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Local Controllability of Models of Combined Anticancer Therapy with Delays in Control

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Abstract. We present sufficient conditions of local controllability for a class of models of treatment response to combined anticancer therapies which include delays in control strategies. The combined therapy is understood as combination of direct anticancer strategy e.g. chemotherapy and indirect modality (in this case antiangiogenic therapy). Controllability of the models in the form of semilinear second order dynamic systems with delays in control enables to answer the questions of realizability of different objectives of multimodal therapy in the presence of PK/PD effects. We compare results for the models without delays and conditions for relative local controllability of models with delays.

Keywords and phrases: multimodal therapy, constrained controllability, semilinear systems, systems with delays

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1. Introduction

It has been discovered that even small tumors need their own supply system in the form of autonomous vascular network for growth, development and, ultimately, for metastasis [13]. To create this vasculature cancer cells release proangiogenic growth factors starting a cascade of signal leading to formation of blood vessels and their loops which are responsible for delivery of nutrients and oxygen. The size of this formatted vascular network becomes a bound for the size of the tumor. Taking this into account Judah Folkman [10], [11] proposed in early seventieth of the previous century a new strategy of combat against cancer called antiangiogenic therapy the idea of which was to break the cascade of signals and events leading to the angiogenesis. The therapy became one of the hopes for efficient cancer treatment with modest side effects and many advantages over standard drug treatments. Since it is directed towards special part of normal tissues and only indirectly destroys tumor cells it has been called by Kerbel [15] a therapy resistant to drug resistance. It has been also found to be efficient for slowly growing tumors which are difficult for classical chemotherapy. Yet another good news is that targeting tumor vasculature rather than tumor cell population would avoid the necessity of having to obtain intra-tumor drug delivery. The drawbacks are: difficulties in observations of the results, high dosage necessary for fast growing tumors,

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side effects related to menstruation, diabetes, wound healing. Nevertheless the enthusiasm related to first experimental successes of antiangiogenic therapy has been followed by more cautious expectations.

In [8] the gap between preclinical (mouse models – localized primary tumor) and clinical testing (late-stage metastatic) is suggested. Antiangiogenic agents make not such impressive results as in preclinical trials. Depending on a disease stage different results were obtained. Hundreds of clinical trials included mostly inhibitor targeting the vascular endothelial growth factor (VEGF) pathways (one of the pro-angiogenic protein). In some cases slowed metastatic disease progression occurs, leading to progression-free survival and overall survival benefits compared with control, but it was not associated with survival improvements. Yet another important constrain in efficient antiangiogenic therapy is the accessibility of antiangiogenic agents. Moreover, contrary to Kerbel's hopes, two types of resistance have been observed. First one – evasive, include revascularization as a result of upregulation of alternative pro-angiogenic signals, protection of the tumor, increased metastatis, second one – intrinsic, includes rapid adaptive responses, in the case of pre-existing conditions defined by the absence of any beneficial effect of anti-angiogenic agents [1].

Nowadays antiangiogenic therapy is considered rather as an essential component of multidrug cancer therapy [20], [21], especially with chemotherapy. Although tumor eradication in such combined therapy may be still the primary goal the chaotic structure of the angiogenically created network leads to another target for antiangiogenic agents. Namely using angiogenic inhibitors to normalization of the abnormal vasculature (the so called pruning effect) facilitate drug delivery [6], [14]. Smaller dose of anti-angiogenic agents (bevacizumab 5 mg/kg) shows significantly different (higher) median survival from chemotherapy alone in the treatment group when the dose 10 mg/kg can even increase survival compared to chemotherapy alone in the treatment group. The continuous treatment with angiogenic inhibitors ultimately leads to a decrease in tumor blood flow and a decreased tumor uptake of co-administrated cytotoxic drugs. In the periodic therapy the main goal of anti-angiogenic agents is to normalize tumor vasculature. Yet another difficulty in planning treatment protocols in the combined therapy is related to pharmacokinetic-pharmacodynamic (PK/PD) properties of antiangiogenic and cytostatic agents. Modeling of those effects leads to extension of the model by additional differential equations for PK and introduction of additional nonlinearities for PD description. We overcome this problem by including time-delays different for both types of agents. Although such description is far from accurate illustration of biological processes behind PK/PD phenomena but for the simplified model used in this paper it is adequate way of modeling the important changes in effects of therapy caused by them. Pharmacokinetic factors may also contribute towards mechanisms of resistance. The half life time for cytostatic drugs is rather short usually few hours but for example for commonly used Cisplatin it changes from 30-100 hours (mean: 65). For antiangiogenic agents the half life may vary over a wide range (for example from 15 minutes for angiostatin up to 20 days bevacizumab). Yet another reason for including delays in control variables describing effects of chemotherapy is related to the idea of normalization of vasculature using angiogenic inhibitors (as discussed above). The cytostatic agents should be administered with delay necessary for pruning vessels by antiangiogenic drugs.

