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NEW APPROACH TO MODELING OF ANTIANGIOGENIC TREATMENT ON THE BASIS OF HAHNFELDT ET AL. MODEL

Jan Poleszczuk, Marek Bodnar and Urszula Foryś

University of Warsaw, Faculty of Mathematics, Informatics and Mechanics
Institute of Applied Mathematics and Mechanics
Banacha 2, 02-097 Warsaw, Poland

Abstract. In the paper we propose a new methodology in modeling of antiangiogenic treatment on the basis of well recognized model formulated by Hahnfeldt et al. in 1999. On the basis of the Hahnfeldt et al. model, with the usage of the optimal control theory, some protocols of antiangiogenic treatment were proposed. However, in our opinion the formulation of that model is valid only for the antivascular treatment, that is treatment that is focused on destroying endothelial cells. Therefore, we propose a modification of the original model which is valid in the case of the antiangiogenic treatment, that is treatment which is focused on blocking angiogenic signaling. We analyze basic mathematical properties of the proposed model and present some numerical simulations.

1. **Introduction.** In 1971 Judah Folman in [15] wrote that growth of any tumor is strongly dependent on the amount of blood vessels that it induces to grow. He surmised that, if a tumor could be stopped from growing its own blood supply, it would wither and die. In adults normal physiological role of angiogenesis – the process of new vessels formation – is restricted to wound healing, the menstrual cycle and pregnancy. In addition, angiogenesis is critical during fetal development. Unfortunately, it is also essential for the successful growth and development of solid tumors. After reaching avascular dormant state tumor can grow further only by inducing vessels in host tissue to sprout capillary tubes which migrate towards and ultimately penetrate the tumor, providing it with a circulating blood supply and, therefore, an additional source of nutrients [22, 23].

Despite the essential role of angiogenesis in tumor growth, it has been discovered that tumor angiogenesis is highly pathological. Incorrect structure and poor efficiency of newly formed vessels are common tumour features [22, 23]. Some trials which where developed to investigate tumor biology revealed that most of administrated dose of chemotherapy is not even absorbed by tumor. Moreover, absorbed part of dose was not distributed evenly in particular tumor regions. It makes effective tumour treatment difficult, because cells which does not get sufficient amount of drug can survive and even if they are only few repeated tumor growth is inevitable.

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The growth of tumor under angiogenic signalling was successfully mathematically described by Hahnfeldt et al. in [21]. Confirmed by lab experiments, biological validity of the Hahnfeldt et. al model makes it probably the most important model describing this aspect of tumor development. Several other studies have incorporated mathematical models for the development of tumor under angiogenic signalling: see [31] and references therein or [9], where also other processes connected with tumor growth are presented. A family of models based on the Hahnfeldt et al. model is an object of study of several groups of researchers. D'Onofrio and Gandolfi [10, 11, 12] analysed these models from a dynamical systems point of view. Świerniak, Świerniak et al. [36, 37, 38] and Ledzewicz and Schättler [28, 29, 30, 27] 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 assumptions (see e.g. [3, 2]) and approaches to angiogenesis (see e.g. [6]) different from those of the Hahnfeldt et al. model.

The classical Hahnfeldt et al. model with antiangiogenic treatment reads

$$\begin{aligned} \dot{V}(t) &= -\lambda_1 V(t) \ln \tfrac{V(t)}{K(t)}, \\ \dot{K}(t) &= -\lambda_2 K(t) + bV(t) - dK(t)\big(V(t)\big)^{2/3} - \gamma K(t) I(t), \end{aligned} \tag{1}$$

