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TUMOUR ANGIOGENESIS MODEL WITH VARIABLE VESSELS' EFFECTIVENESS

Abstract. We propose a model of vascular tumour growth, which generalises the well recognised model formulated by Hahnfeldt et al. in 1999. Our model is based on the same idea that the carrying capacity for any solid tumour depends on its vessel density but it also incorporates vasculature quality which may be lost during angiogenesis as recognised by Jain in 2005. In the model we assume that the loss of vessel quality affects the diffusion coefficient inside the tumour. We analyse basic mathematical properties of the proposed model and present some numerical simulations.

1. Introduction. The growth of a tumour under angiogenic signalling was successfully mathematically described by Hahnfeldt et al. in [14]. The biological validity of the Hahnfeldt et al. model confirmed by lab experiments makes it probably the most important model describing this aspect of tumour development. Several other studies have incorporated mathematical models for the development of tumour under angiogenic signalling: see [21] and references therein or [6], where also other processes connected with tumour growth are presented. Several models based on the Hahnfeldt et al. model are studied by different groups of researchers. D'Onofrio and Gandolfi [7, 8, 9] analysed these models from a dynamical systems point of view. Świerniak, Świerniak et al. [26, 27, 28] and Ledzewicz and Schättler [18, 19, 20, 17] studied these models as optimal control problems with the goal of designing optimal and suboptimal antiangiogenic protocols. In the literature we can also find models built on different assumptions (see e.g. [3, 2]) and other approaches to angiogenesis (see e.g. [4]). All models based on the Hahnfeldt et al. model take into account the influence

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of angiogenic stimulators and inhibitors on tumour growth. In our model we also incorporate a changing rate of tumour vessels' impairment. We base our assumptions on the precise description of the mechanism [29, 15, 16] and modulators [30] of angiogenesis.

When a tumour appears it grows without any vasculature as long as the limited oxygen and nutrition supplies from the surrounding tissues are sufficient. For further tumour growth, blood supplies need to be increased [29, 1]. Therefore, the tumour starts to produce chemical signals to begin angiogenesis. This is a process characterised by sprouting new blood vessels from existing ones to supply tissues with all needed components from blood. In adults its normal physiological role is restricted to wound healing, the menstrual cycle and pregnancy. In addition, it is critical during fetal development. Unfortunately, it is also a fundamental process connected with carcinogenesis and it depends on a large variety of stimulating and inhibiting factors [30].

Despite the essential role of angiogenesis in tumour growth, it has been discovered that tumour angiogenesis is highly pathological. Incorrect structure and poor efficiency of newly formed vessels are common tumour features [15, 16]. Healthy tissues are nourished by straight vessels, which ramify in predictable way to smaller ones and at the end to capillary tubes. Vessels which were build due to tumour stimuli are rather arranged in tangled knots. They connect with each other in a random way, some of their branches are excessively big, there appear additional immature capillary tubes or, what can be even worse, they do not exist in some tumour regions. In addition tumour vessels work poorly, because they are build incorrectly. It has been discovered that in some vessels blood stream is excessively rapid, in others excessively slow and in some of them it turns back periodically. This makes even distribution of drugs very difficult. In addition, some parts of vessels walls are poorly permeable, whereas other parts are very leaky. This is caused by incorrect structure of pores in vessels walls, which can have almost one hundred times larger diameter than in healthy tissue. Hence, it is almost impossible to maintain correct pressure gradient, which is essential in efficient exchange of oxygen, nutrient and drugs between vessels and cells. This also causes an increase of interstitial pressure which may lead to necrosis in some tumour regions. Some trials which were developed to investigate the tumour biology revealed that most of the administered dose of chemotherapy is not even absorbed by the tumour. Moreover, the absorbed part of the dose may not be evenly distributed in particular tumour regions. This makes effective tumour treatment difficult, because cells which do not get a sufficient amount of drug can survive, and even if they are only few, repeated tumour growth is inevitable.

In this paper, we propose a qualitative model for tumour growth under angiogenic stimulator/inhibitor control which incorporates a changing rate of tumour vessels' impairment. A simple analysis is followed by numerical simulations of untreated tumour growth as well as tumour growth under antiangiogenic treatment, chemotherapy and combined therapy. The model proposed follows the approach presented in [24, 25]. In those papers we have proposed an arbitrary form of the equation of vessels' impairment, while in the present work we try to combine it with the diffusion process.

2. Model presentation

2.1. Model derivation. Following the idea that the volume of any solid tumour depends on the vessels' carrying capacity, let the variables V, K denote the tumour volume and the vessels' carrying capacity, respectively. In [14] the basic Gompertzian [13] type of growth was proposed to describe the evolution of the tumour volume,

$$\dot{V} = -\lambda_1 V \ln\left(\frac{V}{K}\right), \tag{2.1}$$

which may be understood as a bi-directional control process: the tumour regulates the associated vascular growth or suppression, and in turn the tumour vasculature controls the tumour growth through its usual nutritive function [14]. In the case of constant carrying capacity dependent only on vessels in the tumour surroundings it illustrates well the empirically observed phenomenon that a tumour without any vasculature grows to a limited size.

