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Controllability of a model of combined anticancer therapy*

by

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Abstract: Controllability of combination of antiangiogenic treatment and chemotherapy is considered. A model used in the paper is a finite-dimensional dynamical control system described by second order semilinear time invariant ordinary differential state equations. Using a generalized open mapping theorem, sufficient conditions for constrained local controllability in a given time interval are formulated and proved. These conditions require verification of constrained global controllability of the associated linear second-order dynamical control system.

Keywords: controllability, semilinear systems, biomathematical modelling, cancer therapy

1. Introduction

Cancer is a disease of molecules and genes, and our increasing understanding of these genes and molecules makes possible the development of exciting new strategies for avoiding, preventing, and even correcting the changes that lead to cancer (see, e.g., Camidge and Jordell, 2005). The site of action of almost all traditional cytotoxic drugs is the cellular DNA or the processes associated with this DNA. Drugs may interact directly with the DNA, intercalating between the bases, chemically altering the structure of DNA (adduct formation) or substituting the bases with analogous structures. Some agents may deplete the pool of bases required for DNA (and RNA) synthesis. Other group of drugs may affect the microtubules that organize the chromosomes during mitosis. Drug resistance in cancer is common. Some tumours are inherently unresponsive to cytotoxic chemotherapy. Others may respond well initially but relapse rapidly with drug-resistant disease. Many factors have been implicated in cellular resistance and these mechanisms may be drug or class specific. Pharmacokinetic factors also contribute towards mechanisms of resistance. For example, it is important to realize that for many anticancer drugs the administered form of

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the drug is not necessarily the active form. Variability in, for example, levels of activating or inactivating enzymes in the host tissues and in the tumour can lead to significant additional inter- and intraindividual variation in terms of normal tissue toxicity and anti-tumour efficacy from such drugs. All of the targets for traditional cytotoxics in malignant dividing cells are also expressed within normal dividing cells. The cells in the normal human body which turnover most rapidly and therefore are the most impacted by traditional cytotoxics are those of the bone marrow, skin, hair follicle, and gastrointestinal mucosa. Different normal tissues recover from a dose of chemotherapy at different rates. Malignant cells tend to have impaired DNA damage repair machinery compared to normal cells. If treatment is given intermittently, subsequent doses can be timed to occur when the host has recovered but the tumour has not. For each dose of chemotherapy it is thought that a constant fraction rather than an absolute number of malignant cells are killed (the Skipper hypothesis). More than sixty years ago, Glenn Algire, when studying physiological responses to tumour growth in mice at the National Cancer Institute, observed that the growth of tumour is dependent on the development of vascular supply. After observing the same phenomenon, Judah Folkman (1971) suggested the substantial potential of tumour angiogenesis as a therapeutic target.

Tumours, like normal tissues, have physiological constraints, on growth, such as access to oxygen and nutrients for metabolism. The diffusion of oxygen in tissues is limited to a distance of about 150μm, thus tissue growth is restricted to a few cubic millimetres if no new vasculature is formed. For this reason, tumours remain in a dormant state restricted to a few millimetres in diameter unless they develop in a well-vascularised area or are able to recruit their own vasculature. For vascularisation to occur, the nearest vessel or capillary needs to become destabilised so that the endothelial cells lining the vessel can loosen from their neighbours, migrate through the extracellular matrix towards the tumour. Only after a tumour has recruited its own blood supply, it can expand in size. Tumours do this via the production of angiogenic factors secreted into local tissues and stroma; this process has been termed the angiogenic switch. The angiogenic switch is a discrete step in tumour development that can occur at different stages in the tumour-progression pathway, depending on the nature of the tumour and its microenvironment. Most tumours start growing as avascular nodules (dormant) (**a**) until they reach a steady-state level of proliferating and apoptosing cells. The initiation of angiogenesis, or the 'angiogenic switch', has to occur to ensure exponential tumour growth. The switch begins with perivascular detachment and vessel dilation (**b**), followed by angiogenic sprouting (**c**), new vessel formation and maturation, and the recruitment of perivascular cells (**d**). Blood-vessel formation will continue as long as the tumour grows, and the blood vessels specifically feed hypoxic and necrotic areas of the tumour to provide it with essential nutrients and oxygen (**e**). Activators of endothelial-cell proliferation and migration are mainly receptor tyrosine kinase ligands, such as vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF). Re-

markably, many inhibitory molecules, such as 'statins', are derived from larger proteins that have no effect on angiogenesis. In general, the levels of activators and inhibitors dictate whether an endothelial cell will be in a quiescent or an angiogenic state. It is believed that changes in the angiogenic balance mediate the angiogenic switch.