where V reflects the tumor volume and K is its carrying capacity, that is maximal tumor volume that current vasculature can support. The function $I(t)$ describes the concentration of drug which is typically referred as to antiangiogenic. However, the term $-\gamma K(t)I(t)$ is formed in the same way as the first term in the equation for $\dot{K}(t)$ which is assumed to describe the spontaneous loss of functional vasculature [21]. Therefore, we claim that this kind of treatment modeling can be referred only as to antivascular treatment, that is the treatment with the usage of vascular targeting agents (VTAs) which are designed to cause a rapid and selective shutdown of the blood vessels of tumors [39, 26]. In opposite to VTAs, antiangiogenic drugs are designed to inhibit the formation of new vessels on the level of signaling and therefore, in our opinion treatment with their usage needs another mathematical description. In this paper we make such description by modifying the derivation of the Hahnfeldt et. al model. We try to describe only those antiangiogenic agents which are designed to bind and block the proteins that are responsible for inducing growth of blood vessels (*eg.* VEGF — vascular endothelial growth factor [22, 23]). An example of such agent is the widely used bevacizumab (trade name Avastin, Genentech/Roche) which is a humanized monoclonal antibody that recognizes and blocks vascular endothelial growth factor A (VEGF-A) [41]. We will refer further as to antiangiogenic only to the treatment that is focused on blocking the signaling of angiogenesis process.

2. **Model derivation.**

The key element in introducing antiangiogenic treatment to the Hahnfeldt et al. model is to modify the derivation of equation for carrying capacity dynamics. Hahnfeldt et al. proposed at the beginning the following general form of that equation

$$\dot{K} = -\lambda_2 K(t) + bS(V,K) - dI(V,K) - \gamma K(t) I(t)\,,$$

where the first term represents the spontaneous loss of functional vasculature; the second term represents the stimulatory capacity of the tumor upon the inducible vasculature (through, e.g. angiogenic factors like vascular endothelial growth factor [22,

23]); the third term reflects endogenous inhibition of previously generated vasculature (through, e.g. endothelial cell death or disaggregation); and the last term represents inhibition of tumor vasculature due to administered inhibitors. To obtain the exact forms of both functions $S(V,K)$ and $I(V,K)$ the following diffusion–consumption equation for the concentration $n(t,x)$ of stimulators/inhibitors was used

$$\frac{\partial n(x,t)}{\partial t} = D^2\Delta_x n(x,t) - cn(x,t) + s\mathbb{1}_{[0,r_0)}(||x||)\,, \tag{2}$$

where D^2 denotes the diffusion coefficient, c is the stimulator/inhibitor clearance rate, s is the rate of stimulator/inhibitor secretion and r_0 is the radius of the tumor, which is assumed to be a three dimensional spheroid.

We assume that administered drugs are proteins that bind and block angiogenic stimulators and therefore, we propose a modification of Eq. (2) of the following form

$$\frac{\partial n(x,t)}{\partial t} = D^2\Delta_x n(x,t) - (c + f(x,I(t)))n(x,t) + s\mathbb{1}_{[0,r_0)}(||x||)\,, \tag{3}$$

where $n(x,t)$ is the concentration of stimulators and $I(t)$ is the concentration of drug in the normal tissue at time t. Due to the pathology of tumor angiogenesis we assume that the concentration of drug inside the tumor is different than outside, therefore we propose the following simple form of the function $f(x,I(t))$

$$f(x,I(t)) = \begin{cases} I(t) & \text{for} \quad ||x|| \in [r_0,\infty), \\ dI(t) & \text{for} \quad ||x|| < r_0, \end{cases} \tag{4}$$

where the parameter $d \in \mathbb{R}^+$ describes the change in drug concentration caused by the incorrect structure of vessels inside the tumor. Let us further assume that the diffusion process is in a quasi-stationary state, namely that the growth rate of the tumor and change rate of the drug concentration are are small relative to the rate of distribution of stimulatory factor. Then $\dfrac{\partial n(x,t)}{\partial t} = 0$ and $I(t) = const = I$. Following [21] we assume also that the concentration of stimulator is radially symmetric: $||x|| = ||y|| \Rightarrow n(x) = n(y)$. Under those assumptions, Eq. (3) simplifies to the following ordinary differential equation of the second order:

$$n''(r) + \frac{2}{r}n'(r) - \frac{(c + f(r,I))}{D^2}n(r) + \frac{s\mathbb{1}_{[0,r_0)}(r)}{D^2} = 0 \tag{5}$$

