

---

# Tumor Development under Combination Treatments with Anti-Angiogenic Therapies

Alberto d’Onofrio<sup>1</sup>, Urszula Ledzewicz<sup>2</sup>, and Heinz Schättler<sup>3</sup>

<sup>1</sup> Dept. of Experimental Oncology, European Institute of Oncology, 20139 Milan, Italy, [alberto.donofrio@ifom-ieo-campus.it](mailto:alberto.donofrio@ifom-ieo-campus.it)

<sup>2</sup> Dept. of Mathematics and Statistics, Southern Illinois University Edwardsville, Edwardsville, Illinois, 62026-1653, USA, [uledzew@siue.edu](mailto:uledzew@siue.edu)

<sup>3</sup> Dept. of Electrical and Systems Engineering, Washington University, St. Louis, Missouri, 63130-4899, USA, [hms@wustl.edu](mailto:hms@wustl.edu)

## 1 Introduction

Tumors are a family of high-mortality diseases, each differing from the other, but all exhibiting a derangement of cellular proliferation and characterized by a remarkable lack of symptoms [52] and by time courses that, in a broad sense, may be classified as nonlinear. As a consequence, despite the enormous strides in prevention and, to a certain extent, cure, cancer is one of the leading causes of death worldwide, and, unfortunately, is likely to remain so for many years to come [4, 53].

Phenomenal progress in the field of molecular biology has qualitatively suggested how the macroscopic complexity of tumor behavior reflects the intricacy of its underlying deregulating microscopic biochemical mechanisms. At an inter-cellular level, considering tumor cell populations as ecosystems [57], further sources of complexity arise from its internal cell-to-cell cooperative and competitive interactions [10]. Additional interactions, which are critically relevant for the survival of a cancer, are its relationships with external populations, such as blood vessels, lymphatic vessels and with the cells of the immune system. Moreover, the responses of tumor cells (TCs) to these interactions are characterized by a considerable evolutionary ability via changes by means of mutations to enhance their survival in a hostile environment. Summarizing, cancer is a disease with at times anti-intuitive behavior whose macroscopic time course reflects intra-cellular and inter-cellular phenomena that are strongly nonlinear and time-varying.

In this framework, methods of modern mathematics, such as the theory of finite and infinite dimensional dynamical systems, can play an important role in better understanding, preventing and treating the family of bio-physical phenomena collectively called cancer. As Bellomo and Maini stressed in [3]: "the heuristic experimental approach, which is the traditional investigative

method in the biological sciences,” and in medicine, “should be complemented by the mathematical modeling approach. The latter can be used as a hypothesis-testing and indeed, hypothesis-generating, tool which can help to direct experimental research. In turn, the results of experiments help to refine the modeling. The goal of this research is that, by iterating back and forth between experiment and theory, we eventually arrive at a deeper conceptual understanding of how the highly nonlinear processes in biology interact. *The ultimate goal in the clinical setting is to use mathematical models to help design therapeutic strategies* [our emphasis]”.

In this paper, we describe some of the fundamental principles that underlie the mathematical modeling of the evolution of a tumor that need to be taken into account in any treatment approach. Clearly, no attempt can be made to be comprehensive in a short paper and for this reason we focus on one particular topic, combination therapies that involve anti-angiogenic treatments. We start with a brief discussion of various mathematical models for tumor growth which form the basis on which any kind of treatment needs to be imposed. Of these, by far the most important ones are chemo- and radiotherapies and we discuss their benefits and shortcomings. Anti-angiogenic therapies target the vasculature of a developing tumor and in combination with these traditional treatment approaches provide a two-pronged attack on both the cancer cells and the vasculature that supports them. Starting with general models that capture the characteristic features of these treatment approaches, we lead over to more detailed models as they are needed to optimize treatment protocols and discuss the implications of our mathematical analysis.

## 2 Phenomenological Models of Tumor Growth

A phenomenological model that describes the growth of a population of cells may be written in the general form

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

where  $p$  is the size (measured as volume, number of cells, density of cells etc.) of the population and  $R(\cdot)$  models the net proliferation rate, i.e., the difference between the proliferation rate of the tumor cells,  $\Pi(p)$ , and their death and apoptosis rate  $M(p)$ . Ideally, these rates are constant and then the growth law is a pure exponential [64]. In the biological reality, however, the rate  $R(p)$  normally is a decreasing function of  $p$ . Indeed, due to limited amounts of nutrients, the proliferation rate is a decreasing function of the population size whereas the rate  $M(p)$  is an increasing function and, typically, the net effect will be positive. We shall use mainly the net proliferation rate since generally it is difficult to infer  $\Pi$  and  $M$  separately from external growth measurements. If  $\Pi(0) > M(0)$ , then it is easy to show that the tumor size is globally attracted by the unique solution  $K$  of the equation  $\Pi(p) = M(p)$ . This value  $K$ , called

the *carrying capacity*, then represents the maximum sustainable size of the population. Unfortunately, in the vast majority of cases, the value  $K$  well exceeds values compatible with the life of the host.

Initially, for a small tumor size  $p(0)$ , an *exponential* growth law is appropriate for tumor growth. For  $p \ll K$  higher-order terms can be neglected and approximatively it holds that

$$\dot{p} \simeq R(p(0))p. \quad (2)$$

However, as the tumor grows, these neglected terms matter. One of the most commonly used laws to describe tumor growth is the *Gompertz law* [64],

$$R(p) = a - b \ln(p), \quad a > b > 0. \quad (3)$$

The parameter  $a$  represents a baseline proliferation rate, while  $b$  summarizes the effects of mutual inhibitions between cells and competition for nutrients; it sometimes is called the growth retardation factor. Normalizing  $p(0) = 1$ , the tumor size then becomes

$$p(t) = \exp\left(\frac{a}{b}(1 - e^{-bt})\right), \quad (4)$$

which has a typical double exponential structure. The normalized carrying capacity is  $K = \exp\left(\frac{a}{b}\right)$  and thus it is convenient to rewrite  $R(p)$  in the form  $R(p) = \xi \ln\left(\frac{K}{p}\right)$ , with the coefficient  $\xi$  a growth parameter that determines the rate of convergence of  $p$  to  $K$ .

The Gompertz law belongs to the class of phenomenological growth models that are based on competition between processes associated with proliferation and death. The number of such models is amazingly large, and, as another prolific example, we only mention the ubiquitous generalized logistic law,

$$R(p) = a \left(1 - \left(\frac{p}{K}\right)^\nu\right), \quad a > 0, \quad \nu > 0, \quad (5)$$

notwithstanding the existence of various other models (e.g., see, [10, 26, 28]).

Indeed, both the Gompertz and logistic models were generalized in many ways, and the recurrent question which model is more realistic [44] has no correct answer. Since populations of cancer cells of different types and/or in different conditions may behave very differently, it should not be surprising that models of cancer growth can be so diversified. Indeed, any macroscopic growth law has to mirror a set of phenomena that occur at the cellular scale including metabolic processes and inter-cellular interactions that vary considerably from case to case [46, 10]. Concerning specifically Gompertz-like models, as pointed out in [8, 64], all growth laws that produce a relative growth rate  $\frac{p'}{p}$  that tends to  $\infty$  as the size  $p$  tends to zero are clearly not adequate to describe the growth of small aggregate tumors whose doubling time, a quantity related to a complex set of biological processes such as cell

division cycle and apoptosis, cannot be arbitrarily small. The Gomp-ex law by Wheldon [64]

$$\dot{p} = \begin{cases} p(a - b \ln(C)) & \text{if } 0 < p < C, \\ p(a - b \ln(p)) & \text{if } p \geq C. \end{cases} \quad (6)$$

provides a modification that uses the Gompertz law above a certain threshold  $C$ , but uses a simple exponential growth for smaller tumor sizes. Even if the tumor size is measured in terms of cells, this stabilizes the ratio  $\frac{p'}{p}$  for small populations. For another generalization of the Gompertz law, see [11].

All of these models were obtained by qualitative reasoning and then, for specific cases, validated by means of data fitting, e.g., [47, 49]. Some of them are remarkably successful in the process of data-based validation. It is thus natural to ask to what extent these models reproduce at a large degree of approximation finer microscopical details, for example, of intercellular inhibitions. A second natural question then arises as to whether these models can be unified in some general framework. Can each of them be considered as a particular instance of some metamodel? Among the few works aimed at introducing a mechanistic theory that links macroscopic phenomenological models to microscopic interactions and parameters, we cite the simple, yet plausible model in [46] which is based on the realistic hypothesis of long range interactions between cells in a population whose “structure is fractal”. This approach, significantly extended by one of us in [10], allows to show that *apparently contradictory growth models* (logistic, generalized logistic, Gompertzian, exponential, von Bertalanffy, power law, del Santo-Guiot) *are simply macroscopic different manifestations of a common physical microscopic framework*. In other words, different values of the parameters of the microscopic law result in different analytical laws for  $R(p)$ . Thus, while one of these models may be more appropriate depending on a specific medical situation, in principle they all become viable alternatives in the investigation of the development of a tumor under treatment.

### 3 Cancer Chemotherapy

Cancer chemotherapy, and notwithstanding significant and very interesting recent developments towards novel cancer therapies such as immunotherapy, to this day remains the elective non-surgical choice for treatment of tumors. Strictly speaking, chemotherapy merely indicates the use of a chemical to cure a disease, especially due to proliferating pathogens such as bacteria, tumor cells etc.. However, chemotherapy has so important a clinical role in oncology that in the common usage of language the word chemotherapy nowadays uniquely denotes *anti-tumor chemotherapy*. The use of chemotherapies in oncology, indeed, has been one of the major steps forward in the so called

“war against cancer” [4]. There not only exists a huge body of experimental and clinical literature that has been produced in the last 60 years, but chemotherapy also triggered a large amount of theoretical research in connection with its apparently simple translation into mathematical models (e.g., [1, 34, 38, 39, 51, 54, 58, 59, 60, 61, 64]). Also, and unlike in other fields of biomedicine, on this topic there has been a small, but important interplay between theoretical and experimental-clinical scientists [25, 48, 63].

