CONTROL PROPERTIES OF TWO- AND THREE-COMPARTMENTAL MODELS OF COMBINED ANTICANCER THERAPY

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ABSTRACT
We present results of analysis and simulation experiments for a class of two- and three compartmental models of tumor response to anticancer combined therapy. Treatment protocols are treated as control actions for a dynamical system which describes vascular growth of tumor. The therapy consists of direct modality represented by chemotherapy and indirect one in the form of antiangiogenic therapy. We discuss differences in control properties of the models and compare results of simulations of theoretical and realistic protocols.

KEY WORDS
Combined anticancer therapy, biomedical modeling, antiangiogenic treatment

1. Introduction
It has been discovered than even small tumors need their own supply system in the form of autonomous vascular network for growth, development and, ultimately, for metastasis [11]. 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 in account Judah Folkman [8], [9] 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 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 by Kerbel [13] 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 [6] 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 [2].

Nowadays antiangiogenic therapy is considered rather as an essential component of multidrug cancer therapy [18, 19], 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 [4], [12]. 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-
administred cytotoxic drugs. In the periodic therapy the main goal of anti-angiogenic agents is to normalize tumor vasculature.

In the paper we analyze some models proposed in the literature from the point of view of these two aspects of the combined therapy and we compare some results related to these models presented in our previous papers and published by others.

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 behaviour and spatial organization leading to models in the form of partial differential equations (see e.g. [20]). Nevertheless, such models are difficult for mathematical analysis and almost not tractable when used for designing of treatment protocols.

Hahnfeldt et al. in 1999 [10] proposed a model 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 vascular network growth, includes stimuliators of angiogenesis (SF-characterized by parameter \( \gamma \)), inhibitory factors secreted by tumor cells (IF-characterized by \( \lambda \)) and natural mortality of the endothelial cells (MF-characterized by \( \mu \)). In this model \( \beta \) 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. 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 (see e.g. [20]). Nevertheless, such models are difficult for mathematical analysis and almost not tractable when used for designing of treatment protocols.

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:

\[
\dot{K} = \gamma K - \lambda KN^{2/3} - \mu K - \eta uK - \xi vK
\]  

Yet another simplification of the original Hahnfeldt model was proposed by Ergun et al. in 2003 [7].

The modification of this model, proposed by D’Onofrio and Gandolfi [5] 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 tumor and the same to the square of the tumor radius:

\[
\dot{K} = \gamma K - \lambda KN^{2/3} - \mu K - \eta uK - \xi vK
\]  

Combining two models of tumor growth and three associated models of vascular network growth we obtain six two-compartmental models properties of which have been compared in [21]. The interesting finding is that all these models when uncontrolled (without therapy) have the same equilibrium point defined by the same values of both variables \( N \) and \( K \). This equilibrium point is both locally and globally asymptotically stable. The line of reasoning is based on the Lyapunov type analysis.

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 but still they are closely related by linear map. More precisely condition for constant doses of antiangiogenic \( U \) and cytotoxic \( V \) drugs ensuring complete asymptotic removal of the tumor is given by:

\[
U + \xi V / \eta = (\gamma - \mu) / \eta \Rightarrow K^{*}, N^{*} \rightarrow 0
\]  

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.

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, and side effects cause that the parameters of treatment protocols and cumulated dose of the drugs should be

\[
\dot{N} = -\beta N \ln \left( \frac{N}{K} \right) - \psi v N
\]  

\[
\dot{K} = \gamma N - \lambda KN^{2/3} - \mu K - \eta uK - \xi vK
\]
bounded. Thus realistic control problems related to the combined anticancer therapy should be formulated as finite horizon control problems. In [3] results of simulation for simple protocols of continuous and periodic therapy for finite treatment horizons are presented. Parameters proposed by Hahnfeldt et al. [10] are 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 antiangiogenic 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.