The questions which of the goals mentioned above could be reached in finite treatment horizon could be answered, at least theoretically, by analysis of controllability of dynamical systems used as models of the processes of tumor growth in the presence of vascularization. Controllability is a qualitative property of dynamical control systems and its meaning, roughly speaking, is following: a dynamical system is controllable if it is possible to steer it from an arbitrary initial state to an arbitrary final state using the set of admissible controls. In the existing literature there are many different definitions of controllability strongly depending on the class of dynamical control systems (see e.g. [16]-[18], [2], [3]). In the present paper, we consider relative constrained local controllability for second-order finite-dimensional semilinear stationary dynamical systems described by the set of two ordinary differential state equations with delays. More precisely we discuss a class of models proposed in [12] to which two control variables describing two treatment modalities have been introduced and those variables may exhibit different delays. To our knowledge, the problem of controllability for such models is absent in the literature except of our previous

studies in which controllability of the simplified model of this class proposed in [7] for antiangiogenic therapy [26] and combined therapy [19] have been studied. The results are based on theorems proved in [17] for nonlinear systems without delays. The theorems have been extended in [18] for the case when control variables have multiple delays. The idea of the theorems is that under suitable assumptions constrained global relative controllability of a linear associated approximated dynamical system with delays implies constrained local relative controllability near the origin of the original semilinear second-order dynamical system with delays. In the paper we compare conditions for the original Hahnfeldt et al. model [12] and the model which includes delays in control variables.

2. Models of cancer growth including vascularization and combination of two treatments

Phenomena related to tumor growth in the presence of its vascularization and anticancer treatment are very complex. Thus their modeling should take into account their dynamical behavior and spatial organization leading to models in the form of partial differential equations (see e.g. [21]). Nevertheless, such models are difficult for mathematical analysis and almost not tractable when used for designing of treatment protocols.

Hahnfeldt et al. in 1999 [12] proposed a model (or more precisely a class of models) based on experimental data from anti-angiogenic therapy and non therapy trials of Lewis lung tumors in mice. 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. If N denotes size of cancer cells population and K a parameter describing the size of vascular network then such growth could be expressed by Gompertz type growth equation.

Second equation describes dynamics of vascular network growth K and includes stimulators of angiogenesis (characterized by parameter γ), inhibitory factors secreted by tumor cells (characterized by λ) and natural mortality of the endothelial cells (characterized by μ). In this model β denotes proliferation ability of the cells. Inhibitory factors are proportional to the tumor volume to the power 2/3 because they concentrate nearby the area of the active surface between the tumor and vascular network and the same their effect is proportional to the square of the tumor radius. The effect of therapy in such models can be included in the form of control actions entering the system as multipliers in the bilinear terms. Since antiangiogenic agents disturb directly only the vascular network the control variable (u) is present only in the first equation. The second variable (v) related to chemotherapy appears in both equations [25]. The coefficients ψ, η, ξ are non-negative constants that relate the dosages of anti-angiogenic (u) and cytostatic (v) agents (ψ is much greater than η).

$$\dot{N} = -\beta N \ln(N/K) - \psi v N \tag{2.1}$$

$$\dot{K} = \gamma N - \lambda K N^{2/3} - \mu K - \eta\mu K - \xi v K \tag{2.2}$$

Both control variables are nonnegative and bounded by their maximal doses $U_{\max}$, $V_{\max}$, respectively. Similar behavior could be obtained if Gompertz type growth is substituted by logistic type one.

$$\dot{N} = -\beta N (1 - N/K) - \psi v N \tag{2.3}$$

The modification of this model, proposed by D'Onofrio and Gandolfi [7] which also satisfies Hahnfeldt's suggestions described above assumes that the effect of stimulators of angiogenesis on the relative velocity of growth is constant, in other words angiogenesis is vascular-induced and not cancer-induced (as in (2.2)):

$$\dot{K} = \gamma K - \lambda K N^{2/3} - \mu K - \eta\mu K - \xi v K \tag{2.4}$$

Combining the models of tumor growth and the associated models of vascular network growth we obtain a set of two-compartmental models properties of which have been compared in [24]. The interesting

finding [7] is that all these models when uncontrolled (without therapy) have the same equilibrium point defined by the same values of both variables N and K:

$$N^* = K^* = \left((\gamma - \mu)/\lambda\right)^{3/2} \tag{2.5}$$

This equilibrium point is both locally and globally asymptotically stable. The line of reasoning is based on the Lyapunov type analysis.