Broadly speaking, we may consider two major classes of actions of chemotherapeutic drugs: *cytostatic*, where the chemical decelerates or blocks the tumor cells’ proliferation, and *cytotoxic*, where the agent kills the neoplastic cell. This, of course, is a highly idealized description and often it is not clear how to classify the actions of a specific drug. For example, paclitaxel, still one of the more commonly used drugs in chemotherapy, binds to tubulin which locks microtubules in place and thus prevents cell-duplication. In principle, this is a blocking action. However, generally, a drug that prevents the further duplication of cancer cells indefinitely is considered cytotoxic even when it does not induce apoptosis.

The main adverse effects of chemotherapy are due to the fact that drugs are rarely selective to identify tumor cells, but, especially in the first stages of modern chemotherapy, target all or at least large classes of proliferating cells. The mechanism of action for these drugs is to interfere with one or more biochemical pathways and thus the more the targeted pathway is specific to cancer cells, the less severe side effects are. Since its first use, it has been plain that for this reason - the scarce selectivity of chemotherapeutic agents - a number of serious side effects are related to the use of cytotoxic chemicals to cure tumors. They simply also kill a more or less wide range of physiologically proliferating cells important for life.

Even when side effects are limited, a high number of failures of chemotherapy due to both *intrinsic* and *acquired drug resistance* plagues this treatment approach. Cancer cells often are genetically unstable and, coupled with high proliferation rates, this leads to significantly higher mutation rates than in healthy cells [25]. If a mutated cell has a biochemical structure that invalidates the mechanism of attack of the chemotherapeutic agent, these cells have acquired drug resistance. Indeed, the response of tumor cells to chemotherapy is characterized by a considerable evolutionary ability to enhance the cell survival in an environment that is becoming hostile. Moreover, and more importantly, because of the tremendous heterogeneity of cancer cells, often small sub-populations of cells are intrinsically not sensitive to the treatment *ab initio* (intrinsic resistance). In this case, as the sensitive cells are killed by the treatment, a tiny fraction of remaining, intrinsically resistant tumor cells can grow to become the dominant remaining population leading to the failure of therapy, possibly only after many years of seeming remission of the cancer. Considerable research efforts thus have been, and still are being devoted to finding means to overcome drug resistance [24]. Tumor anti-angiogenic therapy falls into the realm of these procedures [31, 32] and, for this reason, com-

binations of chemotherapy with anti-angiogenic treatments offer synergistic advantages.

We briefly extend the growth model considered in the previous section to include chemotherapy. In this model we assumed that  $M(0) < \Pi(0)$  since a negative net proliferation rate  $R(p) < 0$  implies the self-extinction of the neoplasm, a case only of interest for immunogenic tumors. But a negative net proliferation rate is exactly what chemotherapeutic agents aim at and thus this has relevance in the theoretical analysis of chemotherapy were the agents either reduce the proliferation rate or increase the death rate of the neoplastic cells. When a drug is delivered to a human or an animal host, two different types of processes take place called *pharmacokinetics (PK)* and *pharmacodynamics (PD)*: pharmacokinetics determines the density of the drug in the blood, i.e., *what the body does to the drug*, and pharmacodynamics models the effects the drugs have, *what the drug does to the body*. If we administer a drug whose density profile in the blood is  $c(t)$ , in many cases it is considered realistic [64] to assume that the number of cells killed per time unit is proportional to  $c(t)p(t)$ , i.e., the pharmacodynamic model is linear in both the concentration  $c$  and  $p$ . This hypothesis is called the *linear log-kill hypothesis*, and it modifies the basic growth model to become

$$\dot{p} = pR(p) - \varphi cp \quad (7)$$

with  $\varphi$  a positive parameter. For example, a simple model of chemotherapy assuming a Gompertz law for unperturbed growth can be written as

$$\dot{p}(t) = -\xi p(t) \ln \left( \frac{p(t)}{p_\infty} \right) - \varphi c(t)p(t), \quad (8)$$

where  $p_\infty$  denotes the (constant) carrying capacity. In a more general setting, one can assume that the pharmacodynamics still is linear in  $p$ , but nonlinear in  $c$ , say

$$\dot{p} = pR(p) - H(c)p. \quad (9)$$

If the therapy is delivered by constant continuous infusion therapy, after some initial transient, it is reasonable to assume that  $c(t) \approx C$ , and in this case the tumor can be eradicated if  $R(0) < H(C)$ . In the important case of periodic therapy,  $c(t+T) = c(t)$ , this eradication condition becomes  $R(0) < \langle H(c) \rangle$ , where  $\langle f \rangle$  denotes the average of a periodic function  $f$  over one period.

## 4 Modeling Radiotherapeutic Treatments

The log-kill model used in (8) can also be considered a rudimentary approximation for including effects of radiotherapy when only first order killing effects are considered. While such a linear model is reasonable for a cytotoxic agent, it is, however, only a crude approximation for the effects of radiotherapy. It is

more realistic to assume that the damage to DNA made by the effects of ionization radiation consists of a linear component that corresponds to a simultaneous break in both DNA strands caused by a single particle and a quadratic term that accounts for two adjacent breaks on different chromosomes caused by two different particles. This is the so-called linear-quadratic(LQ) model [23, 62, 64] that has become the accepted model in radiotherapy. The damage of radiation to the tumor can then be modelled in the form

$$-p(t) \left( \varphi + \beta \int_0^t w(s) \exp(-\rho(t-s)) ds \right) w(t) \quad (10)$$

where  $w$  represents the radiation dose rate and  $\varphi$ ,  $\beta$  and  $\rho$  are positive constants with  $\varphi$  and  $\beta$  related to the tumor LQ parameters and  $\rho$  the tumor repair rate. A small tumor repair rate implies a larger influence of the integral term that describes the secondary, i.e., quadratic effects, and thus a greater effectiveness of the therapy, while large repair rates imply that the integral can be neglected. Note that the integral term in parenthesis in (10) is simply the solution to the first order linear equation

$$\dot{r} = -\rho r + w, \quad r(0) = 0. \quad (11)$$

Mathematically, the structure of the overall model becomes more transparent if we replace the integral by this differential equation. Briefly, in case of constant  $w(t) = W$  the eradication condition becomes

$$R(0) < \varphi W + (\beta/\rho)W^2, \quad (12)$$

whereas for periodically delivered therapies it is

$$R(0) < \varphi \langle w(t) \rangle + \beta \langle w(t)r(t) \rangle. \quad (13)$$

## 5 Tumor Angiogenesis and Solid Vascularized Tumors

Chemotherapy targets the main characteristic of tumor cells, their proliferative derangement. However, as already mentioned, tumor cells show a vast array of microscopic and macroscopic interactions with other cellular populations. As a consequence, the study of these phenomena may open the way for the creation of new therapies. J. Folkman [20, 21] already stressed in the early seventies that the development of a vascular network inside the tumor mass becomes necessary to support tumor growth. Indeed, primary solid tumors and metastases require the formation of new blood vessels in order to grow beyond 1 to 2  $mm^3$ . Folkman named this process neo-angiogenesis. It is sustained by various mechanisms - tumors may coopt existing vessels, may induce the formation of new vessels from pre-existing ones or may exploit endothelial precursors originating from the bone marrow [22]. Tumor angiogenesis is a

complex process driven by *pro-angiogenic* factors that are being released as the tumor cells lack a full level of nutrients [66]. Interestingly enough, tumor cells also release *anti-angiogenic* chemicals that modulate the growth of the vessel network. In this way, a solid tumor deploys a sophisticated strategy to control its own growth. Folkman suggested that inhibiting the development of the tumoral vessel network could be a powerful way to control, in turn, the neoplastic growth via the reduction of nutrients supply. He termed this new kind of therapy *anti-angiogenic therapy*.

Angiogenic inhibitors are commonly classified [33] as *direct inhibitors* which act on the endothelial cells and inhibit their proliferation and migration or induce their apoptosis, or as *indirect inhibitors* that block the production of angiogenic factors by malignant cells, or as mixed agents that target both endothelial and malignant cells. Most angiogenic inhibitors are cytostatic inhibiting the formation of new blood vessels. Some of the direct inhibitors have a cytotoxic action that induce a rapid destruction of existing blood vessels. Various anti-angiogenic drugs have undergone clinical development in recent years, and some of them have led to improvement in overall survival or disease-free survival in various clinical scenarios. Since the therapy targets healthy cells, namely the endothelial cells forming blood vessels, that are far more genetically stable than tumor cells, anti-angiogenic agents are far less subject to drug resistance [31]. *Per se*, this way of controlling the tumor burden appears intriguing and there is evidence from experimental work that inhibiting angiogenesis may induce tumor regression and sometimes cure [50].

Modeling the interplay between tumor growth and the development of its vascular network, as well as the action of angiogenic inhibitors, is an important step that could help to plan effective anti-angiogenic therapies and a large number of mathematical models have been proposed, e.g., [1, 2, 12, 13, 15, 27, 45]. Quite interestingly, Folkman himself and his coworkers formulated a simple, but largely influential mathematical model in [27] that describes the vascular phase of tumor growth assuming that this growth is strictly controlled by the dynamics of the vascular network and that the vascular dynamics is the result of the opposite influence of pro-angiogenic and anti-angiogenic factors produced by the tumor itself. This model provides a framework to portray the effects of anti-angiogenic therapies and it was successful in fitting experimental data on the growth and response to different anti-angiogenic drugs for Lewis lung carcinomas implanted in mice.