Since in normal healthy adults, the process of angiogenesis is very limited, thus it should, at least in theory, be possible to inhibit tumour angiogenesis without affecting normal tissues. Antiangiogenic therapies have become one of the most promising approaches in the anti-cancer drug development. Successful preclinical research data lead to clinical trials based on different strategies. Approaches currently under evaluation for inhibiting angiogenesis may either be direct (targeting cell surface bound proteins/receptors) or indirect (targeting growth factor molecules). Because angiogenesis is a complex process with multiple, sequential, and interdependent steps, this complexity creates many potential targets for inhibition. Therefore, an antiangiogenic effect can be achieved by targeting angiogenic stimulators, angiogenic receptors, extracellular matrix proteins, extracellular matrix proteolysis, control mechanisms of angiogenesis, or the endothelial cells directly. The targeting of antigens selectively expressed on the surface of tumour capillary endothelial cells or tumour stromal fibroblasts is currently being explored for the immunotherapy of cancer. By targeting or preventing the generation of angiogenic blood vessels or tumour stroma, tumour lesions are deprived of the essential support functions or nutrients required for survival and growth. This targeting approach may also be applicable to many tumour types because it is not dependant on a specific tumour cell type. The theoretical advantages that antiangiogenic therapeutics may have in the treatment of cancer are several-fold. First, endothelial cells involved in angiogenesis show several fundamental differences compared with quiescent endothelial cells, primarily their proliferation rate and antigen expression, which can be exploited so that antiangiogenic therapeutics specifically target tumour endothelial cells and not normal endothelium. Tumour blood vessels are also highly irregular (varying diameters), tortuous, have arterio-venous shunts, blind ends, lack smooth muscle, or enervation and have incomplete endothelial linings and basement membranes. As a result, blood flow is often slow or highly irregular, and the vessels are much 'leakier' than those in normal tissues, enabling the passage of large macromolecules. Second, antiangiogenic therapy may circumvent insufficient drug penetration into the interior of a tumour mass due to high interstitial pressure gradients within tumours, because endothelial cells are highly accessible to circulating drugs. Third, unlike targeting of tumour cells, where failure to destroy a proportion of the cells results in those cells proliferating and subsequent regrowth of the tumour, successful targeting of a few endothelial cells within a growing vessel may be sufficient to completely destroy that vessel. Consequently, disruption of a small percentage of the angiogenic vasculature may result in ischaemic necrosis of a substantial volume of tumour. Preclinical models support the use of antiangiogenic therapy as a single agent for cancer treatment, but also suggest that the combination with chemother-

apy might improve therapy effect. A number of antiangiogenic clinical trials currently in progress have been designed to compare the effects of a particular cytotoxic agent alone with the effects of the same agent in combination with an angiogenesis inhibitor. The genetic instability and high mutation rate of tumour cells is responsible, in part, for the frequent emergence of acquired drug resistance with conventional cytotoxic anticancer therapy.

However, vascular endothelial cells, like bone marrow cells, are genetically stable and have a low mutation rate. Therefore, Kerbel (1991) proposed a hypothesis that antiangiogenic therapy would be a strategy to bypass drug resistance. It is also worth mentioning that antiangiogenic therapy was found to be efficient for slowly growing tumours, which are a difficult target for classical chemotherapy. The administration of cytotoxic drugs often results in significant side effects. Drug side-effects may reflect either the primary anti-proliferative action of the drug, some less well understood but predictable toxicological effects, or they may be entirely idiosyncratic. Whereas over the years of application, side-effects of chemotherapy are already relatively well investigated, we still do not know much about side-effects of antiangiogenic therapy. Obvious complications might be related to menstruation, diabetes and wound healing. Nevertheless, long-term effects of therapy require attention. Additionally, it has been observed that antiangiogenic agents do require a very high dose to fulfill their function. These effects of combination therapy, which have also been observed for the combination of radiation therapy and angiogenesis inhibitors, could play a significant role in the clinical evaluation and effects of angiogenesis inhibitors. In some sense drawbacks of chemotherapy (induced drug resistance, smaller efficiency for slowly growing tumours) could be supported by advantages of antiangiogenic therapy and drawbacks of this therapy could be at least slightly moderated by the advantages of chemotherapy. From the control theoretic point of view the combined therapy means that both direct and indirect control is used to destroy cancer population (see Swierniak, 2008). Over the past decades, there has been considerable progress in mathematical modelling of tumour growth and associated vascular network development. Regrettably, while most realistic models reflect these complex biological processes very accurately, due to their complexity, they become difficult or even not suitable for analysis of therapy protocols, see, e.g., Bartha and Rieger (2006). Hopefully, with a few simplifying assumptions, it is possible to propose and carefully validate models useful for analysis, preceding experimental and clinical studies. In our study we consider a model of combined therapy, which belongs to the class of models proposed in Hahnfeldt et al. (1999), where the authors suggested that the tumor growth with incorporated vascularization mechanism can be described by the Gompertz or logistic type equation with variable carrying capacity which defines the dynamics of the vascular network. Roughly speaking, the main idea of this class of models is to incorporate the spatial aspects of the diffusion of factors that stimulate and inhibit angiogenesis into a non-spatial two-compartmental model for cancer cells and vascular endothelial cells. Control properties of such models in the context of the combined therapy were discussed in Swierniak

