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Comparison of Controllability Conditions for Models of Antiangiogenic and Combined Anticancer Therapy

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Abstract: We compare sufficient conditions for local controllability for a class of models of treatment response to antiangiogenic and combined anticancer therapies. The combined therapy is understood as combination of direct anticancer strategy e.g. chemotherapy and indirect modality (in this case antiangiogenic therapy). We discuss different control objectives related to multimodal therapies in the light of present knowledge of self-organization of tumor cell populations treated by anticancer drugs. Controllability of the models in the form of semilinear second order dynamic systems enables to expect that the objectives could be reached.

Keywords: multimodal therapy, constrained controllability, semilinear systems, cancer modeling.

1. INTRODUCTION

Self-organization of tumor cells is nowadays understood as a major obstacle against successful anticancer therapies. It leads among others to emergency of drug resistance in the response to chemotherapy and development of autonomous vascular network in the process of tumor angiogenesis. The site of action of almost all traditional cytotoxic drugs is the cellular DNA or the processes associated with this DNA. Drug resistance in cancer is common. Some tumors 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. 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. 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 [Hanahan et al. (2011)]. 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 formated vascular network becomes a bound for the size of the tumor. Taking this in account Judah Folkman [Folkman (1971, 1972)] proposed 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 in an arbitrary point. 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 in [Kerbel (1997)] a therapy resistant to drug resistance. Being directed against tumor vasculature the therapy does not exploit tumor cell sensitivity, relying instead on tumor suppression consequent to inhibition of associated vasculature. 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, 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 [Ebos et al. (2011)] 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 [Bergers et al. (2008)]. Nowadays antiangiogenic therapy is considered rather as an essential component of multidrug cancer therapy ([Li-Song et al. (2010)], [Ma et al. (2010)]), 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 [D'Onofrio et al. (2010)], [Jain (2011)]. 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.

The questions which of these goals 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. [Klamka (1991, 1996)], and references therein). In the present paper, we consider constrained local controllability problems for second-order finite-dimensional semilinear stationary dynamical systems described by the set of two ordinary differential state equations. More precisely we discuss a class of models proposed in [Hahnfeldt et al. (1999)] to which two control variables describing two treatment modalities have been introduced. 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 [D'Onofrio et al. (1999)] for antiangiogenic therapy [Swierniak et al. (2011)] and combined therapy [Klamka et al. (2013)] have been studied. The results are based on theorems proved in [Klamka (1996)]. The idea of the theorems is that under suitable assumptions constrained global controllability of a linear first-order associated approximated dynamical system implies constrained local controllability near the origin of the original semilinear second-order dynamical system. Moreover we find similar conditions for controllability for the original Hahnfeldt et al. model [Hahnfeldt et al. (1999)] and discuss differences and similarities. We compare results published by us previously with those obtained recently (not published yet).

2. TWO COMPARTMENTAL MODELS OF CANCER GROWTH INCLUDING VASCULARIZATION

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. [McDougall et al. (2010)]). Nevertheless, such models are difficult for mathematical analysis and almost not tractable when used for designing of treatment protocols. In [Hahnfeldt et al. (1999)] a model based on experimental data from anti-angiogenic therapy and non-therapy trials of Lewis lung tumors in mice is proposed. 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 vascular network growth, 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. 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 [Swierniak (2008)]. The coefficients ψ, η, ξ are non-negative constants (conversion factors) that relate the dosages of anti-angiogenic (u) and cytostatic (v) agents (ψ is much greater than ξ).

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

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

Similar behaviour could be obtained if Gompertz type growth is substituted by logistic type one.

$$\dot{N} = -\beta N(1 - N/K) - \psi v N \tag{3}$$

The modification of this model, proposed in [D'Onofrio et al. (2004)] which also satisfies Hahnfeldt's suggestions described above assumes that the effect of *SF* and *MF* on the relative velocity of growth is constant while the *IF* is proportional to the active surface of the area of tumor being in contact with the vascular network and the same to the square of the tumor radius:

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

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 [Swierniak (2009)]. The interesting finding [D'Onofrio et al. (2004)] 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:

$$N^* = K^* = \left((\gamma - \mu)/\lambda\right)^{3/2} \tag{5}$$

This equilibrium point is both locally and globally asymptotically stable. The line of reasoning is based on the Lyapunov type analysis. In [Ergun et al. (2003)] yet another simplified model which also satisfies assertions proposed in [Hahnfeldt et al. (1999)] has been proposed but the dynamics of vessel carrying support is independent of the size of the tumor:

$$\dot{K} = \gamma K^{2/3} - \lambda K^{4/3} - \eta u K - \xi v K \tag{6}$$

Moreover this model does not contain the natural mortality factor. Although this term has been present in previously discussed models all simulation results presented by the authors are obtained for $\mu = 0$. 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. (2003)] model:

$$N^* = K^* = (\gamma/\lambda)^{3/2} \tag{7}$$

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 [Swierniak (2008)] 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 (1), (4) or (3), (4) is given by:

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

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. 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 [Dolbniak et al. (2013)] results of simulation for simple protocols of continuous and periodic therapy for finite treatment horizons are presented. Parameters proposed by Hahnfeldt et al. [Hahnfeldt et al. (1999)] were used in order to implement each model under similar conditions. In periodic treatment angiogenic treatment as the starting therapy has been implemented, to use a fact, that vascular network should be normalized before chemotherapy. Period for this protocols is 5 days. 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 volume was greater than for larger ones. In periodic protocols dose of the anti-angiogenic agents for Hahnfeldt et al. and its modifications was changed to a higher one. It was due to the fact that the previous value had no effect (d'Onofrio–Gandolfi modification) or only a small treatment effect (in Hahnfeldt et al. model). The therapeutic effect was smaller than during the continuous therapy. The dynamics of all models was similar.

In [D'Onofrio et al. (2010)] the role of vessel density (which can modulate the effect of drugs) and the effect of vascular "pruning" (by using anti-angiogenic drug in a combined therapy) was analysed and the authors proposed to modify the equation of tumor growth to the form

$$\dot{N} = -\beta N \ln(N/K) - \psi(K/N) v N \tag{8}$$

where $\psi(K/N)$ 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 in and inadequate for delivery of drugs or oxygen Based on functions described in [D'Onofrio et al. (2010)], it has been observed 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.

3. MODELS OF COMBINED THERAPY AS SEMILINEAR DYNAMICAL SYSTEMS

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

$$\dot{\underline{x}}(t) = A\underline{x}(t) + F\left(\underline{x}(t), \underline{u}(t)\right) + B\underline{u}(t) \tag{9}$$

with initial conditions: $\underline{x}(0)$, where the state $\underline{x}(t) \in \mathbb{R}^n$ and the control $\underline{u}(t) \in \mathbb{R}^n$, 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 $F(0,0) = 0$, and X and U 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 (9) is defined as:

$$\dot{\underline{z}}(t) = C\underline{z}(t) + B\underline{u}(t) \quad \text{for} \quad t \in [0, T] \tag{10}$$

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

$$C = A + F_x(0,0) \tag{11}$$

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 transformations 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:

$$\begin{aligned} &x = \ln N/N^*, \quad && y = \ln K/K^*, && x^* = y^* = 0, \\ &\tau = \beta t, && \vartheta = \gamma/\beta, && \overline{\vartheta} = (\lambda\gamma)^{1/2}/\beta, \\ &\dot{x} = dx/d\tau, && \dot{y} = dy/d\tau \end{aligned} \tag{12}$$

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

$$\begin{aligned} &\dot{x}(t) = y(t) - x(t) - \varepsilon v(t), \\ &\dot{y}(t) = \vartheta\left(1 - e^{(2/3)x(t)}\right) - \sigma u(t) - \varsigma v(t), \\ &\sigma = \eta/\beta \ , \varepsilon = \psi/\beta \ , \varsigma = \xi/\beta \end{aligned} \tag{13}$$

If Gompertz type growth of the tumor is substituted by the logistic type one (3) then the first equation of the model (13) has the form:

$$\dot{x}(t) = 1 - e^{y(t)-x(t)} - \varepsilon v(t) \tag{14}$$

Similarly if the dynamics of vasculature capacity is modelled by (2) as in Hanfeldt et al. study or by (6) as in [Ergun et al. (2003)] then the second equation of (13) should be substituted by:

$$\dot{y}(t) = \vartheta\left(e^{x(t)-y(t)} - e^{(2/3)x(t)}\right) - \sigma u(t) - \varsigma v(t) \tag{15}$$

or

$$\dot{y}(t) = \overline{\vartheta}\left(e^{-(1/3)y(t)} - e^{(1/3)y(t)}\right) - \sigma u(t) - \varsigma v(t) \tag{16}$$

