for the model [CC] as well. The only difference is that the order of the singular control (e.g., see [17]) increases by 2 because of the augmentation with a 2-compartment model for PK. In the case when only a 1-compartment model is considered, this order increases by 1. Thus, for the example considered here, one needs to compute the sixth derivative of the switching to get to the relevant expressions and these reduce to the same terms that arise for the order 1 singular control of the simplified model. These computations simplify since the multiplier μ is constant, but are left to the interested reader to verify. □

In earlier work, we already have analyzed the optimality of singular controls for the reduced model and have seen that singular controls are not optimal for both u and v [9]. Thus we have the following corollary.

Corollary 2. *If* $(N_*, c_*, d_*; u_*, v_*)$ *is an optimal controlled trajectory for problem [CC], then there does not exist an interval on which either of the controls* u_* *or* v_* *is singular.*

Thus bang-bang controls become the natural candidates for optimality. Figure 4 shows a typical example of optimal controls u and v. The local optimality of these controls has been verified using the algorithmic procedure developed in [18] that allows us to determine the optimality of bang-bang controls. The cell cycle parameters were taken from [24] as $a_1 = 0.197$, $a_2 = 0.395$ and $a_3 = 0.107$ and the corresponding steady-state proportions are given by $x_* = 0.3866$, $y_* = 0.1722$ and $z_* = 0.4412$. Thus, on average only about 61% of the cancer cells are cycling in this case. The limits on the controls are $u_{\max} = 1$ and $v_{\max} = 1$, i.e., we consider the ideal situation that the cytotoxic agent is able to kill all of the cycling cells and the cytostatic agent can achieve a complete reduction in the flow from S into G_2/M. The weights for the cancer cells in the objective at the terminal time were taken to

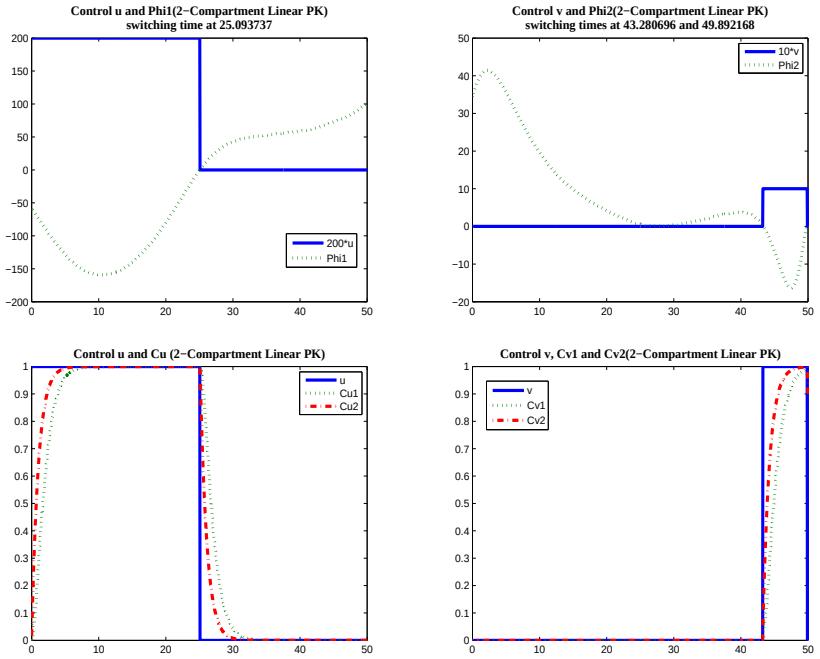

FIGURE 4. Examples of locally optimal controls u (cytotoxic agent) (top,left), v (cytostatic agent) (top,right) with corresponding switching functions and concentrations (bottom)