(2012), Swierniak and Ploskonski (2010), where, following the line of reasoning proposed in d'Onofrio and Gandolfi (2004), conditions for asymptotic tumour eradication by constant and periodic therapy were given. Moreover, necessary conditions for optimal treatment protocols in given finite time were considered. The interesting finding is that for d'Onofrio-Gandolfi version of the model the optimal trajectory does not contain singular arcs. This property was previously found for a part of the models of this class for the antiangiogenic therapy, see Swierniak (2009), while for the remaining models from this class the existence of intervals of singular optimal control was rigorously proved by Ledzewicz and Schättler (2007, 2008) and complete synthesis of optimal treatment protocols was proposed. All the considerations related to finite time control are, however, conditioned on the concept of controllability of the discussed dynamical system.

Systematic study of controllability was started at the beginning of the 1960s, when the theory of controllability, based on description in the form of state space for both time-invariant and time-varying linear control systems was worked out. Roughly speaking, controllability generally means that it is possible to steer in some time interval, the dynamical control system from an arbitrary initial state to an arbitrary final state, using controls taken from the set of admissible controls. Literature provides many different definitions of controllability, strongly depending on the class of dynamical control systems and on the set of admissible controls (see Klamka, 1991, 1993, 1996, 2004). In recent years various controllability problems for different types of nonlinear dynamical systems have been considered in many publications and monographs. However, it should be stressed that most of literature in this direction has been mainly concerned with controllability problems for finite-dimensional nonlinear dynamical systems with unconstrained controls and without delays or for linear dynamical systems with constrained controls and delays. Monographs by Kaczorek (1993, 2007) present many valuable results for controllability, observability and duality for different types of continuous and discrete linear dynamical systems. Similarly, Kaczorek (2002) presents controllability, observability and duality results for continuous and discrete positive linear dynamical systems. In the present paper, we shall consider constrained local controllability problems for second-order finite-dimensional semilinear stationary dynamical systems with point delay in control, described by the set of ordinary differential state equations. The line of reasoning is similar to that of our previous study, Swierniak and Klamka (2011), in which, though, only antiangiogenic therapy was considered, in other words – only one control variable was used.

The philosophy of this paper results from our experience. The first author has spent almost four decades on studying conditions of controllability and observability of various dynamical systems. The other author has been involved for the last thirty years in modeling cancer growth in the context of anticancer therapies, studying properties of models constructed in cooperation with clinicians and biologists, and searching for optimal treatment protocols. In the paper we formulate and prove sufficient conditions for constrained local controllability in a prescribed time interval for semilinear second-order stationary

dynamical systems, whose nonlinear term is continuously differentiable near the origin, and apply them for the discuused model of the combined anticancer therapy. It is generally assumed that the values of admissible controls are in a given convex and closed cone with vertex at zero, or in a cone with nonempty interior. Proof of the main result is based on the so called generalized open mapping theorem, presented in a simplified version in Klamka (2004). Roughly speaking, it will be proved that under suitable assumptions constrained global relative controllability of a linear first-order associated approximated dynamical system implies constrained local relative controllability near the origin of the original semilinear second-order dynamical system. This is a generalization of some previous results concerning controllability of linear dynamical systems with unconstrained controls to the case of constrained controllability. On the other hand, the conditions are formulated and then used in the way suitable for the considered models of anticancer therapy.