Reachability of desired states of dynamical systems in finite control horizons could be checked using conditions of system controllability. Roughly speaking a system is controllable if it can be steered in finite time from arbitrary initial state into arbitrary final one using admissible set of controls. In the case of therapy protocols control variables are conically constrained. To our knowledge this important problem for the models of antiangiogenic and combined anticancer therapies was almost not considered in literature. In [14] we have proved that for the two-compartmental models of combined therapy sufficient conditions of local constrained controllability are satisfied independently of the parameters of these models. This statement is not true in the case of single input control system which is the case when only antiangiogenic therapy is applied. In this case parameters of the model should satisfy additional conditions to insure local constrained controllability. It is important to note that controllability property enables other formulation of control goals than only eradication of the tumor. For example we may require to ensure that vascular network in some control interval should have pre-specified size which is the case of normalization process mentioned in the introduction and discussed below.

In 2009 d’Onofrio and Gandolfi analyzed the role of vessel density [4] (which can modulate the effect of drugs) and the effect of vascular “pruning” (by using anti-angiogenic drug in a combined therapy).

\[ \dot{N} = -\beta N \ln \left( \frac{N}{K} \right) - \psi \left( \frac{K}{N} \right) v N \]  

(7)

\[ K = \gamma N - \lambda K N^{2/3} - \mu K - \eta uK - \xi vK \]  

(8)

where \( \psi \) is a function of vessel density \( K/N \). 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. This aspect is not included in original Hahnfeldt et al. model and it is the reason why we have decided to include modification of d’Onofrio – Gandolfi suggesting pruning effect in simulations [3]. During continuous treatment cancer has been easily eliminated, only when we have assumed that pruning effect is stabilizing on some level. Based on functions described in [4], it has been observed that the best properties of vascular network are when density (endothelial cells/cancer cells) is 2. If it is bigger than vascular network is unstable if less than 2, there are not enough blood vessels.

One way of overcoming drawbacks of asymptotic results is optimization of the combined therapy in finite optimization horizon. The first paper dealing with optimization of therapy combined of antiangiogenic treatment and radiotherapy is [7] where the simplified model (5) of vascular network growth is used and effect of radiotherapy is modeled by the so called linear-quadratic model. The control objective was formulated as maximization of tumor cure probability (TCP) that under assumptions about constant tumor cell density and clonogenic fraction leads to minimization of the final size of cancer cells population. Constraints on the size of cumulative dose of antiangiogenic agents and cumulative irradiation doses are introduced in the performance index due to the isoperimetric form of the optimal control problem. Ledzewicz and Schättler presented the rigorous mathematical treatment of optimal control problem for this model related to anti-angiogenic therapy [15] and they confirmed the results from [7] that optimal trajectory contains singular arcs. The same authors have considered an original Hahnfeldt et al. model [16] and found once more singular strategies as parts of optimal antiangiogenic protocols. Meanwhile in [24] optimal antiangiogenic strategies for d’Onofrio-Gandolfi model [5] have been considered and it has been proved that singular arcs are not feasible since there are no finite intervals of constant solutions to the adjoint equations. This leads to the conclusion that intermediate doses of the drug are not optimal and that the optimal protocol contains only switches between maximal dose and no drug intervals. The form of conditions allows to find recurrently the solution of the TPBVP composed of the state and co-state equations with bang-bang control found from the switching condition by using for example shooting algorithm. Depending on the values of system parameters there may be only one switch of the optimal control or the solution may be quasi periodic. The interesting finding is that a necessary condition for the multi-switching strategy is at the same time a sufficient condition of the local controllability of the model of antiangiogenic therapy. In [23] contrary to Ergun et al and Ledzewicz and Schattler where optimal control problem with free terminal time was discussed it has been proposed to optimize the protocol in
the fixed finite time of therapy. Similar properties were found for Hahnfeldt et al. model with logistic tumor growth [21]. Basing on these studies we have concluded that singularity of the optimal antiangiogenic strategies is not a generic property of this class of models but depends on the chosen form of this model and formulation of the primary optimization goal. Additionally it has been proposed to modify the control objective by including the measure of the vascular network in the performance index. By playing with weighting parameters we can take into account requirements related to the size of the vascular network in addition to minimization of the tumor size. Optimization of combination of antiangiogenic and chemo-therapies can be found only in few studies (one of the first papers is [17] containing a preliminary results for Hahnfeldt model). In [24] once more the model of d’Onofrio and Gandolfi [5] has been discussed and singular strategies for both therapies are not optimal. Moreover by selecting properly weighing coefficients one can find optimal strategies which could be regarded as realistic treatment protocols. Although pruning effect is not included explicitly in the model the optimal strategy is designed in a way which ensures such action (see [3]).