The appreciation of the role of angiogenesis in tumor development has led Folkman and his coworkers to introduce the concept of a varying carrying capacity,  $q(t)$ , defined as the tumor size potentially sustainable by the existing vascular network at a given time [27]. This carrying capacity may be assumed proportional to the extent of the actual tumor vasculature. Making the carrying capacity in equation (8) variable, and following [27] in modeling, the sophisticated, tightly controlled strategy for the production of vessels reduces to the following dynamical system for tumor size and carrying capacity under chemotherapy:



$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right) - \varphi cp, \quad (14)$$

$$\dot{q} = bp - dq^{\frac{2}{3}}q - \mu q. \quad (15)$$

Here  $bp$  models the growth stimulated by the pro-angiogenic factors,  $dq^{2/3}$  is a variable loss rate ‘constant’ due to the endogenous anti-angiogenic factors produced autonomously by tumor cells,  $\mu$  is the natural loss rate constant of the vasculature and  $c$  denotes the concentration of the chemotherapeutic agent. This model was obtained under a series of simplifying assumptions that include spherical symmetry of the tumor, a fast degradation of pro-angiogenic factors and a slow degradation of inhibitory factors. The slow dynamics of anti-angiogenic factors leads to an interaction term between the surface area of the spheroid and the vasculature of the form  $dp^{\frac{2}{3}}q$ , whereas the fast dynamics of the pro-angiogenic factors suggests the term  $bp$ . A mathematical analysis of this model was presented in [12], focusing on the tumor eradication under regimens of continuous or periodic anti-angiogenic therapy; the problem of determining optimal treatment schedules for a given amount of inhibitors has been solved in [40].

By relaxing the assumptions made in [27], and also by considering more general laws of tumor growth, the above model was generalized in [14] assuming that the specific growth rate of the tumor,  $\frac{\dot{p}}{p}$ , and the specific birth rate of vessels depend on the ratio between the carrying capacity and the tumor size. Since the ratio  $\frac{q}{p}$  may be interpreted as proportional to the tumor vessel density, the second assumption agrees with the model proposed by Agur et al. [1]. In the absence of therapy, the model proposed in [14], takes the form

$$\dot{p} = pF\left(\frac{q}{p}\right) \quad (16)$$

$$\dot{q} = q\left(\beta\left(\frac{q}{p}\right) - I(p) - \mu\right) \quad (17)$$

where the growth function  $F : (0, \infty) \rightarrow \mathbb{R}$  is strictly increasing and satisfies

$$-\infty \leq \lim_{\rho \rightarrow 0^+} F(\rho) < 0, \quad F(1) = 0, \quad \text{and} \quad 0 < \lim_{\rho \rightarrow +\infty} F(\rho) \leq +\infty.$$

The stimulation term  $\beta : (0, \infty) \rightarrow \mathbb{R}$  is strictly decreasing and satisfies  $\beta(+\infty) = 0$  and  $\beta(1) > \mu$ . It may be unbounded, like in the biologically important case of power laws,  $\beta(\rho) = b\rho^{-\delta}$ ,  $\delta > 0$ , or bounded such as

$$\beta(\rho) = \frac{\beta_M}{1 + k\rho^n}, \quad n \geq 1.$$

In this case,  $\lim_{\rho \rightarrow 0^+} \beta(\rho)$  is finite and  $\beta$  is a decreasing Hill function. Also, combinations of the above two expressions are allowed. The inhibition term is a strictly increasing function  $I : [0, \infty) \rightarrow [0, \infty)$  that satisfies  $I(0) = 0$  and  $\lim_{p \rightarrow +\infty} I(p) = +\infty$ . Equations (16) and (17) together provide a general mathematical framework within which the time evolution of solid vascularized tumors can be analyzed.

## 6 Combinations of Chemo- and Anti-Angiogenic Therapies of Vascularized Tumors

Anti-angiogenic therapy is an indirect approach that only limits the tumor’s support mechanism without actually killing the cancer cells. Therefore it is only natural, and this has been observed consistently, that therapeutic effects are only temporary and, in the absence of further treatment, the tumor will grow back once treatment is halted. Thus tumor anti-angiogenesis is not efficient as a stand-alone or monotherapy treatment, but it needs to be combined with other mechanisms like traditional chemotherapy or radiotherapy treatments that kill cancer cells. In this context, it is worth noting that tumors differ from normal tissues also in density, topology and functionality of their vessel network. Tumor vasculature is characterized by a remarkable degree of intricacy as well as by a variety of disfunctionalities. Since the neovessel network that brings nutrients to the tumor is also the route to deliver chemotherapeutic drugs, R.K. Jain hypothesized that the preliminary delivery of a vessel disruptive anti-angiogenic agent, by ‘pruning’ the vessel network, may regularize it with beneficial consequences for the successive delivery of cytotoxic chemotherapeutic agents [29, 30]. If treatment schedules are optimized to minimize the tumor volume, such a structure of protocols is confirmed as optimal [18] and our results support this hypothesis.

Experimental studies on mouse models and clinical trials [6, 7] showed that some cell cytotoxic agents (e.g., cyclophosphamide) also have significant anti-angiogenic effects. In [9], this effect was modelled for a chemotherapeutic monotherapy that also has a vessel disruptive action. On the other hand, here we are interested to fully assess the effects of a combined therapy when three classes of drugs are co-present: (i) an anti-angiogenic agent  $u$  having effects of vessel disruption, (ii) a chemotherapeutic agent  $v$  which may or may not have effects of vessel disruption or inhibition, and (iii) an anti-angiogenic agent  $w$  inhibiting the proliferation of the tumor vessels. Generalizing the model in [18], these effects are included in the following equations:

$$\dot{p} = pF\left(\frac{q}{p}\right) - \varphi vp. \quad (18)$$

$$\dot{q} = q\left(\theta(w, v) \cdot \beta\left(\frac{q}{p}\right) - I(p) - \mu - \gamma u - \eta v\right). \quad (19)$$

Here  $\theta = \theta(w, v)$  is a function that takes values in the interval  $[0, 1]$  and is decreasing in both variables. We also assume that  $0 \leq \eta \leq \varphi$  since, for biological reasons, the log-kill effect on the carrying capacity, if it exists, is not the prevalent one. However, this assumption has no consequences on the asymptotic behavior of the solutions of the proposed system. The model considered in [18] was the special case  $\beta(\rho) = \frac{b}{\rho}$  so that  $q\beta\left(\frac{q}{p}\right) = bp$ .

We first analyze the behavior of the tumor and its vessels in the absence of therapies or under continuous infusion therapies (CITs) of infinite temporal

length, i.e., for  $v(t) \equiv V \geq 0$ ,  $u(t) \equiv U \geq 0$  and  $w(t) = W \geq 0$ . If  $F(0)$  is small enough, then the tumor can in fact be eradicated by anti-angiogenic action alone.

**Lemma 1.** *If  $\varphi V > F(\infty)$ , then, in the limit  $t \rightarrow \infty$ , the tumor is eradicated,  $\lim_{t \rightarrow +\infty} p(t) = 0$ .  $\square$*

The  $p$ -nullcline,  $\dot{p} = 0$ , is given by  $q = A(V)p$  where  $A(V) = F^{-1}(\varphi V)$  and, setting  $\dot{q} = 0$ , we obtain that

$$q = Q(p) = p\beta^{-1} \left( \frac{I(p) + \mu + \gamma U + \eta V}{\theta(W, V)} \right). \quad (20)$$

It is then straightforward to prove the following proposition:

**Proposition 1.** *Under continuous infusion therapies,  $U \geq 0$  and  $V \geq 0$ , if*

$$\theta(W, V)\beta(A(V)) > (\mu + \gamma U + \eta V), \quad (21)$$

*then there exists a unique, non-null, globally asymptotically stable equilibrium point  $EQ = (p_e(U, V, W), q_e(U, V, W))$  that satisfies*

$$q_e(U, V, W) = p_e(U, V, W)A(V) \quad (22)$$

and

$$p_e(U, V, W) = I^{-1} [\theta(W, V)\beta(A(V)) - (\mu + \gamma U + \eta V)]. \quad (23)$$

Moreover, the orbits of the system are bounded and the set

$$\Omega_{(U, V, W)} = \left\{ (p, q) \in \mathbb{R}_+^2 : q \leq M = \max_{p \in [0, p_e]} Q(p) \text{ and } 0 \leq p \leq \frac{M}{A(V)} \right\}$$

is positively invariant and attractive.  $\square$

Thus, in case of infinitely long therapies, in principle it is possible to eradicate the tumor under suitable constraints on the drug density in the blood. A first condition to reach this target has been illustrated in Lemma 1, but it is simply the translation to the angiogenic setting of the eradication constraint  $R(0) < H(C)$  from the chemotherapy setting. Here we are interested in results that genuinely relate to the tumor-vessel interaction, and we also would like to show possible synergies between chemotherapy and the anti-angiogenic therapies. This leads to the following proposition:

**Proposition 2.** *Under continuous infusion therapy, if*

$$\theta(W, V)\beta(A(V)) \leq \mu + \gamma U + \eta V \quad (24)$$

*then, independently from the initial burden of the tumor and of the vessels (i.e., for all initial conditions  $(p(0), q(0)) \in \mathbb{R}_+^2$ ), the tumor is eradicated,*

$\lim_{t \rightarrow +\infty} (p(t), q(t)) = (0^+, 0^+)$ . Moreover, under generic time varying therapies, a sufficient condition for eradication is that

$$\theta(w_{\min}, v_{\min})\beta(A(v_{\min})) - (\mu + \gamma u_{\min} + \eta v_{\min}) \leq 0 \quad (25)$$

where  $u_{\min}$ ,  $v_{\min}$  and  $w_{\min}$  denote the minimal values during therapy.