2. Models of cancer growth including vascularization and therapy

The class of models proposed in Hahnfeldt et al. (1999) is based on the idea that the tumour growth with incorporated vascularization mechanism can be described by self limiting growth mechanism (e.g. Gompertz or logistic type equation) with variable carrying capacity, which defines the dynamics of the vascular network. It is assumed that tumour cells multiply exponentially during the early phases of tumour growth. The growth rate declines as tumour mass increases, which results in a sigmoid exponential growth curve. This assumption is justified by the existence of a geometric gradient of availability of oxygen and nutrients, causing stratification in viability of cells: usually cycling cells are near the surface or near blood vessels; further layers are occupied by dormant cells, while the deepest regions form a necrotic core. Self-limiting growth might be illustrated by the non-linear Gompertz-type equation. Hahnfeldt et al. (1999) proposed modifying original Gompertzian equation, in order to describe proportional relation between size of cancer cells population and parameter describing the size of vascular network. To be more precise, Hahnfeldt suggested treating the carrying capacity, which constraints tumour growth, as a varying tumour volume sustainable by the vessels and roughly proportional to the vessel volume. The complete model requires additional equation describing changes of the volume of the vessels. Equation below expresses the Gompertz–type growth

$$\frac{dN(t)}{dt} = -\beta N(t) \ln \frac{N(t)}{K(t)}. \tag{1}$$

Here, N represents tumour volume as the size of cancerous cells population, K describes the maximum tumour volume sustainable by supporting vascular network, and β is a growth parameter. Likewise, the process of angiogenesis is very complex, being a well-orchestrated sequence of events involving endothelial cell migration; proliferation; degradation of tissue; new capillary vessel (sprout)

formation; loop formation (anastomosis) and crucially, blood flow through the network. Once there is blood flow associated with the nascent network, the subsequent growth of the network evolves both temporally and spatially in response to the combined effects of angiogenic factors, migratory cues via extracellular matrix and perfusion-related haemodynamic forces.

The spatial aspects are usually approximated by simple reaction-diffusion process, thus relating the change in number of tumour cells to their diffusion in space, as well as their proliferation. As another point of view, there are several models of angiogenesis, mainly focused on the proliferation and migration of the endothelial cells in response to different molecular signals, e.g. those associated with tumour angiogenesis factors. Recently, blood flow modelling in a tumour-induced micro-capillary network has been suggested in order to study the application of antiangiogenic and chemotherapy agents. Majority of models mentioned above, intend to fully reflect the complexity of the biological process and allow accurate simulations. Nevertheless, following the reasoning explained earlier, it is wise to start analysis with models under simplifying assumptions. Models considered in this study are based on that proposed by Hahnfeldt et al., who have developed and biologically validated a two-dimensional model of ordinary differential equations for interactions between primary tumour volume and the carrying capacity of the vasculature network, which, in turn, is proportional to the square of the tumour diameter. For simplification, it was necessary to assume spherical symmetry of tumour mass. Therefore the expression for K has the following form

$$\frac{dK(t)}{dt} = \gamma N(t) - \lambda N(t)^{\frac{2}{3}} K(t) - \mu K(t) \tag{2}$$

where γ represents the effect of the stimulation, λ the effect of the inhibition, μ the natural cell death. Taking into account that tumour growth is relatively slow compared to the rate of releasing pro- and antiangiogenic factors, it was possible to assume that parameters γ, λ, μ are constant. The model (1), (2) may be modified by introducing logistic type growth equation instead of the Gompertz-type one and by changing the ratio between stimulating and blocking angiogenic factors (see d'Onofrio and Gandolfi, 2004; Ergun et al., 2003). It leads to a set of models which, although they behave similarly when uncontrolled, may have different control properties (see Swierniak, 2009). For example, all the models have the same equilibrium point, which is both locally and globally asymptotically stable:

$$N^* = K^* = \left(\left(\gamma - \mu\right)/\lambda\right)^{3/2}. \tag{3}$$

On the other hand, conditions of tumour eradication under periodic therapy are both sufficient and necessary for all the models except of the original Hanhfeldt model, for which they are only necessary. Similar differences are observed when optimal antiangiogenic treatment protocols are considered. Once more the original Hahnfeldt model contains singular arcs in optimal trajectories, which are

absent in other models. Ledzewicz and Schättler (2007, 2008) treat singular arcs as a generic property of optimal protocols of antiangiogenic therapy. We suggested in Swierniak (2008, 2009) that it is rather an exception than a rule. To focus the attention we consider modification of the Hahnfeldt model proposed in d'Onofrio and Gandolfi (2004), where inhibitors of angiogenesis act in the same way as natural mortality factors:

$$\frac{dK(t)}{dt} = \gamma K(t) - \lambda N(t)^{\frac{2}{3}} K(t) - \mu K(t). \tag{4}$$

The model is strongly nonlinear but by logarithmic change of variable and some scaling transformation we are able to transform it into the semilinear form.