Yet another simplification of the original Hahnfeldt model was proposed by Ergun et al. in 2003 [9]. This model also satisfies assertions proposed in [12] but the dynamics of vessel carrying support is independent of the size of the tumor:

$$\dot{K} = \gamma K^{2/3} - \lambda K^{4/3} - \eta u\, K - \xi v K \tag{2.6}$$

Moreover this model does not contain the natural mortality factor. But although this term has been present in previously discussed models all simulation results presented by the authors are obtained for $\mu = 0$. The reason is relatively small impact of this term for the dynamics of the considered system. Thus to simplify further considerations and to have possibility of comparison of results for all the models mentioned above we will omit this term in our further consideration.

It leads to the simpler form of the equilibrium which is also relevant for the Ergun et al. [9] model:

$$N^* = K^* = (\gamma/\lambda)^{3/2} \tag{2.7}$$

For constant dosage of antitumor drugs in the combined therapy this result enables to find such continuous protocols which lead to asymptotic eradication of vascular network and in turn the tumor. In this case values of N and K in equilibrium are not the same [14] but still they are closely related by linear map. For example a condition for constant doses of antiangiogenic U and cytotoxic V drugs ensuring complete asymptotic removal of the tumor for model (2.1), (2.2) is given by:

$$U + \frac{\xi V}{\eta} = \frac{\gamma}{\eta} e^{-\psi V/\beta} \Longrightarrow K^*,\ N^* \to 0$$

Similar results are obtained for periodic therapies with mean values defined by analysis of asymptotic effects of constant continuous therapy for all these models excluding the original Hahnfeldt model (with Gompertz–type growth equation). For this model the eradication condition is only necessary but not sufficient. Efficiency of the periodic therapy for this model depends on the shape of pulses used in the periodic treatment [5].

Constant or periodic therapies which ensure tumor eradication discussed previously have an important drawback. They should be applied for long therapy horizon. Shortage in the antiangiogenic drugs, their costs, emergency of resistance and side effects cause that the parameters of treatment protocols and cumulated dose of the drugs should be bounded. Thus realistic control problems related to the combined anticancer therapy should be formulated as finite horizon control problems. In [4] results of simulation for simple protocols of continuous and periodic therapy for finite treatment horizons are presented. Parameters proposed by Hahnfeldt et al. [12] were used in order to implement each model under similar conditions. There was no significant variation in tumor volume after therapy when greater dose was used. In the case of ten time lower doses effect of therapy were highly related to the length of the cycle, for shorter periods tumor volme was greater than for larger ones. In periodic protocols therapeutic effect was smaller than during the continuous therapy. The dynamics of all models was similar.

In 2009 d'Onofrio and Gandolfi analyzed the role of vessel density [5] (which can modulate the effect of drugs) and the effect of vascular "pruning" (by using anti-angiogenic drug in a combined therapy) and they proposed to modify the equation of tumor growth to the form.

$$\dot{N} = -\beta N \ln\left(N/K\right) - \psi\left(K/N\right) v N \tag{2.8}$$

Now $\psi(K/N)$ is a function of vessel density. Too aggressive or sustained anti-angiogenic treatment may prune away vascular network, resulting in resistance to further treatment and inadequate delivery of drugs or oxygen. Based on functions described in [5], it has been observed in [4] that the best properties of vascular network are when density (endothelial cells/cancer cells) is 2.

One way of checking, at least theoretically, whether there exist protocols enabling reachability of such different final targets is to find conditions for controllability of the models under discussion.

In [5] d'Onofrio and Gandolfi proposed to include delays in dynamics of tumor and vessel growth and presented a linear analysis of their effects finding that they could destabilize the system via Hopf bifurcations. More general analysis of the Hopf bifurcations for this class of models was given in [23].

In models which we consider in the paper delays are introduced in control variables and not in the state ones. Their role, as mentioned in the introduction, is to describe time lags of effects of the therapy related to PK/PD of the drugs or to include in the model an idea of initial normalization of the vasculature using antiangiogenic agents before the proper therapy is used.

3. Models of combined therapy as semilinear dynamical systems

Semilinear stationary finite-dimensional control system are described by the following ordinary differential state equation:

$$\dot{\underline{x}}(t) = A\underline{x}(t) + F(\underline{x}(t)) + B\underline{u}(t) \tag{3.1}$$

with initial conditions $\underline{x}(0) = \underline{x}_0 \in \mathbb{R}^n$, where t is real nonnegative, the state $\underline{x}(t) \in \mathbb{R}^n$ and the control $\underline{u}(t) \in \mathbb{R}^m$, A is $n \times n$ dimensional constant matrix, B is $n \times m$ dimensional constant matrix. Moreover, let us assume that the nonlinear mapping $F : X \to X$ is continuously differentiable near the origin and such that $F(0) = 0$, and $X = \mathbb{R}^n$, and $U = \mathbb{R}^m$, denote state and control spaces, respectively.