It is interesting to notice the various implications of condition (24) in case of combinations of a non-null chemotherapy ( $V > 0$ ) with anti-angiogenic therapies. We start with the biologically interesting case when no anti-angiogenic agents are present [65], i.e.,  $U = W = 0$ . In this case, the model studies the effects of the inclusion of a varying carrying capacity to a continuous infusion chemotherapy. In the classical setting, with constant carrying capacity  $K > 0$ ,

$$\dot{p} = pF\left(\frac{K}{p}\right) - \varphi V p, \quad (26)$$

it follows that chemotherapy can never eradicate (at least, in theory) the tumor in case of an unbounded value  $F(0)$ . However, with the inclusion of the dynamics of the vessels, there exists a threshold  $V^*$  such that the tumor can be eradicated if  $V \geq V^*$ . It is easily determined from (24) with  $W = U = 0$ :

$$\theta(W, V^*)\beta(A(V^*)) - \mu - \eta V^* = 0 \quad (27)$$

Note that, provided that  $\mu > 0$ , the threshold also exists in case  $\eta = 0$ . Of course, since  $\mu$  usually is small and satisfies  $\mu \ll b$ , such a threshold is very large. On the other hand, if  $\mu = \eta = 0$ , then there cannot be eradication, even if we add a proliferation inhibiting effects, since  $\theta(W, V)\beta(A(V)) > 0$ .

## 7 Beyond Linear Models of Chemotherapy in Vascularized Tumors

For many solid tumors, a log-kill law to model the effects of cytotoxic drugs might be oversimplified. Indeed, the efficacy of a blood-born agent on the tumor cells will depend on its actual concentration at the cell site, and thus it will be influenced by the geometry of the vascular network and by the extent of blood flow. The efficacy of a drug will be higher if vessels are close to each other and sufficiently regular to permit a fast blood flow; it will be lower if vessels are distanced, or irregular and tortuous so to hamper the flow. To represent these phenomena in a simple form, in [16, 17] it has been assumed that the drug action to be included in the equation for  $\dot{p}$  is dependent on the vessel density, i.e., in our model on the ratio  $\rho = q/p$ . If  $v(t)$  is the concentration of the agent in blood, we assume that its effectiveness is modulated by an unimodal non-negative function  $\gamma(\rho)$  with  $\gamma(0) = 0$ . This leads to the new equation

$$\dot{p} = pF\left(\frac{q}{p}\right) - \gamma\left(\frac{q}{p}\right)v(t)p, \quad (28)$$

while the equation for  $q$  is unchanged. The above change deeply impacts the behavior of the dynamical system. It is not difficult to show that, under constant continuous infusion therapy, the model allows that the tumor-vessels system is multi-stable. This multi-stability may have both beneficial and detrimental “side effects” [16, 17]. On one hand, multi-stability allowed [16] to explain the pruning effect as a change of attractor of a tumor under chemotherapy. For example, the temporary delivery of anti-angiogenic therapy before an uninterrupted chemotherapy may move an orbit in the  $(p, q)$  space from the basin of attraction of a locally stable equilibrium with a large tumor size to the basin of attraction of another equilibrium with a small tumor size. On the other hand, the actual drug concentration profiles are affected by large bounded stochastic fluctuations, so that - as shown in [17] - the tumor volume may undergo detrimental noise-induced transitions from small to large equilibrium sizes. These stochastic transition phenomena might thus explain some cases of resistance to chemotherapy as due to non-genetic mechanisms.

## 8 Optimal Protocols for Combined Anti-Angiogenic and Chemotherapies

In view of the high cost of anti-angiogenic agents, and because of harmful side effects, it is not feasible to give indefinite administrations of agents. The practically relevant question is how an a priori given, limited amount of anti-angiogenic and chemotherapeutic agents is best administered. Clearly, while anti-angiogenic agents are mostly limited because of their cost, chemotherapeutic agents must be limited because of their toxic side effects. For optimization problems, it is no longer possible to keep the model general, but a specific choice needs to be made for the growth function  $F$  and all the other functional terms that define the model. Here, for sake of definiteness, we consider the following model that is based on the model for tumor anti-angiogenesis from [27]:

[AC] for a free terminal time  $T$ , minimize the objective  $J(u) = p(T)$  subject to the dynamics

$$\dot{p} = \xi p \ln\left(\frac{q}{p}\right) - \varphi p v, \quad p(0) = p_0, \quad (29)$$

$$\dot{q} = bp - dp^{\frac{2}{3}}q - \mu q - \gamma q u - \eta q v, \quad q(0) = q_0, \quad (30)$$

$$\dot{y} = u, \quad y(0) = 0, \quad (31)$$

$$\dot{z} = v, \quad z(0) = 0, \quad (32)$$

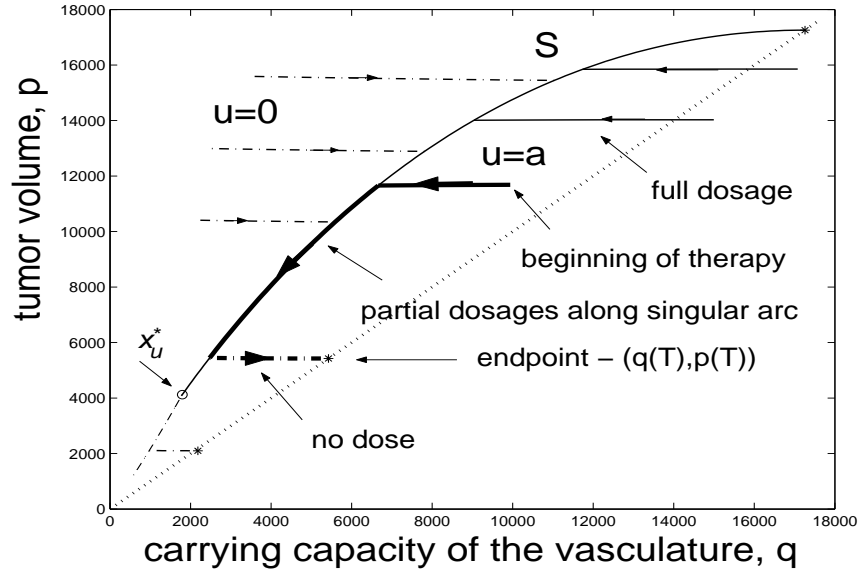
over all piecewise continuous (respectively, Lebesgue measurable) functions  $u : [0, T] \rightarrow [0, u_{\max}]$  and  $v : [0, T] \rightarrow [0, v_{\max}]$  for which the cor-

responding trajectory satisfies the endpoint constraints  $y(T) \leq y_{\max}$  and  $z(T) \leq z_{\max}$ .

The constants  $u_{\max}$  and  $v_{\max}$  denote the maximum dose rates of the anti-angiogenic and cytotoxic agents, respectively, and equations (31) and (32) limit the overall amounts of each drug given to  $y_{\max}$  and  $z_{\max}$ . In this formulation, for the moment, the dosages  $u$  and  $v$  are identified with their concentrations. We comment on the changes that occur to the optimal solutions if a standard linear model for the pharmacokinetics of the drugs is included in Sect. 10.

It follows from the dynamics (in fact, in great generality) that for any admissible control pair  $(u, v)$  defined on  $[0, \infty)$ , solutions to this dynamical system exist for all times and remain positive. Some properties of optimal controls have been established for a more general formulation in [18], but complete solutions require a specification of the dynamics. We also denote by **[A]** the special case of problem **[AC]** that corresponds to a anti-angiogenic monotherapy. This problem is obtained from the formulation above by simply setting  $z_{\max} = 0$  which eliminates the chemotherapeutic agent. For the monotherapy problem **[A]**, a complete solution in form of a regular synthesis of optimal controlled trajectories has been given in [40] and the significance of this solution lies in the fact that the optimal solution for the combination therapy problem indeed does build upon this synthesis. This is a non-trivial feature which does not hold for solutions to optimal control problems for nonlinear systems in general, but seems to be prevalent for the models combining anti-angiogenic treatments with chemotherapy and also radiotherapy. We therefore give with a brief review of the optimal synthesis for the monotherapy problem.

An optimal *synthesis* of controlled trajectories acts like a GPS system. It provides a full “road map” of how optimal protocols look like depending on the current conditions of the state variables in the problem, both qualitatively and quantitatively. Given any particular point  $(p, q)$  that represents the tumor volume and the current value of the carrying capacity, and any value  $y$  that represents the amount of inhibitors that have already been used up, equivalently, the amount remaining to be used, it tells us how to choose the control  $u$ . Fig. 1, for specific parameter values that have been taken from [27], gives a two-dimensional rendering of such a synthesis for the monotherapy problem when the variable  $y$  has been omitted. The actual numerical values of the parameters are not important for our presentation here since, indeed, the optimal synthesis looks qualitatively identical regardless of these numerical values [40]. We are not pursuing quantitative results here, but our aim is to develop *robust qualitative results* about optimal controls that are transferable to other models and give insights about the structure of optimal solutions that can be useful in more general situations as well. In fact, given our theoretically optimal analytical solution, for a typical initial condition, a straightforward Matlab code just takes seconds to compute the optimal control and corresponding trajectory. Since we have a full understanding of the



**Fig. 1.** A 2-dimensional projection of the optimal synthesis for the monotherapy model [A] into  $(p, q)$ -space

theoretically optimal solution, no minimization algorithm needs to be invoked, but the procedure consists in evaluating some, albeit somewhat complicated, function.