As in [21] we try further to obtain analytic solution to Eq. (5) formulated above. As we are interested in radially symmetric, continuously differentiable and bounded solutions, we need to have the following conditions fulfilled

$$n'(0) = 0 \quad \text{and} \quad \sup_{r\in[0,+\infty)} |n(r)| < +\infty\,. \tag{6}$$

Making the substitutions (u,z) for (r,n), where $u = r\sqrt{c+dI}/D$, $z = r^{1/2}(n - s/(c+dI))$ for $r < r_0$ and $u = r\sqrt{c+I}/D$, $z = r^{1/2}n$ for $r \geq r_0$ we obtain in both cases the modified Bessel equation in $z(u)$ of order $1/2$, from which under the assumptions (6) we obtain the following form of the solution $n(r)$

$$n(r) = \begin{cases} b_1 \dfrac{D\exp\left(-r\sqrt{c+I}/D\right)}{r\sqrt{c+I}} & \text{for} \quad r \in [r_0,\infty), \\ \dfrac{s}{c+dI} + b_2\dfrac{D\sinh(r\sqrt{c+dI}/D)}{r\sqrt{c+dI}} & \text{for} \quad r < r_0, \end{cases}$$

where b_1, b_2 are some constants. We obtain the exact expressions for b_1, b_2 by making sure that

$$\lim_{r\to r_0^-} n(r) = \lim_{r\to r_0^+} n(r) \quad \text{and} \quad \lim_{r\to r_0^-} n'(r) = \lim_{r\to r_0^+} n'(r)\,.$$

Conditions above yield

$$b_1 = \frac{s\sqrt{c_2}\exp\left(\frac{\sqrt{c_2}r_0}{D}\right)\left(\sqrt{c_1}r_0\cosh\left(\frac{\sqrt{c_1}r_0}{D}\right) - D\sinh\left(\frac{\sqrt{c_1}r_0}{D}\right)\right)}{c_1 D\left(\sqrt{c_1}\cosh\left(\frac{\sqrt{c_1}r_0}{D}\right) + \sqrt{c_2}\sinh\left(\frac{\sqrt{c_1}r_0}{D}\right)\right)},$$
$$b_2 = -\frac{\left(D+\sqrt{c_2}r_0\right)s}{c_1 D\cosh\left(\frac{\sqrt{c_1}r_0}{D}\right) + \sqrt{c_1 c_2}D\sinh\left(\frac{\sqrt{c_1}r_0}{D}\right)},$$

where $c_1 = c+dI$ and $c_2 = c+I$. In [21] it was assumed that c (stimulator clearance rate) is large and the exact solution $n(r)$ was approximated. In our derivation we have proposed that the stimulator clearance rate is also monotonically increasing function of the drug concentration and it is always grater that the clearance rate c in the absence of treatment. Therefore, we can make similar approximation from which we obtain

$$n(r) \approx \begin{cases} \dfrac{s}{c+dI} & \text{for} \quad r < r_0, \\ 0 & \text{for} \quad r \in [r_0, \infty). \end{cases}$$

Our main goal is to propose the form of the function $S(V,K)$ using the expressions above. Therefore, we calculate the total amount of stimulators inside the tumor

$$L(r_0, I) = \gamma\int_0^{r_0} n(r)r^2 dr \approx \gamma\frac{s}{c+dI}r_0^3,$$

where γ is some constant. We see that L depends on r_0^3 and $V = \frac{4}{3}\pi r_0^3$ which yields

$$L(r_0, I) = L(V, I) \approx \frac{\alpha}{c+dI}V, \quad \alpha = \tfrac{3}{4\pi}\gamma s. \tag{7}$$