In practice admissible controls are always required to satisfy certain additional constraints. 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.

The associated linear dynamical system for semilinear dynamical system (3.1) is defined as:

$$\dot{\underline{z}}(t) = C\underline{z}(t) + B\underline{u}(t) \tag{3.2}$$

for $t \in [0, T]$ with zero initial condition $z(0) = 0$, where

$$C = A + F_{\underline{x}}(0) \tag{3.3}$$

is an $n \times n$ dimensional constant matrix.

The models considered in the previous section are strongly nonlinear but by logarithmic change of variables and some scaling transformation we are able to transform them into the semilinear form. As mentioned before, for practical reasons, we omit the natural mortality factor represented by parameter μ. Defining:

$$\begin{array}{lll} x = \ln N/N^*, & y = \ln K/K^*, & x^* = y^* = 0, \\ \tau = \beta t, & \vartheta = \gamma/\beta, & \overline{\vartheta} = (\lambda\gamma)^{1/2}/\beta, \\ \dot{x} = dx/d\tau & \dot{y} = dy/d\tau & \end{array}$$

we are led to the following system for model (2.1), (2.2):

$$\dot{x}(t) = y(t) - x(t) - \varepsilon v(t) \tag{3.4}$$

$$\dot{y}(t) = \vartheta\left(e^{x(t)-y(t)} - e^{(2/3)x(t)}\right) - \sigma u(t) - \varsigma v(t) \tag{3.5}$$

If Gompertz type growth of the tumor is substituted by the logistic type one (2.3) then the first equation of the model (3.5) has the form:

$$\dot{x}(t) = 1 - e^{x(t)-y(t)} - \varepsilon v(t) \tag{3.6}$$

but in this case (3.4) is a linear approximation of this equation.

Similarly if the dynamics of vasculature capacity is modeled by (2.4) or by (2.6) then (3.5) should be substituted by:

$$\dot{y}(t) = \vartheta\left(1 - e^{(2/3)x(t)}\right) - \sigma u(t) - \varsigma v(t) \tag{3.7}$$

or

$$\dot{y}(t) = \overline{\vartheta}\left(e^{-(1/3)y(t)} - e^{(1/3)y(t)}\right) - \sigma u(t) - \varsigma v(t)$$

respectively, where

$$\sigma = \eta/\beta,\ \varepsilon = \psi/\beta,\ \varsigma = \xi/\beta$$

It is worth to note that the associated linear system will be the same for both Gompertz type and logistic type growth equations.

Now we introduce time delays into control variables. Equation (3.2) will be substituted by:

$$\dot{\underline{x}}(t) = A\underline{x}(t) + F(\underline{x}(t)) + B\underline{u}(t) + B_1\underline{u}(t-h) \tag{3.8}$$

with initial conditions $\underline{x}(0) = \underline{x}_0 \in \mathbb{R}^n$, $\underline{u}_0 \in L_\infty([-h,0], U_c)$, where B_1 is $n \times m$ dimensional constant matrix, $\underline{x}_0$ is a given point, and $\underline{u}_0$ – a given function. The associated linear dynamical system for semilinear dynamical system with delays (3.8) is defined as:

$$\dot{\underline{z}}(t) = C\underline{z}(t) + B\underline{u}(t) + B_1\underline{u}(t-h) \tag{3.9}$$

To make the problem as simple as possible without losing qualitative effects we assume that only one control variable is delayed and our choice is to include delays in chemotherapy protocols for the reasons discussed in the introduction. One type of multidrug protocols which may match such a model is combination of Sunitinib (angiogenic inhibitor) with Cisplatin. Let us notice that in this case (3.8) can be modified as follows:

$$\dot{\underline{x}}(t) = A\underline{x}(t) + F(\underline{x}(t)) + b_0 u(t) + b_1 v(t-h) \tag{3.10}$$

and similarly (3.9) can be written as:

$$\dot{\underline{z}}(t) = C\underline{z}(t) + b_0 u(t) + b_1 v(t-h) \tag{3.11}$$

where b_0 and b_1 are vectors from $\mathbb{R}^n$.