To ascertain the nature of the carrying capacity dynamics, a diffusion-consumption equation was considered in [14]. This equation reads

$$D^2 \cdot \nabla^2 n(x,t) - cn(x,t) + s = \frac{\partial n(x,t)}{\partial t}, \qquad x \in \mathbb{R}^3, \tag{2.2}$$

where n is the concentration of a stimulator or inhibitor inside and outside the tumour, D^2 is the constant diffusion coefficient, c is the clearance rate, while $s = s_0$ inside and $s = 0$ outside the tumour is the rate of stimulator or inhibitor secretion. We suggest that D^2 is lower inside the tumour than outside. As in the case of the parameter s, the discontinuity of D^2 is biologically reasonable, because the microenvironment inside is highly pathological. Therefore, let us write $D^2 = \widetilde{D}^2$ inside and $D^2 = \overline{D}^2$ outside the tumour, where $\widetilde{D} < \overline{D}$.

Using equation (2.2) and assuming that the tumour is in a quasi-steady state and the concentration n is radially symmetric, the same derivation as in [14] leads to

$$\dot{K} = -\lambda_2 K + bV - d\frac{KV^{2/3}}{\widetilde{D}^2}. \tag{2.3}$$

The right-hand side terms are interpreted as the vessels' natural mortality, the effect of tumour stimulation, and the endogenous inhibition of previously generated vasculature, respectively. Using the argument from [14] we observe that $\widetilde{D}^2$ affects only the endogenous inhibition term, which is multiplied by $I = 1/\widetilde{D}^2$. I should be understood as a measure of vessels' impairment. For almost healthy vessels, the inhibition is slightly increased. If the vasculature is impaired significantly, that is, for large values of I, the inhibition is enormously large. Therefore, I should not be constant any longer. We suggest choosing for I a decreasing function of vessels' effectiveness, which is bounded by 1 and by the maximum admissible value of impairment. We do not consider infinite impairment, because a too high rate of it is lethal.

Now, we want to introduce the average value of vessels' effectiveness inside the tumour. It only depends on time and we denote it by $E(t)$. Let $E(t)$ be the ratio of the amount of nutrients and oxygen which may diffuse to tissue by pathological vessels to the maximal amount in the case of healthy vessels.

The vessels' impairment I decreases with the vessels' effectiveness E, so for simplicity we choose $E = 1/I$. Therefore,

$$E : \mathbb{R}_+ \to [E_{\min}, 1], \tag{2.4}$$

where $0 < E_{\min} = 1/I_{\max}$ is the minimal admissible effectiveness.

Of course, there are other possibilities of incorporating vessels' effectiveness defined as above in the Hahnfeldt et al. model. We may e.g. change the carrying capacity in the equation for V with a function of vessels' amount and their effectiveness.

To obtain the full description of the model we shall formulate an ODE for the variable E. As the variables V and K tend to move together [14], their difference reflects quite well the actual state of the angiogenesis process, that is, whether it is conducting or reversing. It has been experimentally confirmed that pathological angiogenesis is caused by overexpression of proangiogenic factors, e.g. VEGF, the vascular endothelial growth factor [15, 16]. In healthy tissue proangiogenic factors are balanced by natural inhibitors, e.g. trombospodin. The actual state of angiogenesis is strictly dependent on imbalance between stimulation and inhibition. Therefore, as the difference of V and K reflects the actual state of the angiogenesis process, we assume that the vessels' effectiveness starts to decrease when the carrying capacity overtakes the tumour volume. The dynamics of E should be a process bi-directionally controlled by V and K: E increases for $V > K$ and decreases for $V < K$. More precisely, in the case when $V > K$ we may expect that the carrying capacity decreases due to the inhibition of angiogenesis—the vessels' effectiveness increases. On the other hand, in the case when $V < K$ the tumour growth under angiogenic stimulation pro-

ceeds, so the overexpression of proangiogenic factors occurs—the vessels' effectiveness decreases. Of course, the dynamics of E should also depend on the magnitude of the angiogenic factors imbalance. We also incorporate the following assertions that are based on the definition of E:

(1) E is bounded by some positive minimum and maximum constant values ($E \in [E_{\min}, 1]$, where $0 < E_{\min}$).
(2) E changes faster in its middle values and more slowly near extreme values.

The above assumptions about the nature of the dynamics of E are satisfied for instance in the case of the following equation:

$$\dot{E} = g(1-E)(E-E_{\min})\left(\frac{V}{K}-1\right). \tag{2.5}$$

Combining equations (2.1), (2.3) and (2.5), we propose the following system of three ODEs describing tumour development under angiogenic signalling with dependence on vessel quality:

$$\begin{cases} \dot{V} = -\lambda_1 V \ln\left(\dfrac{V}{K}\right), \\ \dot{K} = -\lambda_2 K + bV - d\dfrac{KV^{2/3}}{E}, \\ \dot{E} = g(1-E)(E-E_{\min})\left(\dfrac{V}{K}-1\right). \end{cases} \tag{2.6}$$

Note that the value of the parameter g plays an essential role in the dynamics of E. Setting $g = 0$ and $E = 1$, we obtain the model of Hahnfeldt et al. from [14].

2.2. Basic mathematical properties of the model. In this subsection we prove theorems about existence and uniqueness of solutions and of an invariant set for the model (2.6). We analyse (2.6) in the phase space $\mathcal{S} = \{(v,k,e) : v,k \in \mathbb{R}_+, e \in [E_{\min}, 1]\}$ under the assumption that all the parameters are positive, in particular $E_{\min} < 1$.

THEOREM 2.1. *Every solution to* (2.6) *with initial data* (V_0, K_0, E_0) *in* $\mathcal{S}$ *exists and is unique on some interval* $(-\delta, +\delta)$.