3. Three compartmental models of treatment response to combined therapy

Two-compartmental models do not include many effects which are essential for efficiency of the combination of standard chemotherapy with antiangiogenic treatment. The only model from this class which takes into account the role of vascularisation in drug delivery is the one proposed by d’Onofrio and Gandolfi (7), (8). Nevertheless this model does not include any measure of quality of the vascular network. This aspect is considered by Benzekry et al [1] in the three-compartmental model where division on mature and immature blood vessels is suggested. The model is described by the following equations:

\[ \dot{N} = -\beta N \ln \left( \frac{N}{M} \right) - \psi v NQM \] (9)
\[ \dot{M} = \varepsilon M - \tau I \] (10)
\[ \dot{I} = -\varepsilon M + \gamma N - \lambda IN^{2/3} - \eta uNQM \] (11)
\[ Q(t) = \frac{M(t)}{M(t) + I(t)} \] (12)

This model should be also treated as a modification of the Hahnfeldt et al model and includes stable (M – mature) and unstable (I – immature) vessels. Only stable vessels supply nutrients and oxygen and they are carrying capacity for cancer cells. Unstable vessels mature with a constant rate denoted by \( \varepsilon \), mature vessels have natural mortality \( \tau \). Stable vessels transport anti-angiogenic and cytostatic agents. Quality of vascular network (Q) is calculated and included in factors determining efficiency of the therapy. Simulations [3] show that this model especially for periodic therapies is the only one which allows to show that sometimes patients receiving a higher dose of antiangiogenic agent had shorter progression-free survival than those receiving a lower dose. On the other hand it does not allow to include pruning effect of the angiogenic agents, answering only in part for the question related to normalization procedures in the combined therapy. The theoretical analysis of the model and its use for synthesis of optimal and sub optimal protocols is much more difficult than for two-compartmental models.

All models discussed before neglect a few major obstacles limiting successful chemotherapy, among which, it is worth to mention drug resistance, phase dependence and pharmacodynamics / pharmacokinetics. When it comes to the emergency of the drug resistance in tumor chemotherapy, a possible solution might be a model combining one of the previously discussed models of angiogenesis with the simplest model of drug resistance.

Three-compartmental model of such type was proposed in [23], and it includes Hahnfeldt et al. model of vessel growth and two more equations. The first describes sensitive cancer cells (\( S \)), second - resistant cancer cells (\( R \)). \( N \) is the sum of all cancer cells:

\[ \dot{S} = -aS + \left( 1 - v - \frac{S}{K} \right) (2 - q) aS + rcR \] (13)
\[ \dot{R} = -cR + (2 - r) cR (1 - \frac{R}{K}) + (1 - v) qaS \] (14)
\[ \dot{K} = \gamma N - \lambda KN^{2/3} - \mu K - \eta uK - \xi vK \] (15)

Coefficients \( a \) and \( c \) stand for the inverse of the average transit times through compartments. The probability of mutations occurring during the process is described with \( q \) – the probability of mutation into resistive cell and \( r \) – the probability of mutation into sensitive cell. Chemotherapy and anti-angiogenic therapy are already incorporated into equations in the similar way as in previously discussed models. As in the original Hahnfeldt model the coefficients \( \eta, \xi \) are non-negative constants (conversion factors) that relate the dosages of anti-angiogenic (\( u \)) and cytostatic (\( v \)) agents.