More precisely, by transformation:

$$\begin{array}{l} x = \ln N/N^*, \\ y = \ln K/K^* \\ x^* = y^* = 0, \tau = \beta t \\ \vartheta = (\gamma - \mu)/\beta \\ x' = dx/d\tau, \\ y' = dy/d\tau \end{array} \tag{5}$$

we are led for the model (1), (4) to the following quasi-linear system:

$$\begin{array}{l} x'(t) = y(t) - x(t), \\ y'(t) = \vartheta(e^{(2/3)x(t)} - 1). \end{array} \tag{6}$$

Application of antiangiogenic therapy can be incorporated into the model by a factor increasing multiplicatively the mortal loss rate of the vessels. It leads to the following equation:

$$\frac{dK(t)}{dt} = \gamma K(t) - \lambda N(t)^{\frac{2}{3}} K(t) - \mu K(t) - \eta K(t) u(t) \tag{7}$$

where $u(t)$denotes the dose of the agent scaled to its effect on vascular network and η is a constant parameter playing the role of a control variable. For the constant dose U, the equilibrium points take the form:

$$N^* = K^* = \left(\left(\gamma - \mu - \eta U \right) / \lambda \right)^{3/2}, \tag{8}$$

which, according to the conditions of stability given in d'Onofrio and Gandolfi (2004) leads to the conclusion that for:

$$U = (\gamma - \mu)/\eta \Rightarrow K^*, N^* = 0. \tag{9}$$

In other words, the vascular network and, in turn the tumour, can be eradicated. This conclusion is crucial for the philosophy of the entire analysis. It is enough to ensure that population of endothelial cells responsible for the angiogenesis behave in the required way because the size of tumour population in some sense

tracks the same transients. The similar line of reasoning could be applied in the case of combined antiangiogenic and chemo-therapy. In this case two control variables are present. The main difference is that chemotoxic agents kill both cancer and critical normal tissues, including endothelial cells. Thus, their effect should be enclosed in both equations. In the case of d'Onofrio-Gandolfi model the equations take the following form:

$$\frac{dN(t)}{dt} = -\beta N(t) \ln \frac{N(t)}{K(t)} - \psi v(t) \tag{10}$$

$$\frac{dK(t)}{dt} = \gamma K(t) - \lambda N(t)^{\frac{2}{3}} K(t) - \mu K(t) - \eta K(t) u(t) - \xi K(t) v(t) \tag{11}$$

where $v(t)$, the second control variable, denotes the dose of the chemotherapy, scaled to its effect on tumour and normal tissues, and ξ and ψ are constant scaling parameters. Of course, the additional chemotherapy supports the effect of antiangiogenic therapy. Moreover, the effect of tumour eradication may be achieved easier and faster, although still the theoretical results based on theory of stability have asymptotic form. For constant doses of antiangiogenic and chemotoxic agents (denoted by $U$and V, respectively) the equilibrium point is given by (see Swierniak, 2012):

$$\begin{array}{l} N^* = ((\gamma - \mu - \eta U - \xi V)/\lambda)^{3/2} \\ K^* = N^* e^{\xi V/\beta} \end{array} . \tag{12}$$

In this case the equilibrium point is not the same for both populations but it is related very closely, and it can be easily noticed that conditions of its asymptotic stability, both local and global, are similar to those given above. The main difference is that now both control actions "collaborate" in conditions for convergence of solutions of the model equations to 0. More precisely, condition (9) should be substituted by:

$$U + \xi V/\eta = (\gamma - \mu)/\eta \Rightarrow K^*, N^* = 0. \tag{13}$$

The use of the previously considered transformation of variables leads to the following semilinear model of the combined anticancer therapy:

$$\begin{array}{l} x'(t) = y(t) - x(t) - \varepsilon v(t), \\ y'(t) = \vartheta(1 - e^{(2/3)x(t)}) + \sigma u(t) + \varsigma v(t), \\ \sigma = -\eta/\beta, \\ \varepsilon = \psi/\beta, \\ \varsigma = -\xi/\beta. \end{array} \tag{14}$$

3. Semilinear system description

In this section we study the general form of the semilinear stationary finite-dimensional control system described by the following ordinary differential state equation

$$\underline{x}'(t) = A\underline{x}(t) + F(\underline{x}(t), \underline{u}(t)) + B\underline{u}(t) \text{ for } t \in [0, T],\ T{>}0 \tag{15}$$

with zero initial conditions: $\underline{x}(0) = 0$, where the state $\underline{x}(t) \in R^n = X$ and the control $\underline{u}(t) \in R^m = U$, A is $n \times n$ dimensional constant matrix, B is $n \times m$ dimensional constant matrix. Moreover, let us assume that the nonlinear mapping $F : X \times U \to X$ is continuously differentiable near the origin and such that $F(0,0)=0$.