We briefly describe the structure of optimal controlled trajectories. First of all, note that we plot the tumor-volume  $p$  vertically and the carrying capacity  $q$  horizontally in Fig. 1. This simply better visualizes a decrease or increase in the primary cancer volume. The anchor piece of the synthesis is an optimal singular arc  $\mathcal{S}$  shown in blue. This is a unique curve defined in  $(p, q)$ -space along which the *optimal tumor reductions* occur and optimal controls follow this curve whenever the data allow. That is, if  $(p, q)$  happens to lie on  $\mathcal{S}$ , and if angiogenic inhibitors  $y$  are still available, then the optimal control consists in giving a specific time-varying dosage that makes the system stay on this curve, i.e., makes the singular arc invariant. There is a unique control that has this property, the corresponding singular control, and as long as its values lie in the admissible range  $[0, u_{\max}]$ , this is the optimal control. For the model by Hahnfeldt et al., there is a unique point on the singular arc when the control reaches its saturation limit  $u_{\max}$  which is denoted by  $x_u^*$  in Fig. 1. Mathematically, the structure of the optimal synthesis near a saturating singular arc is well understood [40, 55], but for simplicity of presentation we limit our discussions here to cases when saturation does not occur. In this case, once  $(p, q)$  lies on  $\mathcal{S}$ , the optimal protocol then simply consists in giving these singular dosages until all inhibitors are exhausted. At that time, the

state of the system lies in the region  $\mathcal{D}_+ = \{(p, q) : p > q\}$  and, because of after effects, the tumor volume will still be decreasing until it reaches the diagonal  $\mathcal{D}_0 = \{(p, q) : p = q\}$  of the system. This behavior is preprogrammed in the properties of the Gompertz growth law which makes the tumor volume decrease in  $\mathcal{D}_+$  regardless of the actual control being used and is true for all growth models  $F$  that are strictly decreasing and satisfy  $F(1) = 0$ .

If the state  $(p, q)$  does not lie on the singular arc and inhibitors are still available, then the optimal policy simply consists in getting to this singular arc in the “best” possible way as measured by the objective. If  $p < q$ , and initially this clearly is the medically relevant case, then this is done by simply giving a full dose treatment until the singular arc is reached and then the control switches to the singular regime. In such a case, since the carrying capacity is high, immediate action needs to be taken and it would not be optimal to let the tumor grow further. These are the trajectories in Fig. 1 that are shown by solid green curves. Note that these curves are almost horizontal and thus show little tumor reduction. Of course, the beneficial effect of this full dose segment is that it prevents the tumor increase that otherwise would have occurred. Significant reductions in tumor volume only arise as the singular arc is reached. Mathematically, it is no problem to include in the solution initial conditions when  $p > q$ , but, from the medical side, this case is less interesting. Here the optimal solution consists of giving no anti-angiogenic agents, but to wait until the system reaches the singular arc as the carrying capacity increases and then to start treatment when the singular arc is reached by once more following the singular regime. Intuitively, inhibitors are put to better use along this curve than if they would have been applied directly. For small tumor volumes (e.g., those that lie below the saturation level  $x_u^*$  for the singular control,) anti-angiogenic agents are always given at maximum dose. The minimum tumor volumes are realized when, after all inhibitors have been exhausted, the trajectory corresponding to  $u = 0$  crosses the diagonal after termination of treatment.

The interesting feature of this synthesis is the relative simplicity and full robustness of the resulting optimal controls once the singular curve  $\mathcal{S}$  is known. Furthermore, for the model considered here, but also for various of its modifications [19, 56], it is possible to determine this singular arc and its corresponding control analytically by means of well-known procedures in geometric optimal control theory which makes the construction of this synthesis and the resulting computations of optimal protocols a worthwhile endeavor [40, 37].

Below, we give the explicit formulas for the singular arc and control. They equally apply to the monotherapy problem [A] and to the combination therapy problem [AC] when no chemotherapeutic drugs are administered.

**Proposition 3.** [40] *If an optimal control  $u_*$  is singular on an interval  $(\alpha, \beta)$  and  $v \equiv 0$  on  $(\alpha, \beta)$ , then the corresponding trajectory  $(p_*, q_*)$  follows a uniquely defined singular curve  $\mathcal{S}$  which, defining  $x = \frac{p}{q}$ , can be parameterized*



in the variables  $(p, x)$  in the form

$$dp^{\frac{2}{3}} + bx(\ln x - 1) + \mu = 0 \quad (33)$$

with  $x$  in some interval  $[x_1, x_2] \subset (0, \infty)$ . The singular control  $u_{\text{sin}}$  that keeps this curve  $\mathcal{S}$  invariant is given as a feedback function of  $p$  and  $q$  in the form

$$\gamma u_{\text{sin}}(p, q) = \Psi(p, q) = \left( \xi \ln \left( \frac{p}{q} \right) + b \frac{p}{q} + \frac{2}{3} \xi \frac{d}{b} \frac{q}{p^{1/3}} - (\mu + p^{2/3}) \right) \quad (34)$$

or, equivalently, using (33), in terms of  $x$  by

$$\gamma u_{\text{sin}}(x) = \left( \frac{1}{3} \xi + bx \right) \ln x + \frac{2}{3} \xi \left( 1 - \frac{\mu}{bx} \right). \quad (35)$$

There exists exactly one connected arc on the singular curve  $\mathcal{S}$  along which the singular control is admissible, i.e., satisfies the bounds  $0 \leq u_{\text{sin}}(x) \leq u_{\text{max}}$ . This arc is defined over an interval  $[x_\ell^*, x_u^*]$  where  $x_\ell^*$  and  $x_u^*$  are the unique solutions to the equations  $u_{\text{sin}}(x_\ell^*) = 0$  and  $u_{\text{sin}}(x_u^*) = u_{\text{max}}$ . At these points the singular control saturates at the control limits  $u = 0$  and  $u = u_{\text{max}}$ .  $\square$

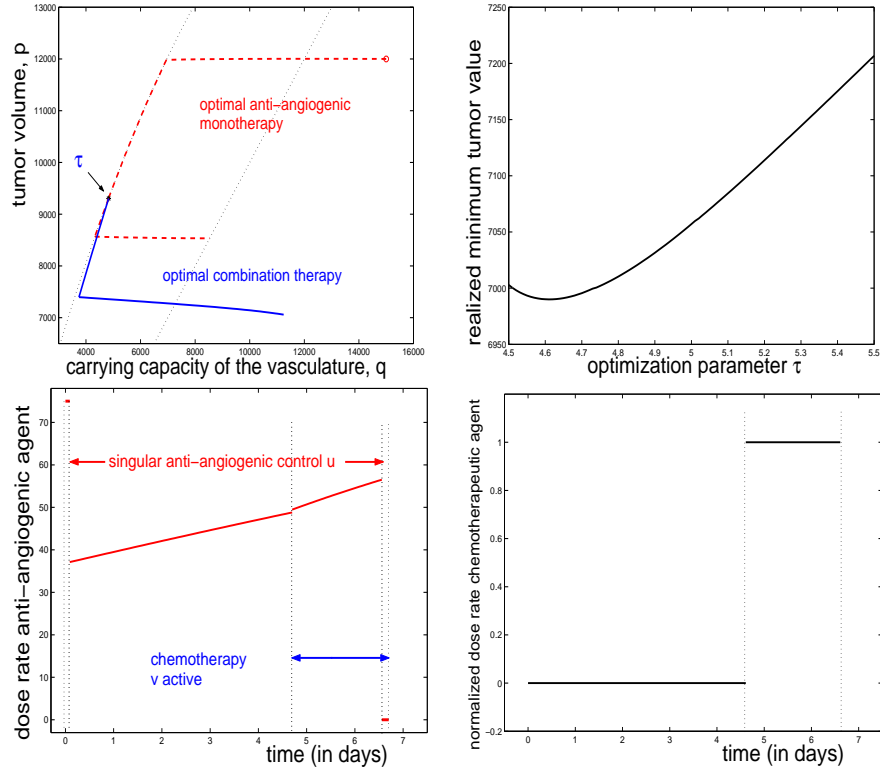
An important feature of this solution is that it becomes the basis for the optimal solution of the combination therapy problem [AC]. Indeed, for a typical initial condition with  $p < q$ , optimal controls for the combination therapy problem have the following structure: *optimal controls for the anti-angiogenic agent follow the optimal angio-monotherapy and then, at a specific time, chemotherapy becomes active and is given in one full dose session.* The formulas for the singular control and singular arc need to be adjusted to the presence of chemotherapy, but in this case it is not possible that both controls are singular simultaneously. More specifically, we have the following result:

**Proposition 4.** *If the optimal anti-angiogenic dose rate  $u$  follows a singular control on an open interval  $I$ , then the chemotherapeutic agent  $v$  is bang-bang on  $I$  with at most one switching on  $I$  from  $v = 0$  to  $v = v_{\text{max}}$  and we have the following relation between the controls  $u$  and  $v$ :*

$$\gamma u_{\text{sin}}(t) + (\eta - \varphi) v(t) = \Psi(p(t), q(t)) \quad (36)$$

with  $\Psi$  defined by equation (34). Given  $v$ , this determines the anti-angiogenic dose rate with a jump-discontinuity where chemotherapy becomes active.  $\square$

This structure allows to set up a minimization problem over a 1-dimensional parameter  $\tau$  that denotes the time when chemotherapy becomes active. We illustrate this for an initial condition  $(p_0, q_0)$  with  $p_0 < q_0$  where the anti-angiogenic inhibitor will immediately be applied at full dose. In principle, the time  $\tau$  when chemotherapy is activated can lie anywhere in the interval of definition. For example, if the amount  $z_{\text{max}}$  of chemotherapeutic agents is high, then it is possible that chemotherapy already becomes active along the



**Fig. 2.** Optimal combination therapy: (a, top left) structure of controlled trajectory depending on  $\tau$ , (b, top right) value of the objective as a function of  $\tau$ , (c, bottom left) optimal anti-angiogenic agent  $u$  and (d, bottom right) optimal chemotherapeutic agent  $v$

interval when the anti-angiogenic dose is at maximum. Analogously, if this amount is very low, it is possible that this activation will only occur after all anti-angiogenic inhibitors have been used up. Typically, however, this time  $\tau$  will lie somewhere in the interval where the anti-angiogenic dosage follows the singular monotherapy structure and this is illustrated in Fig. 2(a). It is not difficult to compute the value of the objective as the parameter  $\tau$  in this family of trajectories is varied and Fig. 2(b) gives a representative graph of this value as a function of  $\tau$ . Figs. 2(c) and (d) show the corresponding optimal controls  $u$  and  $v$ .