be equal, $r = (1, 1, 1)$ and smaller during therapy with a slightly higher weight for the cells in synthesis (just for numerical illustration) $q = (0.1, 0.2, 0.1)$. The weight for the killing agent is chosen considerably higher than the weight for the blocking agent, $s_1 = 100$ and $s_2 = 0.2$. For the therapy horizon we chose $T = 50$ [days]. The optimal control u_* follows an MTD scheme and administers all cytotoxic agents upfront at maximum dose rates with the switching at time $t_1 = 25.09$ [days] and and then a rest period of about the same time. Clearly, it would make no sense for the blocking agent to be active during this time and indeed the cytostatic agent is only administered over an interval from $t_2 = 43.28$ to $t_3 = 49.89$ [days] just prior to the end of the therapy interval. Naturally, the timing of these events depends on the parameters in the pharmacokinetic model and in this numerical illustration all these coefficients were set to 1. Figure 5 shows the corresponding optimal controlled trajectory with the initial condition normalized so that $C(0) = 1000$. If one views the whole therapy interval as one coherent unit and only looks at the total number of cancer cells, $C(t) = N_1(t) + N_2(t) + N_3(t)$, then C decreases by slightly less that 60%.

This is just one of many representative examples of this structure: *the cytotoxic agent is administered upfront in one maximum dose session consistent with an MTD approach to chemotherapy scheduling.* When the toxicities are measured by the weighted integrals of the dose rates of the agents and a penalty term on the cancer during treatment is included in the objective (qN), then as much of the killing agent as possible is given upfront, i.e., in a single maximum dose therapy session

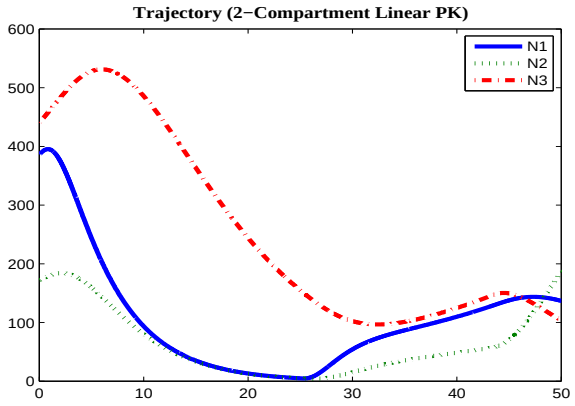

FIGURE 5. The corresponding optimal controlled trajectory

starting at $t = 0$. This is the consistent picture that emerges from various numerical computations. Compared with the results for the reduced model that identifies dose rates with concentrations, linear pharmacokinetic models (be it 1- or 2-compartment models) effect the quantitative values of the switching times, but the variations are minor if the parameters are correctly calibrated between the reduced and augmented model.

Naturally, a linear pharmacokinetic model does not capture all drug effects. For example, blocking agents may at the same time have cytotoxic affects in the sense that once the cells are released, some of them may fail to divide and may enter apoptosis. Also, some agents (such as cyclophosphamide) that are cytotoxic at high doses, are known to be cytostatic at low doses. Aftereffects due to the accumulation of drugs can result in great individual differences in the effectiveness of treatments (e.g., [15]). Such features are not captured with a simple linear pharmacokinetic model. But within the range of validity of this model, our theoretical results are independent of specific parameter values. The numerical illustrations that were given are only meant to illustrate general principles.

4. **Conclusion.** The scheduling of cancer chemotherapy still is an active area of research, both from the medical and mathematical modeling perspective. The results given in this paper are in agreement with the conventional MTD approach to chemotherapy, even for a cell-cycle specific model that takes into account that only a (possibly small) fraction of cycling cells is chemotherapeutically sensitive. Other modeling aspects, like tumor heterogeneity or the tumor's microenvironment, may result in optimal protocols that deviate from an MTD structure and for these cases the question of optimal drug scheduling still is largely unresolved. This is an important medically relevant question since, as experiments and clinical trials show, the same total amounts of drugs applied according to different protocols may lead to very different outcomes.

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