It leads to the following modification of model (3.4), (3.5):

$$\dot{x}(t) = y(t) - x(t) - \varepsilon v(t-h) \tag{3.12}$$

$$\dot{y}(t) = \vartheta\left(e^{x(t)-y(t)} - e^{(2/3)x(t)}\right) - \sigma u(t) - \varsigma v(t-h) \tag{3.13}$$

with initial conditions $x(0) = x_0$, $y(0) = y_0$, $v_0 \in L_\infty([-h,0],[0,V_{\max}])$.

Once more (3.10) may be also treated as a linear associated equation for logistic type equation of tumor growth.

4. Sufficient conditions of controllability

For the semilinear dynamical system (3.1), it is possible to define many different concepts of controllability. 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:

$$K_T(U_c) = \{\underline{x} \in X : \underline{x} = \underline{x}(T, \underline{u}),\ \underline{u}(t) \in U_c\} \tag{4.1}$$

where $\underline{x}(t, \underline{u})$, $t > 0$ is the unique solution of the differential state equation (3.1) with zero initial conditions and a given admissible control. Under the assumptions stated on the nonlinear term F such solution always exists. Now, using the concept of the attainable set, we recall the well known definitions of constrained controllability in $[0,T]$ for semilinear dynamical system.

Definition 4.1. The dynamical system (3.1) 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 4.2. The dynamical system (3.1) is said to be U_c-globally controllable in $[0,T]$ if $K_T(U_c) = X$.

The main result is the following sufficient condition for constrained local controllability of the semilinear dynamical system (3.1) which will be used to study controllability of the models of combined anticancer therapy:

Theorem 4.3. *[17]. Suppose that*

1. $F(0) = 0$,
2. $U_c \subset U$ *is a closed and convex cone with vertex at zero,*
3. *the associated linear control system (3.2) is* U_c*-globally controllable in* $[0,T]$.

Then the semilinear stationary dynamical control system (3.1) is U_c*-locally controllable in* $[0,T]$.

To verify the assumption (3) about constrained global controllability of the linear time invariant dynamical system, we may use the following Theorem 4.4.

Theorem 4.4. *[17]. Suppose the set* U_c *is a cone with vertex at zero and nonempty interior in the space* $\mathbb{R}^m$. *Then the associated linear dynamical control system (3.2) is* U_c*-globally controllable in* $[0,T]$ *if and only if*

1. *it is controllable without any constraints, i.e.*

$$rank\left[B, CB, C^2B, \ldots, C^{n-1}B\right] = n \tag{4.2}$$

2. *there is no real eigenvector* $w \in \mathbb{R}^n$ *of the matrix* C^{tr} *satisfying inequalities*

$$w^{tr}Bu \leq 0, \quad for\ all\ \ \underline{u} \in U_c \tag{4.3}$$

where C^{tr} *is a transposition of matrix* C.

The theorems could be proved using the generalized open mapping theorem (for proof see [17]). The second condition could be also interpreted in the following way: For each real eigenvector $w \in \mathbb{R}^n$ of the matrix C^{tr} there exist such controls $\underline{u} \in U_c$ that $w^{tr}B\underline{u}$ changes its sign. Moreover for single input systems this condition is equivalent to the requirement that matrix C has only complex eigenvalues (see Corollary from [17]).

In the case of systems with delays there exist even more possible definitions of controllability which may be used. This variety is related to different understanding of a notion of state of dynamical system in this case. We shall concentrate on two concepts namely constrained relative and constrained absolute controllability.

We use similar definition of the attainable set as before however we should remember that in this case the zero initial conditions are defined as: $\underline{x}_0 = 0$, $\underline{u}_0 = 0$, and the set of admissible controls $L_\infty([0,T], U_c)$ is a cone in the linear space $L_\infty([0,T], U)$. Thus the attainable set at time $T > 0$ from zero initial conditions is defined as:

$$K_T(U_c) = \{\underline{x} \in X : \underline{x} = \underline{x}(T, \underline{u}),\ \underline{u}(t) \in L_\infty([0,T], U_c)\} \tag{4.4}$$

We are led to the following definitions of local and global constrained relative controllability:

Definition 4.5. The dynamical system (3.8) is said to be U_c-locally relatively controllable in $[0,T]$ if the attainable set $K_T(U_c)$ contains a neighborhood of zero in the space X.

Definition 4.6. The dynamical system (3.8) is said to be U_c-globally relatively controllable in $[0,T]$ if $K_T(U_c) = X$.