Proof. The vector field corresponding to (2.6) is of class $\mathbf{C}^\infty$ in $\mathcal{S}$, and therefore the Picard–Lindelöf theorem [5] guarantees the existence and uniqueness of solution through every $x^* \in \mathcal{S}$. ∎

THEOREM 2.2. *The set* $\mathcal{S} = \{(v,k,e) : v,k \in \mathbb{R}_+, e \in [E_{\min}, 1]\}$ *is invariant for the system* (2.6).

Proof. The first equation of (2.6) is equivalent to the integral equation

$$V(t) = V(0)\exp\left(-\lambda \int_0^t \ln \frac{V(s)}{K}\, ds\right).$$

Therefore, $V(0) > 0$ implies $V(t) > 0$ for all $t > 0$.

For $K = 0$ we have $\dot{K} = bV > 0$ due to the positivity of V.

For every solution through $x^* \in \mathcal{S}$ with the last coordinate $E = 1$ or $E = E_{\min}$ we have $\dot{E} = 0$ for all t. Therefore, from the uniqueness of solution through x^*, a solution which starts from $\operatorname{int}(\mathcal{S})$ cannot reach points with the last coordinate equal to $E_{\min}$ or 1. This completes the proof. ∎

THEOREM 2.3. *For every $x^* \in \mathcal{S}$ the solution through x^* exists for every $t \geq 0$.*

Proof. From the forward invariance of the set $\mathcal{S}$ the following inequalities can be obtained easily:

$$E_{\min} \leq E(t) \leq 1 \quad \forall t \geq 0.$$

The inequality

$$\frac{x}{x+1} \leq \ln(1+x) \quad \text{for } x > -1$$

yields

$$\dot{V}(t) \leq -\lambda_1 V(t) + \lambda_1 K(t),$$

which together with the positivity of $V(t)$ implies

$$\dot{V}(t) \leq \lambda_1 K(t).$$

From the equation for $\dot{K}(t)$ we have

$$\dot{K}(t) \leq bV(t).$$

To prove the global existence of solutions one only needs to derive an upper bound of $K(t) + V(t)$. Using the previous inequalities we obtain

$$\frac{d(K(t)+V(t))}{dt} = \dot{V}(t) + \dot{K}(t) \leq \lambda_1 K(t) + bV(t) \leq \max(\lambda_1, b)(K(t)+V(t)).$$

Therefore we have

$$K(t) + V(t) \leq e^{\max(\lambda_1, b)t} \quad \forall t \geq 0,$$

which together with the non-negativity of $K(t)$ and $V(t)$ gives the assertion. ∎

It can be easily seen that steady states in the invariant set $\mathcal{S}$ exist if and only if $\lambda_2 < b$, and they lie on the curve

$$s(e) = \left(\left(\frac{(b-\lambda_2)e}{d}\right)^{3/2}, \left(\frac{(b-\lambda_2)e}{d}\right)^{3/2}, e\right),$$

where $e \in [E_{\min}, 1]$ is an arbitrary parameter. Therefore, we can expect that depending on the initial values, the solution can tend to different steady states.

2.3. Numerical simulations of tumour growth. This subsection presents the result of numerical simulations of the model described by (2.6). We performed a series of numerical simulations to see how the evolution of the vessels efficiency E influences the tumour growth. The following model parameters are fixed for all simulations:

$$\lambda_1 = 0.192, \quad \lambda_2 = 0, \quad b = 5.85, \quad d = 0.00873, \quad E_{\min} = 0.4.$$

The first four parameters have the same meaning as in the Hahnnfeldt et al. model, and their values were obtained in [14] by fitting model solutions to the results of laboratory experiments. The value of $E_{\min}$ is chosen arbitrarily. We also fixed the initial conditions at the following values:

$$V_0 = 200, \quad K_0 = 625, \quad E_0 = 0.9,$$

where the initial conditions for V and K are the same as in [14]. We change only the value of the parameter g to see how the dynamics of the variable E affects the tumour growth.

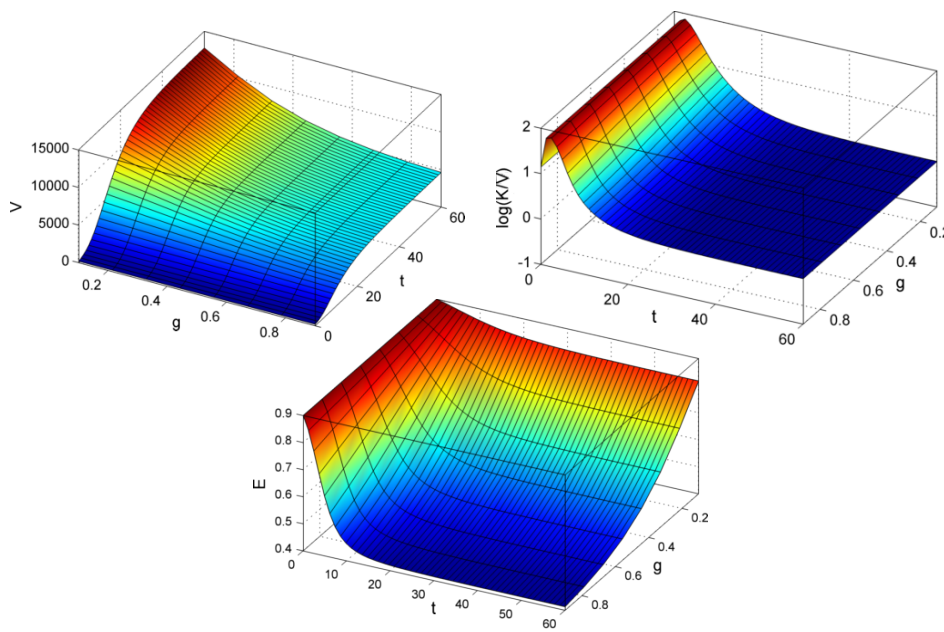

Fig. 1. Comparison between solutions to system (2.6) with different values of g

In Fig. 1 we present numerical simulations of untreated tumour growth. It can be seen that setting different values of the parameter g is reflected in