It is interesting to note that this optimization leads to the conclusion that the anti-angiogenic agent is applied first with the chemotherapeutic agent to follow in one full dose session later on. In a clear sense, the optimal control solution points out a specific “path” that should be followed in order to obtain the best possible tumor reductions. Even in the combination therapy model,

this path is closely linked with the optimal singular arc from the monotherapy problem as shown by equation (34). It lies in the region where the tumor volume  $p$  is higher than its carrying capacity  $q$ , but there exists a specific relation between these variables and clearly  $q$  is not pushed to zero too fast, but a definite balance between these two variables is maintained along the optimal solution. Since the vascular network of the tumor is needed to deliver the chemotherapeutic agents, this perfectly makes sense. Although no “pruning” aspects have been taken into account in the model, it appears that the optimal solutions precisely suggest such a behavior: *give anti-angiogenic agents until an optimal relation between tumor volume and carrying capacity has been established and then apply full dose chemotherapy while still maintaining the optimal relation between  $p$  and  $q$  through the administration of anti-angiogenic agents.* This is in agreement with R. K. Jain’s already mentioned hypothesis that *the preliminary delivery of anti-angiogenic agents may regularize a tumor’s vascular network with beneficial consequences for the successive delivery of cytotoxic chemotherapeutic agents* [29, 30]. Even for combinations of anti-angiogenic therapy with radiotherapy, a similar feature seems to exist.

## 9 Combination of Anti-Angiogenic Treatment with Radiotherapy

Model [AC] has to be modified in order to include effects of radiotherapy on a vascularized tumor. Indeed, as seen in Sect. 4, one has to deal with non-linear delayed cytotoxic effects on tumor cells, to which one has also to add the radiation damage to the carrying capacity  $q$ . Of course, the effects of radiation on tumor cells, endothelial cells and on healthy cells are not necessarily equal and thus may need to be modelled by separate linear-quadratic equations with different sets of parameters. This leads to similar formulations, but in spaces of varying dimension. Mathematically, this generates different behaviors since the structure of singular controls very much depends on the existing degrees of freedom [43]. In the literature, often the effects of radiation therapy on the tumor cells and its vasculature are modelled by one equation (for example, see [19], which also gives numerical values that are based on [5]) and here, for sake of definiteness and simplicity we take this approach as well. As before, we then include separate states  $y$  and  $z$  that keep track of the total amounts of anti-angiogenic agents given, respectively, the total damage done by radiotherapy. This damage is measured in terms of its biologically equivalent dose (BED). We then arrive at the following 6-dimensional optimal control formulation:

[AR] for a free terminal time  $T$ , minimize the objective  $J(u, v) = p(T)$  subject to the dynamics

$$\dot{p} = \xi p \ln \left( \frac{q}{p} \right) - (\varphi + \beta r) p w, \quad p(0) = p_0, \quad (37)$$

$$\dot{q} = bp - dp^{\frac{2}{3}}q - \gamma qu - (\eta + \delta r) qw, \quad q(0) = q_0, \quad (38)$$

$$\dot{r} = -\rho r + w, \quad r(0) = 0, \quad (39)$$

$$\dot{y} = u, \quad y(0) = 0, \quad (40)$$

$$\dot{z} = (1 + \alpha s)w, \quad z(0) = 0, \quad (41)$$

$$\dot{s} = -\sigma s + w, \quad s(0) = 0, \quad (42)$$

over all Lebesgue measurable functions  $u : [0, T] \rightarrow [0, u_{\max}]$  and  $w : [0, T] \rightarrow [0, w_{\max}]$  for which the corresponding trajectory satisfies the endpoint constraints  $y(T) \leq y_{\max}$  and  $z(T) \leq z_{\max}$ .

The coefficients are assumed constant and generally are positive;  $u_{\max}$ ,  $w_{\max}$  represent maximum doses at which the agents can be administered and  $y_{\max}$  and  $z_{\max}$  limit the total amounts administered for the respective agents. A medically reasonable selection for all parameter values is given in Table 1 in [19]. The main difference between model [AR] and the model in [19] is that we dropped the so-called early-tissue constraint which prevents an overestimation of the damage done to the early tissue. Also, rather than distinguishing between variables  $r_p$  and  $r_q$  which model the damage done to  $p$  and  $q$ , here, for simplicity, we only use one variable  $r$  as the numerical values for these coefficients given in [19] agree. Also, we consider a continuous time version of radiotherapy that is not necessarily given in fractionated doses. We shall comment below on how such a treatment protocol can be derived from our version.

The addition of the radio-therapy terms has no structural effects on the anti-angiogenic treatment and if the control  $u$  is singular, then regardless of the form of the radio-therapy schedule, we have the following direct extension of Proposition 4 for model [AR]:

**Proposition 5.** *If the optimal anti-angiogenic dose rate  $u$  follows a singular control on an open interval  $I$  and if the radiotherapy dose rate is given by  $w$ , then we have the following relation between the controls  $u$  and  $w$ :*

$$\gamma u_{\sin}(t) + [(\eta + \delta r) - (\varphi + \beta r)] w(t) = \Psi(p(t), q(t)) \quad (43)$$

with  $\Psi$  the function defined in (34) for the optimal anti-angiogenic monotherapy. Given  $w$ , this determines the anti-angiogenic dose rate.  $\square$

Like for combinations with chemotherapy, also in this case there is an immediate and mathematically simple extension of the formula that determines the optimal singular anti-angiogenic dose rate to the more structured and more complicated mathematical model that describes the combination treatment with radiotherapy. However, now the structure of the second control is very different. In fact, it typically (if the bounds on the dose rates permit) is

singular as well. The controls  $u$  and  $w$  are said to be *totally singular* on an open interval  $I$  if they are singular simultaneously. This is not optimal for the combination therapy model [AC] with chemotherapy, but it is the defining structure for the combination of anti-angiogenic therapy with radiotherapy. For this we need a second equation that links  $u_{\text{sin}}$  with  $w_{\text{sin}}$ .

**Proposition 6.** *If the optimal anti-angiogenic dose rate  $u$  and the radiotherapy dose rate  $w$  both follow singular regimens  $u_{\text{sin}}$  and  $w_{\text{sin}}$  on an open interval  $I$ , then, in addition to equation (43), a second relation of the form*

$$B(x(t))u_{\text{sin}}(t) + w_{\text{sin}}(t) = A(x(t)). \quad (44)$$

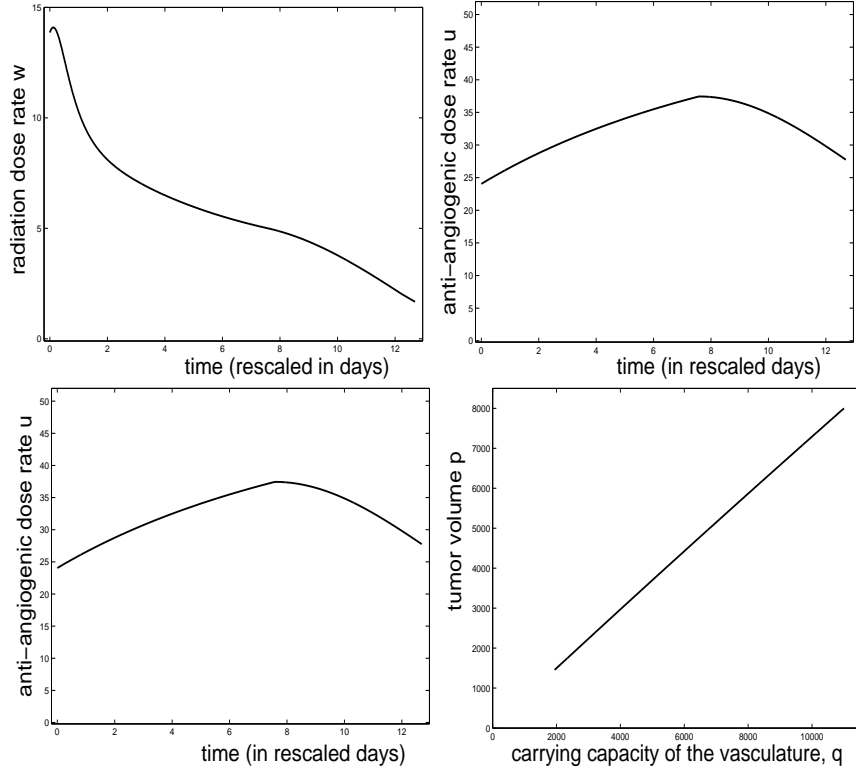
*holds on  $I$  where  $A$  and  $B$  are smooth functions that only depend on the dynamics of the system and can be determined analytically.  $\square$*

Overall,  $(u_{\text{sin}}, w_{\text{sin}})$  thus are the solutions of a  $2 \times 2$  system of linear equations whose coefficients are determined solely by the equations defining the dynamics of the system. It is possible to give explicit expressions for the functions  $A$  and  $B$  and thus also for the controls. However, these formulas depend on the second derivatives of the terms in the dynamics and they are long and unwieldy. On the other hand, given any particular value  $(p, q)$  of the state and specified values of the parameters, it is not difficult to compute these coefficients  $A$  and  $B$  numerically and solve for the controls. Fig. 3 gives an example of a totally singular anti-angiogenic dose rate  $u$  and a radiotherapy dose rate  $w$  that have been computed in this way for parameter values taken from [19]. Part (a) shows the graph of the radiation schedule if no upper limit on the dose rate is imposed. If we set the radiation limit to  $w_{\text{max}} = 5$ , then this upper bound is initially exceeded and part (b) shows the control that has been computed by saturating this schedule at  $w_{\text{max}}$ . Since equation (43) is valid regardless of the structure of  $w$ , the calculations easily adjust. The corresponding graph of the singular control  $u$  is given in part (c). Part (d) shows the corresponding trajectory. Note that this trajectory is almost linear. In fact, whenever the anti-angiogenic control  $u$  follows a singular regimen, then the quotient  $\frac{p}{q}$  follows the simple dynamics

$$\frac{d}{dt} \left( \frac{p}{q} \right) = \frac{2}{3} \xi \frac{d}{b} p^{\frac{2}{3}} \quad (45)$$

and, along this simulation, the right-hand side only varies between 0.03 and 0.09, i.e., is almost constant.