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

4. SUFFICIENT CONDITIONS OF CONTROLLABILITY

For the semilinear dynamical system (9), 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:

$$K_T(U_c) = \left\{\underline{x} \in X:\ \underline{x} = \underline{x}(T,u)\,, \underline{u}(t) \in U_c\right\} \tag{17}$$

where $\underline{x}(t,u)$, $t > 0$ is the unique solution of the differential state equation (9) 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 1 The dynamical system (9) 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 (9) 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 (9) which will be used to study controllability of the models 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 (10) is U_c −globally controllable in $[0,T]$.

Then the semilinear stationary dynamical control system (9) is U_c −locally controllable in $[0,T]$.

To verify the assumption (iii) about constrained global controllability of the linear time-invariant dynamical system, we may use the following Theorem 2.

Theorem 2 [Klamka (1996)]. 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 (10) is U_c −globally controllable in $[0,T]$ if and only if

- it is controllable without any constraints, i.e.

$$rank[B, CB, C^2B, \ldots, C^{n-1}B] = n \tag{18}$$

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

$$w^{tr}B\underline{u} \le 0, \quad for\ all\ \ \underline{u} \in U_c \tag{19}$$

The theorems could be proved using the generalized open mapping theorem. 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} (transposition of matrix C) 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 [Klamka (1996)]).

Now, let us use these conditions to check constrained local controllability of the models of combined anticancer therapy presented in the previous section. 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 $\mathbb{R}^2$.

Taking into account the general form of the semilinear dynamic system we have for (13):

$$A = \begin{bmatrix} -1 & 1 \\ 0 & 0 \end{bmatrix}, \qquad F(x,y,u,v) = \begin{bmatrix} 0 \\ -\vartheta\left(e^{(2/3)x} - 1\right) \end{bmatrix},$$

$$B = \begin{bmatrix} 0 & -\varepsilon \\ -\sigma & -\varsigma \end{bmatrix}$$

Hence, we have

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

$$C = A + F_x(0,0,0,0) = \begin{bmatrix} -1 & 1 \\ -\vartheta^{2/3} & 0 \end{bmatrix} \tag{20}$$

As discussed in our paper [Klamka et al. (2013)] the rank condition for the linear associated system is always satisfied and if $\vartheta > 3/8$ characteristic polynomial have two complex eigenvalues:

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

$$s_2 = 0.5\left(-1 + j\sqrt{\Delta}\right) = 0.5\left(-1 + j\sqrt{1 - (8/3)\vartheta}\right)$$

then the system is constrained controllable.

For $\vartheta = 3/8$ we have one real eigenvalue $s_{12} = -0.5$ with multiplicity 2. The real eigenvector has the following form

$$w = [-1 \quad 2]^T$$

thus

$$w^{tr}B\underline{u} = -2\sigma u + (\varepsilon - 2\varsigma)v. \quad (21)$$

Since ψ is much greater than $\xi(\varepsilon \gg \varsigma)$ thus for each eigenvector (21) is changing sign depending on the values of admissible controls. Hence, taking into account the Theorem 2 the system is locally controllable with positive admissible controls.

For $\vartheta > 3/8$ we have two different real eigenvalues. Real eigenvalues have the following form:

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

$$s_2 = 0.5\left(-1 + \sqrt{1-(8/3)\vartheta}\right) < 0$$

and the corresponding real eigenvectors are

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

Thus,

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

$$w_2^{tr}B\underline{u} = s_2^{-1}\sigma u + (\varepsilon + s_2^{-1}\varsigma)v. \quad (22)$$

And similarly as in the previous case we can prove that the conditions of Theorem 2 are satisfied.