different values of the vessels efficiency that are reached asymptotically. It is obvious that different values of the variable E that are attained for large t provide different quantitative results for final values of the tumour volume and carrying capacity. As can be seen in Fig. 1, small g is reflected in small decrease in the vessels efficiency E which stabilises at a level close to the initial condition E_0. In that case we observe the highest asymptotic value of the tumour volume and carrying capacity. A high level of E indicates that the tumour has proper vessels structure. Thus, this type of tumour should be sensitive to treatment. Small g also provides the same qualitative and similar quantitative result as the Hahnfeldt et al. model.

If the values of g are higher, one can observe major changes of quantitative results for the values of all three modelled variables. For large g we can expect that the steady state with the lowest value of E is reached. In that case also the tumour volume and the vessels carrying capacity stabilise at a much lower level than in the case of small g. For large g the change in qualitative results for the carrying capacity dynamics can also be observed as it is no longer an increasing function. The low level of E indicates that the tumour has incorrect and highly inefficient vessel structure. Thus, despite the lower level of tumour volume, a lower efficiency of treatment is expected than in the case of small g.

Corollary 2.4. *Higher values of g are reflected in a slowdown of the tumour growth and in decrease of tumour vessels' efficiency. A lower value of E indicates worse vessels structure, which may be reflected in uneven spread of drugs, nutrition or oxygen inside the tumour region. Thus, it seems that higher values of the parameter g should make the tumour less responsive to treatment.*

3. Chemotherapy and antiangiogenic treatment. Let us now introduce to the model (2.6) two types of treatment that are common in today's medicine—antiangiogenic treatment and chemotherapy. Influencing the process of angiogenesis is currently one of the most important methods in cancer treatment. This method was proposed by Folkman [10]. However, its implementation was possible due to the discovery of antiangiogenic drugs by O'Reilly et al. (cf. [22, 23] and also [11, 12]). The effectiveness of this method is caused by a very small group of substances that cause formation of new blood vessels. Thus, it is easier to create universal drugs to fight cancer. We assume that chemotherapy and angiogenic inhibitors are administered as boli at times $t_1, \dots, t_n$. Under the usual pharmacokinetic assumptions [14] the concentration of drug at time t has the following form:

$$f(t, c, (A_1, \dots, A_n), (t_1, \dots, t_n)) = \exp(-ct) \sum_{i=1}^{n} A_i \exp(ct_i) \mathbb{1}_{[0,t)}(t_i), \tag{3.1}$$

where A_i is the amount of drug administered at time t_i and c is its clearance rate. The function $f(t,\cdot)$ generally includes partially cleared contributions from prior administration at earlier times $t' < t$. We assume that the same amount of drug is administered at each injection time, that is, $A_i = A$ for $i = 1, \ldots, n$. Exemplary plots of $f(t, c, A, (t_1, \ldots, t_n))$ are presented in Fig. 2.

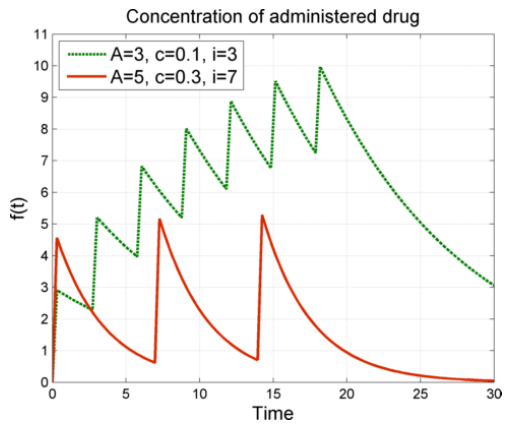

Fig. 2. Exemplary plots of $f(t,\cdot)$. We assume that the drug is administered from $t = 0$ till $t = 20$ at intervals of length i.

Let functions

$$\psi(t, \mathbf{p_a}) = f(t, c_a, A_a, (t_1^a, \ldots, t_n^a)) \quad \text{and} \quad \phi(t, \mathbf{p_c}) = f(t, c_c, A_c, (t_1^c, \ldots, t_n^c))$$

represent the amount of inhibitors and chemotherapy administered at time t, respectively. It is clear that the inhibitors only affect the dynamics of the carrying capacity K as they block signals to the further growth of vessels. For chemotherapy, despite its effect on the dynamics of the tumour volume, the influence on the carrying capacity should be included as chemotherapy is not cell selective and it affects endothelial cells which create vessels. The effectiveness of chemotherapy and antiangiogenic treatment is highly dependent on the possibility of its even distribution in all tumour regions. Therefore, we postulate that the effect of $\phi(t, \mathbf{p_c})$ and $\psi(t, \mathbf{p_a})$ should also be proportional to the vessels efficiency E. Under those assumptions we propose the following modification of the model 2.6:

$$\text{(3.2)} \qquad \begin{cases} \dot{V} = -\lambda_1 V \ln\left(\dfrac{V}{K}\right) - f_1 V E \psi(t, \mathbf{p_c}), \\ \dot{K} = -\lambda_2 K + bV - d\dfrac{KV^{2/3}}{E} - eKE\phi(t, \mathbf{p_a}) - f_2 KE\psi(t, \mathbf{p_c}), \\ \dot{E} = g(1-E)(E - E_{\min})\left(\dfrac{V}{K} - 1\right). \end{cases}$$

To compare the efficiency of each type of treatment we define the following function.