In practice, admissible controls are always required to satisfy certain additional constraints. Generally, for arbitrary control constraints it is rather very difficult to give easily computable criteria for constrained controllability. However, for some special cases of the constraints it is possible to formulate and prove simple algebraic constrained controllability conditions. Therefore, we assume that the set of values of controls $U_c \subset U$ is a given closed and convex cone with nonempty interior and vertex at zero. Then, the set of admissible controls for the dynamical control system (15) has the form $U_{ad} = L_\infty([0,T], U_c)$.

For the semilinear stationary finite-dimensional dynamical system (15), it is possible to define many different concepts of controllability. In the sequel we shall focus our attention on the so called constrained controllability in the time interval $[0, T]$. In order to do that, first of all let us introduce the notion of the attainable set at time $T>0$ from zero initial conditions, denoted shortly by $K_T(U_c)$ and defined as follows:

$$K_T(U_c) = \{\underline{x} \in X : \underline{x} = \underline{x}(T, \underline{u}), \underline{u}(t) \in U_c \quad \text{for a.e. } t \in [0, T]\} \tag{16}$$

where $\underline{x}(t, u),\ t >0$ is the unique solution of the differential state equation (15) with zero initial conditions and a given admissible control $\underline{u} \in U_{ad} = L_\infty([0,T], U_c)$. Under the assumptions stated on the nonlinear term F such solution always exists.

Now, using the concept of the attainable set, let us recall the well known definitions of constrained controllability in $[0,T]$ for semilinear dynamical system (15).

Definition 1 The dynamical system (15) is said to be U_c-locally controllable in $[0, T]$ if the attainable set $K_T(U_c)$ contains a neighborhood of zero in the space X.

Definition 2 The dynamical system (15) is said to be U_c-globally controllable in $[0, T]$ if $K_T(U_c) = X$.

Now, we shall introduce certain notations and present some important facts from the general theory of nonlinear operators.

Let U and X be given spaces and $g(\underline{u})$: $U \to X$ be a mapping continuously differentiable near the origin 0 of U. Let us suppose for convenience that g(0)=0. It is well known from the implicit function theorem that if the derivative $Dg(0):U \to X$ maps the space U onto the whole space X, then the nonlinear map g transforms a neighborhood of zero in the space Uonto some neighborhood of zero in the space X.

Now, let us consider the more general case when the domain of the nonlinear operator g is Ω, an open subset of Ucontaining 0. Let U_c denote a closed and convex cone in U with vertex at 0.

In the sequel, we shall use for controllability investigations some property of the nonlinear mapping g which is a consequence of a generalized open-mapping theorem. This result seems to be widely known, but for the sake of completeness we shall present it here, though without proof and in a slightly less general form sufficient for our purpose.

Lemma 1 *Let X, U, U_c, and Ω be as described above. Let g:$\Omega \to X$ be a nonlinear mapping and suppose that on Ω the nonlinear mapping g has derivative Dg, which is continuous at 0. Moreover, suppose that g(0) = 0 and assume that linear map Dg(0) maps U_c onto the whole space X. Then there exist neighborhoods $N_0 \subset X$ about $0 \in X$ and $M_0 \subset \Omega$ about $0 \in U$ such that the nonlinear equation $\underline{x} = g(\underline{u})$ has, for each $\underline{x} \in N_0$, at least one solution $\underline{u} \in M_0 \cap U_c$, where $M_0 \cap U_c$ is a so called conical neighborhood of zero in the space U.*

4. Controllability conditions

In this section, using Lemma 1, presented previously, we shall study constrained local controllability in $[0,T]$ for semilinear dynamical system (15) using the associated linear dynamical system.

$$\underline{z}'(t) = C\underline{z}(t) + D\underline{u}(t) \quad for \quad t \in [0,T] \tag{17}$$

with zero initial condition $z(0)=0$, where

$C = A + F_x(0,0)D = B + F_u(0,0)$

are $n \times n$-dimensional and $n \times m$-dimensional constant matrices, respectively.

The main result is the following sufficient condition for constrained local controllability of the semilinear dynamical system (15), which will be used to study controllability of the model of combined anticancer therapy:.

Theorem 1 Klamka (1996): *Suppose that*

(i) F(0,0) = 0,

(ii) $U_c \subset U$ is a closed and convex cone with vertex at zero,

(iii) the associated linear control system (17) is U_c-globally controllable in [0,T].

Then the semilinear stationary dynamical control system (17) is U_c-locally controllable in [0,T].