Relative controllability of the system guarantees that $\underline{x}$ reaches a desired point in the given final time T but does not assure that it will stay in this point after T even if the control will be equal to 0. This problem may be solved by absolute controllability. Definitions of the absolute controllability are related to a concept of a complete state of the system with delays in control defined by vectors $\underline{x}(t)$ from space X and functions $\underline{u}$ defined on the interval $[t-h,t]$. More precisely for local (global) absolute constrained controllability we have:

Definition 4.7. The dynamical system (3.8) is said to be U_c-locally absolutely controllable in $[0,T]$, $T > h$, if for any given function $\underline{u}_1 \in L_\infty([T-h,T],U_c)$ the attainable set $K_T(U_c)$ contains a neighborhood of zero in the space X and $\underline{u} = \underline{u}_1$ for $t \in [T-h,T]$.

Definition 4.8. The dynamical system (3.8) is said to be U_c-globally absolutely controllable in $[0,T]$, $T > h$, if for any given function $\underline{u}_1 \in L_\infty([T-h,T],U_c)$ the attainable set $K_T(U_c) = X$ and $\underline{u} = \underline{u}_1$ for $t \in [T-h,T]$.

Before formulating counterparts of Theorems 4.3 and 4.4 for relative controllability of semilinear systems with delays let us denote $D = [b_0 \ b_1]$. Then we have:

Theorem 4.9. *[18]. Suppose that*

1. $F(0) = 0$,
2. $U_c \subset U$ *is a closed and convex cone with vertex at zero,*
3. *the associated linear control system (3.9) is* U_c*-globally relatively controllable in* $[0,T]$*. Then the semilinear stationary dynamical control system (3.1) is* U_c*-locally relatively controllable in* $[0,T]$.

Theorem 4.10. *[18]. Suppose that the set* U_c *is a cone with vertex at zero and nonempty interior in the space* $\mathbb{R}^m$*. Then the associated linear dynamical control system (3.2) is* U_c*-globally relatively controllable in* $[0,T]$, $T > h$ *if and only if*

1. *it is controllable without any constraints, i.e.*

$$rank\left[D, CD, C^2D, \ldots, C^{n-1}D\right] = n \tag{4.5}$$

2. *there is no real eigenvector* $w \in \mathbb{R}^n$ *of the matrix* C^{tr} *satisfying inequalities:*

$$w^{tr} D\underline{u} \leq 0, \quad \text{for all} \quad \underline{u} \in U_c \tag{4.6}$$

Once more the theorems could be proved using the generalized open mapping theorem (for proof see [18]).

Now, let us use conditions given above to check constrained local controllability of the model of combined anticancer therapy presented in the previous section. We start with the model without delays. 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. The admissible controls are assumed to be positive, hence the set of admissible controls is a positive cone U_c in the space $\mathbb{R}^2$. In [19] we have studied controllability properties for the simplified model with vascular- induced angiogenesis and Gompertz type growth of the tumor (eqns. (3.4), (3.7)). We have found that sufficient conditions of constrained local controllability for the combined therapy are always satisfied while for treatment by antiangiogenic agents alone are satisfied only for special combination of model parameters.

In this paper we study constrained local controllability of the original Hahnfeldt model with the combined anticancer therapy described by the semilinear differential state equations (3.4), (3.5) defined in a given time interval $[0,T]$.

Therefore, taking into account the general form of semilinear dynamical systems we have:

$$A = \begin{bmatrix} -1 & 1 \\ 0 & 0 \end{bmatrix}, F(x,y) = \begin{bmatrix} 0 \\ \vartheta\left(e^{x-y} - e^{(2/3)x}\right) \end{bmatrix}, B = \begin{bmatrix} 0 & -\varepsilon \\ -\sigma & \varsigma \end{bmatrix}. \tag{4.7}$$

And we have:

$$F(0,0) = \begin{bmatrix} 0 \\ 0 \end{bmatrix}, F_{\underline{x}}(0,0) = \begin{bmatrix} 0 & 0 \\ -\vartheta^{2/3} & 0 \end{bmatrix}, C = A + F_{\underline{x}}(0,0) = \begin{bmatrix} -1 & 1 \\ -\vartheta^{2/3} & 0 \end{bmatrix}$$

In order to consider controllability of dynamical system (3.1) we use Theorems 4.9 and 4.10 presented in this section.

Characteristic polynomial $P(s)$ for matrix C^{tr} has the form:

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

Hence $\Delta(\vartheta) = \vartheta^2 - \frac{2}{3}\vartheta + 1 > 0$.

It means that there are always two real eigenvalues leading to conclusion that in the case of single input (i.e. monotherapy) sufficient condition of local constrained controllability is not satisfied (see Corollary from [17]).

For controllability verification in the case of two control variables (the combined therapy) we use Theorem 4.4.