Definition 3.1. The function

$$s(t) = 1 - \frac{V^{ac}(t)}{V(t)}$$

is called the *treatment efficiency*, where $V(t)$ is the solution to (2.6), that is, the volume to which the tumour grows without any treatment, and $V^{ac}(t)$ is the solution to (3.2), that is, the volume of the treated tumour.

It is clear that for the same sets of parameters describing the tumour growth only a higher reduction of the tumour volume at time t caused by treatment will be reflected in a higher value of $s(t)$.

3.1. Numerical simulations of tumour treatment. In simulations with included treatment we use the following parameter values:

$$A_a = 8, \quad e = 0.38, \quad c_a = 0.15, \quad t_i^a = i,$$

for antiangiogenic treatment, and

$$A_c = 4, \quad f_1 = 0.15, \quad f_2 = 0.1, \quad c_c = 0.2, \quad t_i^c = 5i$$

for chemotherapy. We assume that the inhibitors and chemotherapy are administered every day and every five days, respectively. The values of the parameters for antiangiogenic treatment are the same as obtained by Hahnfeldt for Angiostatin [22]. We only change the value of g to see how the dynamics of the variable E affects the efficiency of tumour treatment.

3.1.1. *Antiangiogenic treatment.* As can be expected, Figs. 3 and 4 reveal that a strong decrease of E results in a decreased efficiency of antiangiogenic treatment. Therefore, even if a tumour reaches its dormant state at a much lower volume due to the low E, it is far less responsive to the treatment than a much bigger tumour but with a higher value of the vessels' efficiency E. This reflects the fact that if the vessels are of poor quality and are poorly organised the drug cannot be spread evenly and there can even be regions it does not reach. In addition, for medium values of g, antiangiogenic treatment causes normalisation of vasculature [16], that is, the carrying capacity stabilises at the state characterised by appropriate vessels' efficiency.

3.1.2. *Chemotherapy.* In the case of chemotherapy simulations presented in Fig. 6 and the plot of treatment effectiveness in Fig. 5 lead to conclusions similar to the case of antiangiogenic treatment, that is, if g is higher, then the efficiency of treatment is lower.

This also reflects the fact that if the vessels are of poor quality and are poorly organised, the drug cannot be spread evenly and there can even be regions it does not reach. In addition, as can be seen in Fig. 5 for small

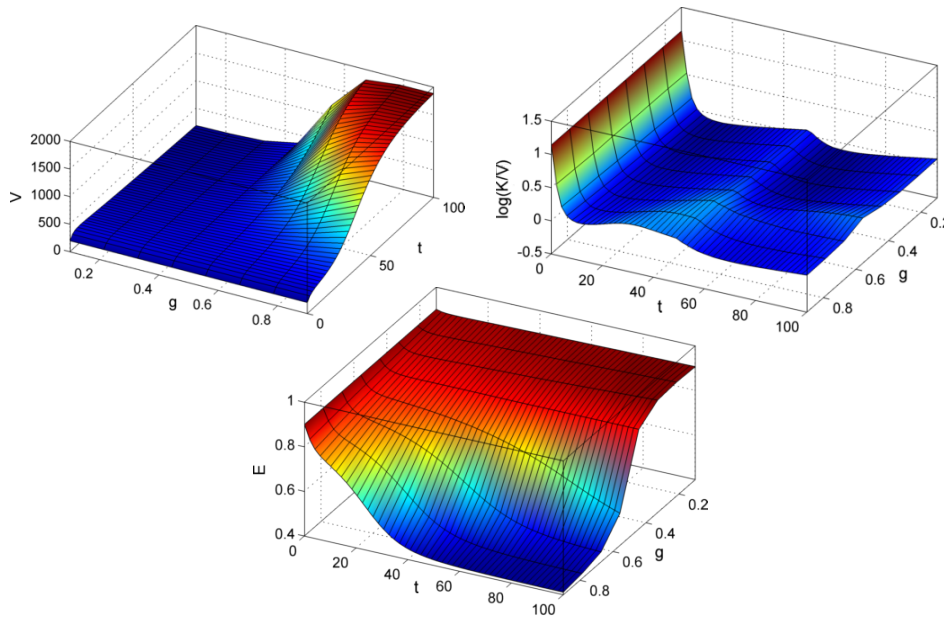

Fig. 3. Comparison between solutions to system (3.2) with only antiangiogenic treatment included and with different values of g

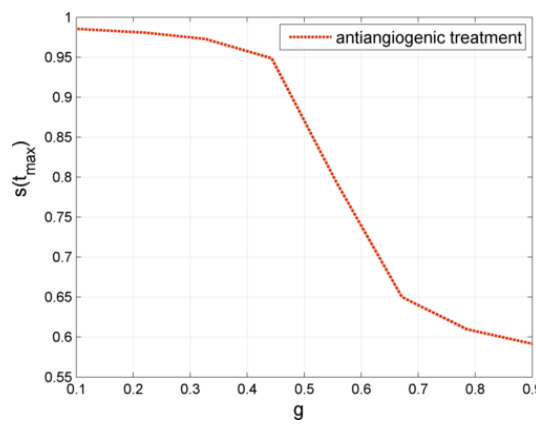

Fig. 4. Efficiency of antiangiogenic treatment at the end of simulation run $t_{\max}$ for different values of g

values of g, by administering chemotherapy we are able to reduce the tumour volume below its initial value. Unfortunately, that kind of reduction is only temporary as the therapy finally gives quantitative results similar to the case of high values of g. This can be explained by decreasing vessels' efficiency, due to the chemotherapy administration (see also the plot of E in Fig. 6). Therefore, independently of the initial value of E, chemotherapy