In the practical applications of Theorem 1, the most difficult problem is to verify the assumption (iii) of constrained global controllability of the linear time invariant dynamical system. In order to avoid this disadvantage, we may use the following theorem:

Theorem 2 Klamka (1996): *Suppose the set U_c is a cone with vertex at zero and nonempty interior in the space R^m. Then the associated linear dynamical control system (17) is U_c-globally controllable in [0,T] if and only if*

1. *it is controllable without any constraints, i.e. rank$[D, CD, C^2D, ..., C^{n-1}D] = n$,*
2. *there is no real eigenvector $w \in R^n$ of the matrix C^{tr} satisfying inequalities*

$w^{tr} D\underline{u} \leqslant 0$, *for all* $\underline{u} \in U_c$.

It should be pointed out that for the single input scalar control associated linear dynamical control system, i.e., for the case $m = 1$, Theorem 2 reduces to the following corollary, which was used by us to check the controllability of the model of antiangiogenic therapy in Swierniak and Klamka (2011).

Corollary Klamka (1996): *Suppose that m=1 and* $U_c = R^+$.

Then the associated linear dynamical control system (17) is U_c*-globally controllable in [0,T] if and only if it is controllable without any constraints i.e.,*

$rank[D, CD, C^2D, ..., C^{n-1}D] = n$,

and matrix C has only complex eigenvalues.

5. Controllability of the model of therapy

Now, let us consider constrained local controllability of the model of combined anticancer therapy described by the semilinear differential state equations (14) defined in a given time interval [0,T]. In this case, the state vector $\underline{x} = [x, y]^T$, the control vector $\underline{u} = [u, v]^T$, and $\underline{z}$ is the state of the associated linear system.

Taking into account the general form of the semi-linear dynamic system we have:

$$A = \begin{bmatrix} -1 & 1 \\ 0 & 0 \end{bmatrix} \quad F(x, y, u, v) = \begin{bmatrix} 0 \\ -\vartheta(e^{(2/3)x} - 1) \end{bmatrix} \quad B = \begin{bmatrix} 0 & -\varepsilon \\ \sigma & \zeta \end{bmatrix}.$$

Hence, we get

$$F(0,0,0,0) = \begin{bmatrix} 0 \\ 0 \end{bmatrix} \quad F_x(0,0,0,0) = \begin{bmatrix} 0 & 0 \\ -\vartheta\frac{2}{3} & 0 \end{bmatrix}$$

$$C = A + F_x(0,0,0,0) = \begin{bmatrix} -1 & 1 \\ -\vartheta\frac{2}{3} & 0 \end{bmatrix}.$$

In order to consider controllability of dynamical system (15) we use the Theorems and the Corollary presented in the previous section.

The admissible controls are assumed to be positive, hence the set of admissible controls is a positive cone U_c in the space R^2.

The characteristic polynomial for matrix C^{tr} has the form

$$P(s) = \det(sI - C^{tr}) = \det \begin{bmatrix} s+1 & \frac{2}{3}\vartheta \\ -1 & s \end{bmatrix} = s^2 + s + \frac{2}{3}\vartheta.$$

Therefore, the discriminate of the characteristic polynomial: $\Delta = 1 - \frac{8}{3}\vartheta$ and characteristic equation $P(s) = 0$ has two roots.

It is necessary to consider the following three cases:

I. $\Delta < 0$, for $\vartheta > \frac{3}{8}$

In this case we have two complex eigenvalues

$$s_1 = 0.5(-1 - j\sqrt{\Delta}) = 0.5(-1 - j\sqrt{1 - \tfrac{8}{3}\vartheta})$$

$$s_2 = 0.5(-1 + j\sqrt{\Delta}) = 0.5(-1 + j\sqrt{1 - \tfrac{8}{3}\vartheta}).$$

Since

$$rank \begin{bmatrix} B & CB \end{bmatrix} = rank \begin{bmatrix} \sigma & \xi + \varepsilon \\ 0 & \frac{2}{3}\vartheta\varepsilon \end{bmatrix} = 2 = n$$

and eigenvalues are complex, then by the Corollary the system is constrained controllable.

II. $\Delta = 0$, for $\vartheta = \frac{3}{8}$

In this case we have one real eigenvalue s_{12} = -0.5 with multiplicity 2. Therefore, for controllability verification it is necessary to use Theorem 2. In order to do that first we find eigenvector w of matrix C^{tr}.