Since $rank B = 2$ then

$$rank\left[B \;\; CB\right] = 2 = n.$$

The eigenvalues have the following form:

$$s_1 = 0.5\left(-1 - \vartheta - \sqrt{\Delta(\vartheta)}\right) < 0$$

$$s_1 = 0.5\left(-1 - \vartheta + \sqrt{\Delta(\vartheta)}\right) < 0$$

and the corresponding real eigenvectors are

$$w_1 = \begin{bmatrix} -1 \\ (\vartheta + s_1)^{-1} \end{bmatrix}, \; w_2 = \begin{bmatrix} -1 \\ (\vartheta + s_2)^{-1} \end{bmatrix}.$$

Thus

$$w_1^{tr} B\underline{u} = -(\vartheta + s_1)^{-1}\sigma u + \left(\varepsilon - (\vartheta + s_1)^{-1}\varsigma\right)v \tag{4.8}$$

$$w_2^{tr} B\underline{u} = -(\vartheta + s_2)^{-1}\sigma u + \left(\varepsilon - (\vartheta + s_2)^{-1}\varsigma\right)v. \tag{4.9}$$

We can check that there exists a combination of admissible controls that the expressions (4.8), (4.9) will change their signs. Therefore the sufficient condition of local constrained controllability is satisfied for the combined therapy. The conditions of local controllability do not change if we model cancer population growth by logistic type equation instead of the Gompertz type one. The reason is the same linear approximation of both equations.

Now we are in position to study local controllability of the model containing delay in control variable v responsible for chemotherapy (3.10), (3.11). From practical point of view relative controllability is more interesting (and easier for study), thus we will concentrate on this type of controllability. Thus we can use Theorems 4.9 and 4.10 to find sufficient conditions of local relative controllability of model (3.12), (3.13). Since in this case matrix C is the same as in the case of the model without delay and matrix $D = B$ defined by (4.7), condition (4.5) is satisfied and formulae (4.8), (4.9) lead to similar conclusions as for the model without delay. Therefore the sufficient condition of local constrained relative controllability is satisfied assuming that the treatment horizon is greater than the delay h. In the case when $T < h$, only one control variable u (without delay) governs the state variables. Thus, as previously found sufficient condition of local constrained controllability is not satisfied (eigenvalues are real).

5. Conclusion

Combination of antiangiogenic therapy with conventional treatment is one of the most inspiring approaches in modern oncology. There are also proposals for multi-inhibiting formation of tumor blood vessels. From a mathematical point of view, the influence of more than one therapy and not only one kind of drugs becomes a multi-control problem. Antiangiogenic agents are not efficient at the level suggested by clinical trials, and depending on the disease stage different results are reported. Two main objectives of such therapy are considered: the first is related to the main goal of any anticancer therapy i.e. eradication of tumor and overall survival benefits, the second is to normalize the abnormal vasculature thereby facilitating drug delivery. It leads to different requirements regarding final states of models describing dynamics of tumor growth in the presence of developing vascularization and anticancer treatment. The natural question arising in this case is whether arbitrary final states could be reached in final treatment time using feasible treatment protocols. This question is, at least theoretically answered by conditions of controllability for such models. In the paper we have analyzed this problem for the model proposed by Hahnfeldt et al. endowed with control variables describing effects of chemotherapy and angiogenic therapy. To include PK/PD effects in the model we propose to introduce delays in control variables. Yet another reason for delays in chemotherapy dosing is related to an idea that angiogenic therapy should be implemented first considering that the vascular network should be normalized before chemotherapy The important finding presented in the paper is that sufficient conditions of local constrained controllability for the simple model of combined therapy are satisfied and it is not true when only antiangiogenic therapy is applied. Moreover for the model with delay in control variable responsible for chemotherapy it is proved that local relative controllability is ensured if only the treatment horizon is greater than the delay. The conditions are independent of the type of growth equation used for description of the cancer growth dynamics (Gompertzian or logistic ones). The problem can be easily extended for the case of different delays appearing in both control variable. The same theorems may be used in this case. Recently results of clinical trials with two angiogenic inhibitors characterized by different half-lives combined with chemostatic agents have been reported. It may be described by the model in which multiple delays for the same control variable are used. The analysis may be based on the same theorems. The qualitatively different machinery should be used when delays in state variables are included in the model as proposed in [5]. Such problems lead to other notions of controllability which should be applied and different mathematical tools for its analysis.

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References

[1] G. Bergers, D. Hanahan. *Modes of resistance to anti-angiogenic therapy.* Nature Reviews Cancer, 8 (2008) 592–603.

[2] A. Czornik, A. Świerniak. *On controllability with respect to the expectation of discrete time jump linear systems.* Journal of the Franklin Institute, 338 (2001), no. 4, 443–453.