Analysis of asymptotic properties of the model is much more difficult than for the two-compartmental models discussed before starting from the problem of finding equilibrium points. There are two such non-trivial equilibria satisfying assumptions imposed on the state variables of the model:
For the set of parameters used in simulation experiments [3] and taken from previously published papers it has been checked (basing on the linearization analysis) that the first equilibrium point is locally unstable while the second one locally asymptotically stable. The interesting finding from simulation experiments presented is that the results of simple continuous and periodic protocols are qualitatively similar for the three compartmental model as for the previously analyzed two-compartmental models [25]. From this point of view taking into account emergency of drug resistance in cancer cells does not change substantially results of the combined therapy. In the case of Bezenkry et al. model results are slightly different because the mature vessel are conserved that may confirm the ability of the combined therapy for vessel pruning. Synthesis of optimal treatment strategies for the three compartmental model is difficult nevertheless using results of optimization for two-compartmental models discussed before we can choose parameters of the performance index in the way which gives very promising results for this model [22]. Figure 1 presents results of such treatment protocol optimal for the Hahnfeldt et al. model applied to the three compartmental model (13)-(15). We can observe that this protocol results in required behavior of vascular network (its development in the first stage allowing for good delivery of chemotherapy) and graduate eradication of tumor. 

In [3] the outcome of combined therapy protocol already studied by experimentalists in which three different drugs were used [24] was studied. As angiogenic inhibitor Sunitinub (SU) was administered oral capsule daily for 2 weeks (14 days) followed by 1 week (7 days) off treatment. As cytostatic drugs: Cisplatin (CIS) [mg/m^2] – intravenous (IV) on Day 1 of each 21-day cycle with Capecitabine (CAP) [mg/m^2] – 800 oral tablets twice-a-day (BID) on Days 1-14 of each 21-day cycle or Oxaliplatin (OXA) [mg/m^2] – on Day 1 of each 21-day cycle with CAP. We assume that 1.7 m^2 is a standard human surface. Half-life of studied medicine: Cisplatin 30 – 100 hours (mean: 65 h ~ 3 days), Sunitinib: 40 – 60 hours (mean: 50 h ~ 2 days), Capecitabine: 38–45 minutes, Oxaliplatin (~10 - 25 minutes). 

In Hahnfeldt et al. model we included second cytostatic agents which have direct influence for cancer cells and indirect for endothelial cells. For protocol including SU, CIS and CAP biological results are quite similar to this obtained by mathematical simulation. The cytostatic drugs have a strong influence for both types of cells, that is why for small doses of anti-angiogenic inhibitors and larger cytotoxic ones we get better results than for bigger angiogenic and smaller cytotoxic ones. In the second case SU, OXA and CAP results were not agreement with the
experimental. Higher dose of all therapeutics cause relatively short progression – free survival, contrary to the mathematical simulation.

4. Conclusion

This paper is devoted to comparison of control properties of a set of two- and three-compartmental models of treatment response to combined anticancer therapy. We have overviewed some previous results giving credits to other authors when necessary. The models belong to the class first proposed by Hahnfeldt and coworkers with different modifications allowing inclusion of some phenomena which may have both negative or positive effect on the results of therapy. This includes dependence of cytotoxic drug delivery on the structure of vascular network, its normalization and pruning by antiangiogenic inhibitors, development of drug resistance in cancer cells. These modification did not change significantly dynamics of models. The models do not include an aspect of hypoxia, which occurs after single anti-angiogenesis monotherapy causing proliferation of cancer cell and metastasis. Examples showed that after anti-angiogenic therapy an average survival of patients could be worse than the survival of patients with no therapy or patient with higher dose on anti-angiogenic medicine have shorter progression-free survivals than this with lower one. Other phenomena which have not been discussed and could be easily incorporated in the models under discussion are phase dependence of the anticancer drugs and 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, their costs, and side effects.

We showed that in some cases simple mathematical protocols with varying treatment doses can predict behavior of results of the therapy or may serve as a basis for design of improved strategies.

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