The controls given in this figure were not computed to be optimal, but they only illustrate totally singular controls for a combination of anti-angiogenic and radiotherapy. Based on our theoretical analysis, it is clear that these controls will play an essential part in the structure of optimal protocols. This is seconded by the structure of optimal protocols computed in [19] where all the solutions given have exactly this structure, but no hard limits on the



**Fig. 3.** Combination with radiotherapy: (a, top left) the unsaturated singular radiation dose rate  $w$ , (b, top right) the radiation dose rate  $w$  with upper limit  $w_{max}$  enforced, (c, bottom left) corresponding singular anti-angiogenic agent  $u$  and (d, bottom right) corresponding trajectory  $(p, q)$ .

dosage rates were imposed. In order to solve the overall optimal control problem, however, it is necessary to take these constraints into account and then to establish the structure of optimal controls before and after the singular segments. Different from the monotherapy problem described earlier, in this case there exists a vector field whose integral curves are the trajectories for totally singular controls everywhere, not just on some lower-dimensional surface. However, it matters which of these trajectories is taken. Research on determining an optimal synthesis is ongoing.

## 10 Suboptimal Protocols and Pharmacokinetic Equations

In all these optimal control problems, singular controls and their corresponding trajectories are the most important feature that determine the structure of optimal protocols. This is true both for the monotherapy case where a complete theoretical solution for the optimal control problem has been given [40] and for combination therapies where similar complete solutions are currently still elusive. But in these cases, explicit formulas for the singular controls allow to utilize numerical procedures to determine optimal solutions for given initial conditions and parameters. However, singular controls are defined in terms of the variables  $p$  and  $q$  (and also  $r$  and  $s$  in the case of the radiation dose) and thus are not practically realizable. Yet, these optimal solutions have bi-fold relevance for designing practical protocols for these therapies: (1) Clearly, the optimal solutions define benchmark values to which other protocols – simple, heuristically chosen and implementable – can be compared and thus they determine a measure for how close to optimal a given general protocol is. (2) Equally important, the structure of optimal controls directly indicates simple, piecewise constant, and thus easily realizable protocols that approximate the optimal solutions well, so-called *suboptimal* protocols. In the papers [35, 41], an extensive analysis of suboptimal protocols for the anti-angiogenic monotherapy problem was undertaken and it was shown that piecewise constant suboptimal protocols with a very small number of switchings exist that are able to replicate the optimal values within 1%. Similar results are valid for the modification of the underlying model by Ergun et al. given in [19]. Since optimal controls for the chemotherapeutic agent in combinations with anti-angiogenic treatments are bang-bang, there is no need to approximate these and thus these results directly carry over to these problems.

These excellent approximation properties remain valid if the model is made more realistic by including pharmacokinetic equations for the anti-angiogenic and chemotherapeutic agents [36]. The models considered so far identify their dosages with their concentrations in the plasma. The controls  $u$  and  $v$ , as they were used, actually represent the concentrations of these agents and linear terms of the type  $-\gamma qu$  model the pharmacodynamics of the drugs. If a standard linear exponential growth/decay model is added for the concentrations of the agents, e.g.,  $\dot{c} = -ac + u$ , then indeed there exist qualitative changes in the optimal solutions that are due to the fact that the so-called intrinsic order of the singular controls changes from 1 to 2 [42]. These make the solutions even more complicated from a mathematical point of view. However, the added complexity disappears if only suboptimal protocols are considered. Then, as in the simplified models, the structure of the theoretically optimal controls immediately suggests how to choose excellent simple approximating protocols [36]. On the level of suboptimal realizable protocols, the simplified modeling that ignores a linear pharmacokinetic model for the therapeutic agents is fully justified.

Similar investigations are ongoing for the model including radiotherapy. Radiation doses are commonly administered in daily fractionated doses (of short durations) and this does not agree with the model considered above. Mathematically, this leads to a more complex, hybrid optimization problem that generally is solved with numerical methods. These methods and solutions, however, do not provide much insight into the underlying principles. A continuous-time formulation, as it was presented here, gives this information about the structure of optimal controls (and why they look the way they do) and this is what makes it rather straightforward (e.g., by averaging) to compute approximating fractionated doses. But our investigations are still preliminary on this topic.

## 11 Conclusion

For various treatment strategies, we have considered optimal control problems to minimize the tumor volume when the overall amounts of agents are limited a priori. This may be simply because only a limited amount of the agents is available, like in the case of anti-angiogenic inhibitors which still are very expensive and thus are only used in limited quantities, or it may be because these treatments have severe side effects that need to be limited and thus a priori decisions are made to limit the total amount of drugs or radiation to be given, a standard medical approach. Then the question how to schedule this agents in time arises naturally. Here we have considered treatment strategies that combine anti-angiogenic therapies with the classical approaches of chemo- and radiotherapy. Our main conclusions are that singular controls (which can be computed analytically using Lie-derivative based calculations) are at the center of optimal solutions for both the mono- and combination therapy treatments. Although these controls are feedback functions, and thus cannot be directly applied, they point the way to simple realizable approximations that generally are excellent.

**Acknowledgements.** We would like to thank an anonymous referee for his careful reading of our paper and several suggestions that we incorporated into the final version. The research of A. d’Onofrio has been done in the framework of the Integrated Project “p-medicine - from data sharing and integration via VPH models to personalized medicine,” project identifier: 270089, which is partially funded by the European Commission under the 7<sup>th</sup> framework program. The research of U. Ledzewicz and H. Schättler has been partially supported by the National Science Foundation under collaborative research grant DMS 1008209/1008221.



## References

1. Agur, Z., Arakelyan, L., Daugulis, P., Ginosar, Y., Hopf point analysis for angiogenesis models. *Discrete and Continuous Dynamical Systems B*, **4**, (2004), pp. 29-38
2. Anderson, A.R.A., Chaplain, M.A., Continuous and discrete mathematical models of tumor-induced angiogenesis. *Bull. Math. Biol.*, **60**, (1998), pp. 857-899
3. Bellomo, N., and Maini, P.K., Introduction to "Special Issue on Cancer Modelling," *Mathematical Models and Methods in Applied Science*, **15**, (2005), pg. iii
4. Boyle, P., d'Onofrio, A., Maisonneuve, P., Severi, G., Robertson, C., Tubiana, M., and Veronesi, U., Measuring progress against cancer in Europe: has the 15% decline targeted for 2000 come about?, *Annals of Oncology*, **14**, (2003), pp. 1312-1325
5. Brenner, D.J., Hall, E.J., Huang, Y., and Sachs, R.K., Optimizing the time course of brachytherapy and other accelerated radiotherapeutic protocols, *Int. J. Radiat. Oncol. Biol. Phys.*, **29**, (1994), pp. 893-901
6. Browder, T., Butterfield, C.E., Kraling, B.M., Shi, B., Marshall, B., O'Reilly, M.S., and Folkman, J., Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer, *Cancer Research*, **60**, (2000), pp. 1878-86
7. Colleoni, M., Rocca, A., Sandri, M.T., Zorzino, L., Masci, G., Nole, F., Peruzzotti, G., Robertson, C., Orlando, L., Cinieri, S., de Braud, F., Viale, G. and Goldhirsch, A., Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: antitumour activity and correlation with vascular endothelial growth factor levels, *Annals of Oncology*, **13**, (2002), pp. 73-80
8. d'Onofrio, A., A general framework for modelling tumor-immune system competition and immunotherapy: Mathematical analysis and biomedical inferences, *Physica D*, **208**, (2005), pp. 202-235
9. d'Onofrio, A., Rapidly acting antitumoral antiangiogenic therapies. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* **76**, (2007), 031920.
10. d'Onofrio, A., Fractal growth of tumors and other cellular populations: Linking the mechanistic to the phenomenological modeling and vice versa, *Chaos, Solitons and Fractals*, **41**, (2009), pp. 875-880
11. d'Onofrio, A., Fasano, A., and Monechi, B., A generalization of Gompertz law compatible with the Gyllenberg-Webb theory for tumour growth *Mathematical Biosciences*, **230** (1), (2011), pg. 45-54
12. d'Onofrio, A., and Gandolfi, A., Tumour eradication by antiangiogenic therapy: analysis and extensions of the model by Hahnfeldt et al., *Mathematical Biosciences*, **191**, (2004), pp. 159-184
13. d'Onofrio, A., and Gandolfi, A., The response to antiangiogenic anticancer drugs that inhibit endothelial cell proliferation, *Appl. Math. and Comp.*, **181**, (2006), pp. 1155-1162
14. d'Onofrio, A., and Gandolfi, A., A family of models of angiogenesis and anti-angiogenesis anti-cancer therapy, *Math. Med. and Biol.*, **26**, (2009), pp. 63-95
15. d'Onofrio, A., Gandolfi, A., and Rocca, A., The dynamics of tumour-vasculature interaction suggests low-dose, time-dense antiangiogenic schedulings, *Cell Prolif.*, **42**, (2009), pp. 317-329