Summarizing semilinear dynamical system (13) is constrained controllable in a given time interval $[0,T]$ with positive controls. The important finding is that this property does not depend on parameters of the model estimation of which may be difficult. This may be not true if only one modality (e.g. only antiangiogenic therapy) is used. As it has been proved in [Swierniak et al. (2011)] local constrained controllability of the model of antiangiogenic therapy is guaranteed only when its parameters satisfy additional condition $\vartheta > 3/8$ which, as mentioned before, is the case of complex eigenvalues of the characteristic polynomial for the associated linear system. The interesting finding is that the obtained controllability conditions do not change if the logistic type growth equation is used instead of the Gompertz type one. The reason is that in both cases the linear associated systems are the same with matrix C given by (20).

Now, let us consider constrained local controllability of the original Hahnfeldt model of the combined anticancer therapy described by the semilinear differential state equations (15) with Gompertz type equation for tumor growth and defined in a given time interval $[0,T]$. Hence

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

$$\dot{y}(t) = \vartheta\left(e^{x(t)-y(t)} - e^{(2/3)x(t)}\right) - \sigma u(t) - \varsigma v(t), \quad (23)$$

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

$$A = \begin{bmatrix} -1 & 1 \\ 0 & 0 \end{bmatrix}, \qquad F(x,y,u,v) = \begin{bmatrix} 0 \\ \vartheta\left(e^{x-y} - e^{(2/3)x}\right) \end{bmatrix},$$

$$B = \begin{bmatrix} 0 & -\varepsilon \\ -\sigma & -\varsigma \end{bmatrix}, \qquad z = \begin{bmatrix} x \\ y \end{bmatrix}.$$

Thus, we have

$$F(0,0,0,0) = \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \quad F_z(0,0,0,0) = \begin{bmatrix} 0 & 0 \\ \frac{1}{3}\vartheta & -\vartheta \end{bmatrix},$$

$$C = A + F_z(0,0,0,0) = \begin{bmatrix} -1 & 1 \\ \frac{1}{3}\vartheta & -\vartheta \end{bmatrix}. \quad (24)$$

In order to consider controllability of dynamical system (23) we use Theorem 2 presented in this section.

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

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

$$s^2 + s(1+\vartheta) + \frac{2}{3}\vartheta.$$

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). For controllability verification in the case of two control variables (the combined therapy) we use, once more, Theorem 2.

Since $rank\ B = 2$ then

$$rank[B \quad CB] = 2 = n$$

The eigenvalues have the following form:

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

$$s_2 = 0.5\left(-1 - \vartheta + \sqrt{\Delta(\vartheta)}\right) < 0$$

and the corresponding real eigenvectors are

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

Thus,

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

$$w_2^{tr}B\underline{u} = -(\vartheta + s_2)^{-1}\sigma u + (\varepsilon - (\vartheta + s_2)^{-1}\varsigma)v. \quad (25)$$

We can check that there exists a combination of admissible controls that the expressions (25) will change their signs. Therefore once more 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.

5. CONCLUSIONS

In this study we have compared controllability conditions for a class of two-compartmental models of treatment response to antiangiogenic therapy and its combination with

chemotherapy. This type of cancer treatment is still in experimental and clinical trials. The results are promising however still 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 far from being complete. The important finding presented in the paper is that sufficient conditions of local constrained controllability for the simple models of combined therapy are satisfied that is generally not true when antiangiogenic therapy as a sinle treatment is used. In the case of the original Hahnfeldt model the sufficient condition of local constrained controllability for monotherapy is not satisfied at all and for its modification proposed by d'Onofrio and Gandolfi its satisfaction needs additional constraints on the system parameters. The conditions are independent of the type of growth equation used for description of the cancer growth dynamics (Gompertzian or logistic ones). The third model of this class presented in the paper proposed by Ergun et al. could be treated in similar way. The models discussed in the paper enable inclusion of some phenomena which may have both negative or positive effect on the results of therapy. One example is dependence of cytotoxic drug delivery on the structure of vascular network, its normalization and pruning by antiangiogenic inhibitors (e.g. (8)). Other phenomena which have not been discussed and could be easily incorporated in the models under discussion are *PK/PD* effects of both types of agents. Especially duration of the treatment protocols and cumulated dose of the drugs should be included because of long half-time of some antiangiogenic drugs One way to take this effect into account is incorporation delays in control dynamics We hope that its controllability could be also examined using theorems presented in [Klamka (2004)] based on the similar mathematical engine (generalized open mapping theorem).

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