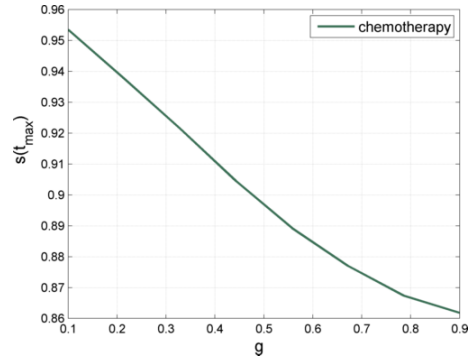

Fig. 5. Efficiency of chemotherapy at the end of simulation run $t_{\max}$ for different values of g

brings finally E to its minimal admissible value, which makes chemotherapy far less efficient.

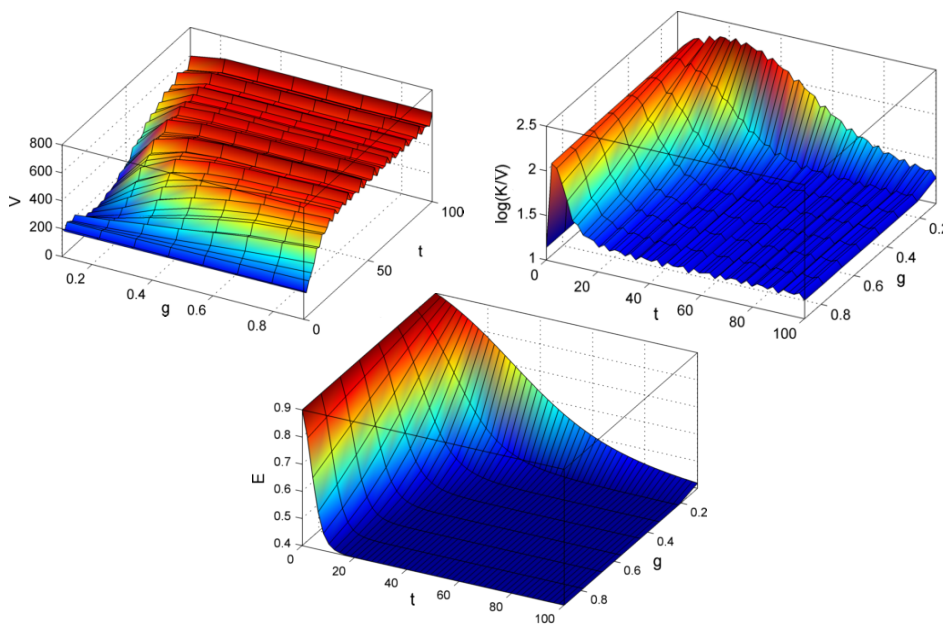

Fig. 6. Comparison between solutions to system (3.2) with only chemotherapy included and with different values of g

3.1.3. *Combined treatment.* As can be seen in Fig. 8, there is a major quantitative change in treatment effectiveness in the case of combined treatment. With the same doses of each treatment as in the case of separate therapies we fully suppress the tumour for all values of g. As in the previous cases, there is a dependence of treatment efficiency on the value of g (see

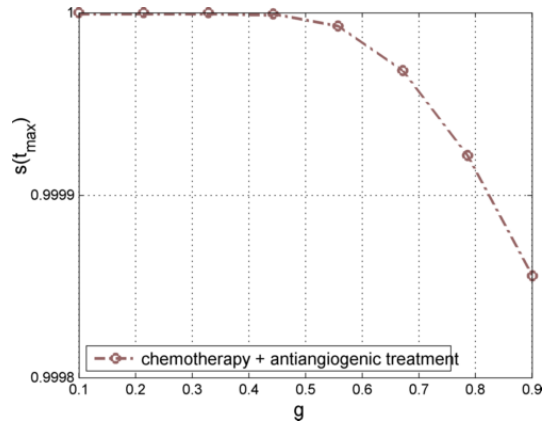

Fig. 7. Efficiency of chemotherapy combined with antiangiogenic treatment at the end of simulation run $t_{\max}$ for different values of g