16. d’Onofrio, A., and Gandolfi, A., Chemotherapy of vascularised tumours: role of vessel density and the effect of vascular "pruning", *J. of Theoretical Biology*, **264**, (2010), pp. 253-265
17. d’Onofrio, A., and Gandolfi, A., Resistance to anti-tumor chemotherapy due to bounded-noise transitions, *Phys. Rev. E.*, **82**, (2010) Art.n. 061901
18. d’Onofrio, A., Ledzewicz, U., Maurer, H., and Schättler, H., On optimal delivery of combination therapy for tumors, *Math. Biosci.*, **222**, (2009), pp. 13-26, doi:10.1016/j.mbs.2009.08.004
19. Ergun, A., Camphausen, K., and Wein, L.M., Optimal scheduling of radiotherapy and angiogenic inhibitors, *Bull. of Math. Biology*, **65**, (2003), pp. 407-424
20. Folkman, J., Tumor angiogenesis: therapeutic implications, *New England J. of Medicine*, **295**, (1971), pp. 1182-1196
21. Folkman, J., Antiangiogenesis: new concept for therapy of solid tumors, *Ann. Surg.*, **175**, (1972), pp. 409-416
22. Folkman, J., Opinion - Angiogenesis: an organizing principle for drug discovery? *Nature Rev. Drug. Disc.*, (2007), **6**, pp. 273-286
23. Fowler, J.F., The linear-quadratic formula and progress in fractionated radiotherapy, *British J. of Radiology*, **62**, (1989), pp. 679-694
24. Frame, D., New strategies in controlling drug resistance. *J. Manag. Care Pharm.* **13**, (2007), pp. 13-17
25. Goldie, J.H., Coldman, A.J., A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat. Rep.* **63**, (1979), pp. 1727-1733
26. Guiot, C., Degiorgis, P.G., Delsanto, P.P., Gabriele, P., and Deisboecke, T.S., Does tumor growth follow a 'universal law'?, *J. of Theoretical Biology*, **225**, (2003), pp. 147-151
27. Hahnfeldt, P., Panigrahy, D., Folkman, J., and Hlatky, L., Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy, *Cancer Research*, **59**, (1999), pp. 4770-4775
28. Hart, D., Shochat, E. and Agur, Z., The growth law of primary breast cancer as inferred from mammography screening trials data, *British J. of Cancer*, **78**, (1999), pp. 382-387
29. Jain, R.K., Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy, *Nature Medicine*, **7**, (2001), pp. 987-989.
30. Jain, R.K., and Munn, L.L., Vascular normalization as a rationale for combining chemotherapy with antiangiogenic agents, *Principles of Practical Oncology*, **21**, (2007), pp. 1-7
31. Kerbel, R.S., A cancer therapy resistant to resistance, *Nature*, **390**, (1997), pp. 335-336
32. Kerbel, R.S., Tumor angiogenesis: past, present and near future, *Carcinogenesis*, **21**, (2000), pp. 505-515
33. Kerbel, R., Folkman, J., Clinical translation of angiogenesis inhibitors. *Nature Rev. Canc.* **2**, (2002), pp. 727-739
34. Kimmel, M., and Swierniak, A., Control theory approach to cancer chemotherapy: benefiting from phase dependence and overcoming drug resistance, in: **Tutorials in Mathematical Biosciences III: Cell Cycle, Proliferation, and Cancer**, Springer Verlag, Berlin-Heidelberg-New York, Lecture Notes in Mathematics, vol. 1872, (2006), pp. 185-221

35. Ledzewicz, U., Marriott, J., Maurer, H., and Schättler, H., Realizable protocols for optimal administration of drugs in mathematical models for novel cancer treatments, *Mathematical Medicine and Biology*, **27**, (2010), pp. 157-179, doi:10.1093/imammb/dqp012
36. Ledzewicz, U., Maurer, H., and Schättler, H., Minimizing tumor volume for a mathematical model of anti-angiogenesis with linear pharmacokinetics, in: *Recent Advances in Optimization and its Applications in Engineering*, Diehl, M., Glineur, F., Jarlebring, E., and Michiels, W., Eds., Springer Verlag, (2010), pp. 267-276
37. Ledzewicz, U., Munden, J., and Schättler, H., Scheduling of anti-angiogenic inhibitors for Gompertzian and logistic tumor growth models, *Discrete and Continuous Dynamical Systems, Series B*, **12**, (2009), pp. 415-439
38. Ledzewicz, U., and Schättler, H., Optimal bang-bang controls for a 2-compartment model in cancer chemotherapy, *Journal of Optimization Theory and Applications - JOTA*, **114**, (2002), pp. 609-637
39. Ledzewicz, U., and Schättler, H., Analysis of a cell-cycle specific model for cancer chemotherapy, *J. of Biological Systems*, **10**, (2002), pp. 183-206
40. Ledzewicz, U., and Schättler, H., Anti-angiogenic therapy in cancer treatment as an optimal control problem, *SIAM J. on Control and Optimization*, **46** (3), (2007), pp. 1052-1079
41. Ledzewicz, U., and Schättler, H., Optimal and suboptimal protocols for a class of mathematical models of tumor anti-angiogenesis, *J. of Theoretical Biology*, **252**, (2008), pp. 295-312
42. Ledzewicz, U., and Schättler, H., Singular controls and chattering arcs in optimal control problems arising in biomedicine, *Control and Cybernetics*, **38**, (2009), pp. 1501-1523
43. Ledzewicz, U., and Schättler, H., Multi-input optimal control problems for combined tumor anti-angiogenic and radiotherapy treatments, *J. of Optimization Theory and Applications - JOTA*, **153**, (2012), to appear
44. Marusic, M., Bajzer, A., Freyer, J.P., and Vuk-Povlovic, S., Analysis of growth of multicellular tumor spheroids by mathematical models, *Cell Proliferation*, **27**, (1994), pp. 73ff
45. McDougall, S.R., Anderson, A.R.A., Chaplain, M.A., Mathematical modelling of dynamic adaptive tumour-induced angiogenesis: Clinical implications and therapeutic targeting strategies, *J. of Theoretical Biology*, **241**, (2006), pp. 564-589
46. Mombach, J.C.M., Lemke, N., Bodmann, B.E.J., Idiart, M.A.P., A mean-field theory of cellular growth, *Europhysics Letters*, **59**, (2002), pp. 923-928
47. Norton, L., A Gompertzian model of human breast cancer growth, *Cancer Research*, **48**, (1988), pp. 7067-7071
48. Norton L., Simon R., The Norton-Simon hypothesis revisited, *Cancer Treat. Rep.* **70**, (1986), pp. 163-169.
49. Norton, L., and Simon, R., Growth curve of an experimental solid tumor following radiotherapy, *J. of the National Cancer Institute*, **58**, (1977), pp. 1735-1741
50. O'Reilly, M.S., Boehm, T., Shing, Y., Fukai, N., Vasios, G., Lane. W.S., Flynn, E., Birkhead, J.R., Olsen, B.R., Folkman, J., Endostatin: an endogenous inhibitor of angiogenesis and tumour growth, *Cell*, **88**, (1997), pp. 277-285
51. Panetta, J.C., A mathematical model of breast and ovarian cancer treated with paclitaxel. *Math Biosci.*, **146**, (1997), pp. 89-113

52. Pekham, M., Pinedo, H.M., and Veronesi, U., Oxford Textbook of Oncology, (Oxford Medical Publications, 1995)
53. Quinn, M.J., d'Onofrio, A., Moeller, B., Black, R., Martinez-Garcia, C., Moeller, H., Rahu, M., Robertson, C., Schouten, L.J., La Vecchia, C., and Boyle, P., Cancer mortality trends in the EU and acceding countries up to 2001, *Annals of Oncology*, **14**, (2003), pp. 1148-1152
54. Ribba, B., Marron, K., Agur, Z., Alarcin, T., Maini, P.K., A mathematical model of Doxorubicin treatment efficacy for non-Hodgkin's lymphoma: investigation of the current protocol through theoretical modelling results, *Bulletin of Mathematical Biology*, **67**, (2005), pp. 79-99
55. Schättler, H., and Jankovic, M., A synthesis of time-optimal controls in the presence of saturated singular arcs, *Forum Mathematicum*, **5**, (1993), pp. 203-241
56. Schättler, H., Ledzewicz, U., and Cardwell, B., Robustness of optimal controls for a class of mathematical models for tumor anti-angiogenesis, *Mathematical Biosciences and Engineering*, **8**, (2011), pp. 355-369, doi:10.3934/mbe.2011.8.355
57. Sole, R.V., Phase transitions in unstable cancer cell populations, *European J. Physics B*, **35**, (2003), pp. 117-124.
58. Skipper, H.E., On mathematical modeling of critical variables in cancer treatment (goals: better understanding of the past and better planning in the future), *Bull. Math. Biol.*, **48**, (1986), pp. 253-278
59. Swan, G.W., Role of optimal control in cancer chemotherapy, *Math. Biosci.*, **101**, (1990), pp. 237-284
60. Swierniak, A., Optimal treatment protocols in leukemia - modelling the proliferation cycle, *Proc. 12th IMACS World Congress*, Paris, 4, (1988), pp. 170-172
61. Swierniak, A., Cell cycle as an object of control, *Journal of Biological Systems*, **3**, (1995), pp. 41-54
62. Thames, H.D., and Hendry, J.H., *Fractionation in Radiotherapy*, Taylor and Francis, London, 1987
63. Ubezio, P., Cameron, D., Cell killing and resistance in pre-operative breast cancer chemotherapy. *BMC Cancer*, **8**, (2008), pp. 201ff
64. Wheldon, T.E., *Mathematical Models in Cancer Research*, Boston-Philadelphia: Hilger Publishing, 1988
65. Wijeratne, N.S., and Hoo, K.A., Understanding the role of the tumour vasculature in the transport of drugs to solid cancer tumors, *Cell Prolif.*, **40**, (2007), pp. 283-301
66. Yu, J.L., Rak, J.W., Host microenvironment in breast cancer development: Inflammatory and immune cells in tumour angiogenesis and arteriogenesis, *Breast Canc. Res.* **5**, (2003), pp. 83-88