From spectral equation $C^{tr}w = -0.5w$ the real eigenvector has the following form

$$w = \begin{bmatrix} -1 \\ 2 \end{bmatrix}$$

thus

$w^{tr}B\underline{u} = \begin{bmatrix} - & 1 & +2 \end{bmatrix} \begin{bmatrix} 0 & -\varepsilon \\ \sigma & \xi \end{bmatrix} \begin{bmatrix} u \\ v \end{bmatrix} = 2\sigma u + (\varepsilon + 2\xi)v > 0$ for all positive controls.

Therefore, there is no real eigenvector satisfying $w^{tr}D\underline{u} \leqslant 0$, for all $\underline{u} \in U_c$.

Hence, taking into account the Theorem, the system is controllable with positive admissible controls.

III. $\Delta > 0$, for $\vartheta < \frac{3}{8}$

In this case we have two different real eiganvalues. Hence, for controllability verification we use Theorem 2.

Real eigenvalues have the following form:

$$s_1 = 0.5(-1 - \sqrt{1 - \tfrac{8}{3}\vartheta}) < 0$$

$$s_2 = 0.5(-1 + \sqrt{1 - \tfrac{8}{3}\vartheta}) < 0.$$

Therefore, the corresponding real eigenvectors are

$w_1 = \begin{bmatrix} -1 \\ -s_1^{-1} \end{bmatrix}$ and $w_2 = \begin{bmatrix} -1 \\ -s_2^{-1} \end{bmatrix}$.

Thus,

$w_1^{tr}B\underline{u} = \begin{bmatrix} -1 & -s_1^{-1} \end{bmatrix} \begin{bmatrix} 0 & -\varepsilon \\ \sigma & \xi \end{bmatrix} \begin{bmatrix} u \\ v \end{bmatrix} = -s_1^{-1}\sigma u + (\varepsilon - s_1^{-1}\xi)v > 0$ for all positive controls;

$w_2^{tr}B\underline{u} = \begin{bmatrix} -1 & -s_2^{-1} \end{bmatrix} \begin{bmatrix} 0 & -\varepsilon \\ \sigma & \xi \end{bmatrix} \begin{bmatrix} u \\ v \end{bmatrix} = -s_2^{-1}\sigma u + (\varepsilon - s_2^{-1}\xi)v > 0$ for all positive controls.

Therefore, there is no real eigenvector satisfying $w^{tr}D\underline{u} \leqslant 0$, for all $\underline{u} \in U_c$.

Hence, taking into account the Theorem the system is controllable with positive admissible controls.

Summarizing the above, the semilinear dynamical system (15) is constrained controllable in a given time interval $[0, T]$ with positive controls. From the biological point of view it means that if the size of the tumour and its vascular network is not too large, then there exists a combination of antiangiogenic therapy and chemotherapy which enables practical eradication of the tumour. This may not be the case if only one modality (e.g. only antiangiogenic therapy) is used. As it has been proved in Swierniak and Klamka (2011), local constrained controllability of the model of antiangiogenic therapy is guaranteed only when its parameters satisfy additional condition related to oscillatory behavior in the untreated case.

6. Conclusions and discussion

In this study we have shown how, using quite simple models, we can analyze and design therapy protocols of combined antiangiogenic and chemotherapy. This type of cancer treatment is still in experimental and clinical trials. The results are promising, but the knowledge of the processes behind the evolution of cancer vascular network, the equilibrium between stimulation and inhibitory factors, different forms of antiangiogenic therapy, its side effects and the results of combined use of different treatment modalities is still far from complete. The important finding presented in the paper is that sufficient conditions of local constraint controllability for the simple model of combined therapy are satisfied independently of its parameters, which is not true for the model of antiangiogenic therapy. A more realistic model should take into account drug resistance of the cancer cell population caused by chemotoxic agents. Of course, the model is more complicated than the two compartmental models considered in the paper but, in our opinion, it may be treated similarly and may lead to similar qualitative results. The simplest example in this class is a three compartmental model proposed in Swierniak (2012).

A similar analysis may be proposed for the combined therapy in which antiangiogenic therapy is associated with radiotherapy. In this case, however, the realistic model should take into account the so called linear-quadratic effect or α/β effect of ionizing radiation. The method presented in the paper is quite general and covers a wide class of semilinear dynamical control systems. Therefore, similar constrained controllability results may be derived for more general class of semilinear dynamical control systems. For example, it seems that it is possible to extend sufficient constrained controllability conditions given in the previous sections for more general class of semilinear dynamical models with single point delay in the control or with multiple point delays in the controls or in the state variables. Such models are also used in analysis of anticancer therapies, e.g. d'Onofrio and Gandolfi (2009), Forys and Poleszczuk (2011).

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