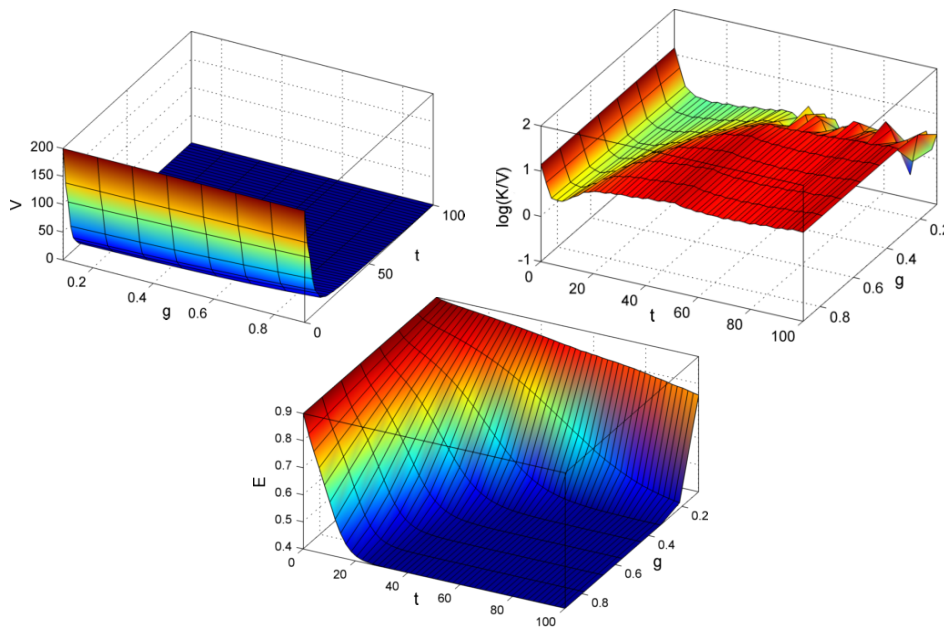

Fig. 8. Comparison between solutions to system (3.2) with both treatments included and with different values of g

Fig. 7) but in this case this dependence is negligible. That kind of change in quantitative results reflects the fact that increased survivorship of patients in the case when chemotherapy and antiangiogenic therapy were combined was observed in clinical trials. Of course, a major role may be played by the effect of accumulation of both therapies. Let us now define chemother-

apy contribution to the treatment as the last term of the first equation of system (3.2) divided by V:

$$C(t) = f_1 E(t)\psi(t, \mathbf{p_c}).$$

As can be seen in Fig. 10, in the case of combined treatment an increase of the mean chemotherapy contribution to the tumour treatment can be observed. In Fig. 10 also the exact value of that increase is presented. That kind of increase of the chemotherapy contribution can be explained biologically by vasculature normalisation effect, that is, increased vessels' effectiveness due to administering antiangiogenic inhibitors, which helps to hold a high chemotherapy efficiency for longer time.

In Fig. 9 we have compared the effectiveness of all types of treatment. It can be seen that combined treatment is far more efficient in every type of tumour growth.

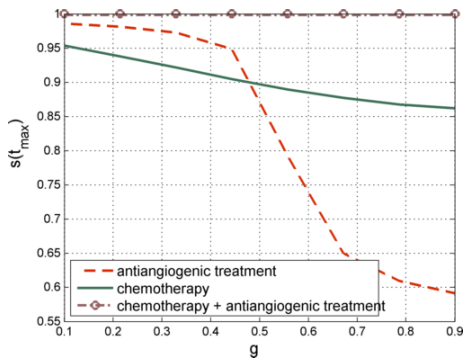

Fig. 9. Comparison of treatment efficiency at the end of simulation run $t_{\max}$ for three types of therapies: chemotherapy, antiangiogenic treatment and combination of those two therapies

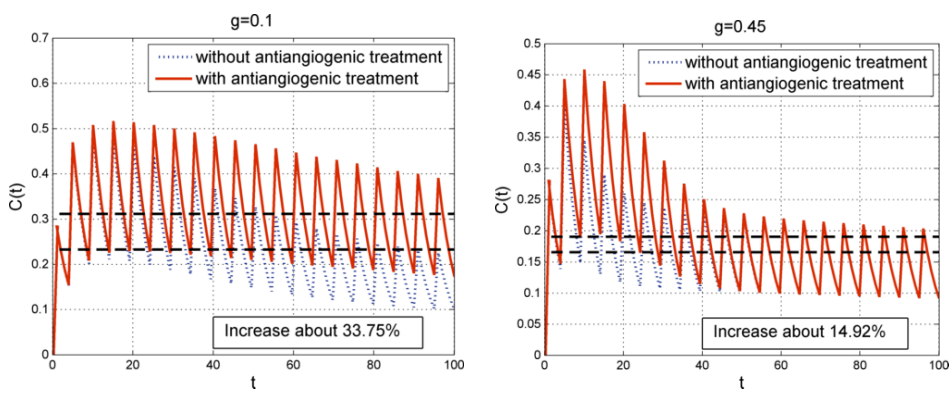

Fig. 10. Comparison between contributions of chemotherapy $C(t)$ to the tumour treatment with different parameter g values and in presence or absence of the antiangiogenic treatment. Horizontal lines are plots of mean chemotherapy contributions.

4. Summary. We have proposed a model of tumour growth described by a system of three ODEs that involve the tumour volume V, the vessel carrying capacity K and the average value E of vessels' effectiveness inside the tumour. We have mainly focused on the influence of the dynamics of E on the tumour growth and the effect of its treatment. Three types of treatment have been included in the model: standard chemotherapy, antiangiogenic therapy and a combined treatment.

In Section 1 we have explained the process of angiogenesis and its pathology in the case of cancerogenesis, while in Section 2 a model without treatment has been proposed. Moreover, in Subsection 2.2 some basic mathematical properties of the model have been described. It has been proven that for every x in an invariant set, there exists a unique solution to the system through x and it exists globally in time ($t \geq 0$). Under some conditions on the parameters, the set of steady states has been found.

Numerical simulations in Subsection 2.3 show that due to the different dynamics of the variable E, which depends on the value of only one parameter, different values of steady states can be reached.