[3] A. Czornik, A. Świerniak. *On direct controllability of discrete time jump linear system.* Journal of the Franklin Institute, 341 (2004), no. 6, 491–503.

[4] M. Dolbniak, A. Swierniak. *Comparison of simple models of periodic protocols for combined anticancer therapy.* Computational and Mathematical Methods in Medicine, (2013), Article ID 567213, doi: 11.1055/2013/567213.

[5] A. D'Onofrio, A. Gandolfi. *A family of models of angiogenesis and antiangiogenesis anti-cancer therapy.* Mathematical Medicine and Biology, 26 (2009), 63–69.

[6] A. D'Onofrio, A. Gandolfi. *Chemotherapy of vascularised tumours: role of vessel density and the effect of vascular "pruning".* Journal of Theoretical Biology, 264 (2010), 253–265.

[7] A. D'Onofrio, A. Gandolfi. *Tumour eradication by antiangiogenic therapy: analysis and extensions of the model by Hahnfeldt et al.* (1999), Mathematical Biosciences, 191 (2004), 159–184.

[8] J.M.L. Ebos, R.S. Kerbel. *Antiangiogenic therapy: impact on invasion, disease progression, and metastasis.* Nature Reviews Clinical Oncology, 8 (2011), 210–221.

[9] A. Ergun, K. Camphausen, L.M. Wein. *Optimal scheduling of radiotherapy and angiogenic inhibitors.* Bulletin of Mathematical Biology, 65 (2003), 407.

[10] J. Folkman. *Tumor angiogenesis: therapeutic implications*, N. Engl. J. Med., 295 (1971), 1182–1186.

[11] J. Folkman. *Antiangiogenesis: new concept for therapy of solid tumors*. Ann. Surg., 175 (1972), 409–416.

[12] P. Hahnfeldt, D. Panigrahy, J. Folkman, L. Hlatky. *Tumor development under angiogenic signaling: A dynamical theory of tumor growth, treatment response and postvascular dormancy*. Cancer Research, 59 (1999), 4770–4775.

[13] D. Hanahan, R.A. Weinberg. *Hallmarks of Cancer: The Next Generation*. Cell, 144 (2011), 647–670.

[14] R.K. Jain. *Normalization of tumor vasculature and microenvironment in antiangiogenic therapies*. ASCO Annual Meeting, (2007), 412–417.

[15] R.S. Kerbel. *A cancer therapy resistant to resistance*. Nature, 390 (1997), 335–340.

[16] J. Klamka, Controllability of Dynamical Systems, Kluwer Academic Publishers, Dordrecht, Netherlands, 1991.

[17] J. Klamka. *Constrained controllability of nonlinear systems*. J. Math. Anal. Appl., 201 (1996), 365–374.

[18] J. Klamka. *Constrained controllability of semilinear systems with multiple delays in control*. Bull. PAS, Techn. Sci., 52 (2004), 25-30.

[19] J. Klamka, A. Swierniak. *Controllability of a model of combined anticancer therapy*. Control and Cybernetics, 42 (2013), 125–138.

[20] T. Li-Song, J. Ke-Tao, H. Kui-Feng, W. Hao-Hao, C. Jiang, Y. De-Cao. *Advances in combination of antiangiogenic agents targeting VEGF-binding and conventional chemotherapy and radiation for cancer treatment*. Journal of the Chinese Medical Association, 73 (2010), no. 6, 281–288.

[21] J. Ma, D.J. Waxman. *Combination of anti-angiogenesis with chemotherapy for more effective cancer treatment*. Molecular Cancer Therapeutics, 7 (2010), no. 12, 3670–3684.

[22] S.R. McDougall, A.R. Anderson, M.A. Chaplain, J.A. Sherratt. *Mathematical modeling of flow through vascular networks: implications for tumour-induced angiogenesis and chemotherapy strategies*. Bulletin of Mathematical Biology, 64 (2002), no. 4, 673–702.

[23] M.J. Piotrowska, U. Forys. *Analysis of the Hopf bifurcation for the family of angiogenic models*. Journal of Mathematical Analysis and Applications, 382 (2011), 180–203.

[24] A. Swierniak. *Comparison of six models of antiangiogenic therapy*. Applicationes Mathematicae, 36 (2009), no. 3, 333–348.

[25] A. Swierniak. *Direct and indirect control of cancer populations*. Bulletin of the Polish Academy of Sciences, Technical Sciences, 56 (2008), 367–378.

[26] A. Swierniak, J. Klamka. *Control properties of models of antiangiogenic therapy*. in: Advances in Automatics and Robotics (K. Malinowski and R. Dindorf R. Eds.), Monograph of Committee of Automatics and Robotics PAS, 16 (2011), no. 2, 300–312.