In Section 3 we have introduced three types of treatment to the model and defined the function of treatment effectiveness. Moreover in Subsection 3.1 we have reported numerical simulations performed to compare results of all three types of treatment. This comparison revealed that a higher loss in the vessel efficiency E is reflected in lower effectiveness of each treatment, but only for combined treatment that effect is negligible. In addition, the numerical simulations show that only with the use of combined treatment we are able to suppress the tumour successfully.

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References

[1] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts and P. Walter, *Molecular Biology of Cell*, Garland Publ., New York, 2007.

[2] Z. Agur, L. Arakelyan, P. Daugulis, Y. Ginosar, *Hopf point analysis for angiogenesis models*, Discrete Contin. Dynam. Systems B 4 (2004), 29–38.

[3] L. Arakelyan, V. Vainstein, Z. Agur, *A computer algorithm describing the process of vessel formation and maturation, and its use for predicting the effects of anti-angiogenic and anti-maturation therapy on vascular tumor growth*, Angiogenesis 5 (2002), 203–214.

[4] M. Bodnar and U. Foryś, *Angiogenesis model with carrying capacity depending on vessel density*, J. Biol. Systems 17 (2009), 1–25.

[5] I. N. Bronshtein, K. A. Semendyayev, G. Musiol and H. Muehlig, *Handbook of Mathematics*, 5th ed., Springer, Berlin, 2007.

[6] *Cancer Modeling and Simulation*, ed. L. Preziosi, Chapman & Hall, 2003.
[7] A. d'Onofrio and A. Gandolfi, *Tumor eradication by antiangiogenic therapy: analysis and extensions of the model by Hahnfeldt et al. (1999)*, Math. Biosci. 191 (2004), 159–184.
[8] —, —, *The response to antiangiogenic anticancer drugs that inhibit endothelial cell proliferation*, Appl. Math. Comput. 181 (2006), 1155–1162.
[9] —, —, *A family of models of angiogenesis and antiangiogenesis anticancer therapy*, Math. Med. Biol. 26 (2009), 63–95.
[10] J. Folkman, *Tumor angiogenesis: Therapeutic implications*, N. Engl. J. Med. 285 (1971), 1182–1186.
[11] —, *Angiogenesis in cancer, vascular, rheumatoid and other disease*, Nat. Med. 1 (1995), 27–31.
[12] J. Folkman, *Angiogenesis*, Ann. Rev. Med. 57 (2006), 1–18.
[13] B. Gompertz, *On the nature of the function expressive of the law of human mortality, and a new mode of determining the value of life contingencies*, Philos. Trans. Roy. Soc. 115 (1825), 513–585.
[14] P. Hahnfeldt, D. Panigrahy, J. Folkman and L. Hlatky, *Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response and postvascular dormancy*, Cancer Res. 59 (1999), 4770–4775.
[15] R. K. Jain, *Taming vessels to treat cancer*, Scientific American 298 (2008), 56–63.
[16] —, *Normalization of tumour vasculature: an emerging concept in antiangiogenic therapy*, Science 307 (2005), 58–62.
[17] U. Ledzewicz and H. Schättler, *Optimal control for a system modeling tumor anti-angiogenesis*, in: Proc. ICGST Int. Conf. on Automatic Control and System Engineering, 2005, 147–152.
[18] —, —, *Antiangiogenic therapy in cancer treatment as an optimal control problem*, SIAM J. Control Optim. 46 (2007), 1052–1079.
[19] —, —, *Analysis of a mathematical model for tumor anti-angiogenesis*, Optim. Control Appl. Meth. 29 (2008), 41–57.
[20] —, —, *Optimal and suboptimal protocols for a class of mathematical models for tumor anti-angiogenesis*, J. Theor. Biol. 252 (2008), 295–312.
[21] N. V. Mantzaris, S. Webb and H. G. Othmer, *Mathematical modeling of tumor-induced angiogenesis*, J. Math. Biol. 49 (2004), 111–187.
[22] M. S. O'Reilly et al., *Angiostatin: A novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma*, Cell 79 (1994), 315–328.
[23] M. S. O'Reilly et al., *Endostatin: An endogenous inhibitor of angiogenesis and tumor growth*, ibid. 88 (1997), 277–285.
[24] J. Poleszczuk, *Tumor development model under angiogenic signaling with dependence on vessel impairment*, in: Proc. 14th National Conference on Application of Mathematics in Biology and Medicine, M. Bodnar and U. Foryś (eds.), Univ. of Warsaw, 2008, 104–109.
[25] J. Poleszczuk and U. Foryś, *Angiogenesis process with vessel impairment for Gompertzian and logistic type of tumour growth*, Appl. Math. (Warsaw) 36 (2009), 313–331.
[26] A. Świerniak, *Comparison of six models of antiangiogenic therapy*, ibid. 36 (2009), 333–348.
[27] A. Świerniak, G. Gala, A. Gandolfi and A. d'Onofrio, *Optimization of anti-angiogenic therapy as optimal control problem*, in: Proc. 4th IASTED Conf. on Biomechanics, ACTA Press, M. Doblaré (ed.), 2006, 56–60.
[28] A. Świerniak, A. d'Onofrio and A. Gandolfi, *Control problems related to tumor angiogenesis*, in: Proc. IEEE Industrial Electronics-IECON2006, Paris, 2006, 677–681.

[29] T. M. Zielonka, *Angiogenesis—Part I. Mechanisms of neovascularization*, Alergia Astma Immunologia 4 (2003), 169–174.

[30] —, *Angiogenesis—Part II. Modulators regulating neovascularization*, ibid. 1 (2004), 25–31.

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