We shall now formulate the law governing the change in drug concentration inside the tumor. We propose that it should be proportional to a bounded and decreasing function of tumor volume V, i.e. we assume that $d \sim 1/(\beta + V^p)$, $p \geq 0$, as the pathology increases during tumor growth and decreases due its reduction during the treatment. Under the obtained approximation (7) and the assumption about the form of the change of drug concentration we formulate the following system describing angiogenesis process with antiangiogenic treatment

$$\begin{aligned} \dot{V} &= -\lambda_1 V\ln\frac{V}{K}, \\ \dot{K} &= -\lambda_2 K + b\frac{(\beta+V^p)V}{a(\beta+V^p)+I(t)} - dKV^{2/3}\,, \end{aligned} \tag{8}$$

where all parameters are non-negative. Under the assumption that the same amount A of antiangiogenic drug is administered as bolus at moments $t_1, ..., t_n$ and under usual pharmacokinetic assumptions we propose the following form of the function $I(t)$

$$I(t) = D\sum_{i=1}^{n} \mathrm{e}^{-g(t-t_i)}\mathrm{l}_{\{t\geq t_i\}}\,, \tag{9}$$

where g is the parameter describing the clearance rate of the drug.

3. **Analysis of the model dynamics for constant treatment.** In this section we study the behavior of the system

$$\begin{aligned} \dot{V} &= -\lambda_1 V \ln \frac{V}{K}, \\ \dot{K} &= b\frac{\beta + V^p}{a(\beta + V^p) + I} V - dKV^{2/3}, \end{aligned} \tag{10}$$

where we assume that $\lambda_2 \equiv 0$ (compare the fitting of the Hahnfeldt et al. model to the experimental data [21]) and $I(t) = \text{const} = I$.

The right-hand side of Eqs. (10) is properly defined in $\mathcal{D} = (\mathbb{R}^+)^2$. Moreover, it is of class $\mathbf{C}^1$ in $\mathcal{D}$ which yields the existence of unique solution for every initial data from $\mathcal{D}$.

Proposition 1. *The set $\mathcal{D}$ is invariant for Eqs. (10).*

Proof. Notice, that the right-hand side of Eqs. (10) can be extended to the boundary of $\mathcal{D}$. Indeed, for every arbitrary $K > 0$ defining

$$F_1(V) = \begin{cases} -\lambda_1 V \ln \frac{V}{K} & \text{for } V > 0, \\ 0 & \text{for } V = 0 \end{cases}$$

one gets a continuous function of V. Similarly,

$$F_2(K) = b\frac{\beta + V^p}{I + a\beta + aV^p} V - dKV^{2/3}$$

is a continuous function of K for every $K \in \mathbb{R}$ and arbitrary $V \geq 0$.

Let $(V_0, K_0) \in \mathcal{D}$ be the initial point for $t_0 = 0$. We know that the unique solution exists on some time interval $[0, t^*)$. If $\mathcal{D}$ is not invariant, then there exists such initial data and time $t_1 > 0$ for which the solution reaches the boundary of $\mathcal{D}$. Therefore, either $\lim_{t \to t_1^-} V(t) = 0$ or $\lim_{t \to t_1^-} K(t) = 0$. However, the extended functions F_1 and F_2 of the right-hand side show that if $V(t_1) = 0$, then $\dot{V}(t_1) = 0$ and if $K(t_1) = 0$, then $\dot{K}(t_1) \geq 0$. Therefore, the solution to Eqs. (10) cannot leave the set $\mathcal{D}$. □

The general behavior of solutions to Eqs. (10) can be analyzed through the phase-space portrait. Analyzing the phase-space portrait we calculate the null-clines for Eqs. (10), that is

1. for V the null-cline in $\mathcal{D}$ is $V = K$;
2. for K the null-cline in $\mathcal{D}$ is $K = \dfrac{b}{d}\dfrac{\beta + V^p}{a\beta + I + aV^p} V^{1/3}$.

The dynamics of Eqs. (10) depends on the shape of the null-cline $K(V)$. We see that

$$K(V) \sim CV^{1/3}, \quad \text{as} \quad V \to \infty, \qquad \text{as well as } V \to 0,$$

where for $p > 0$ there is $C = \frac{b}{ad}$ for $V \to \infty$ and $C = \frac{b\beta}{d(a\beta + I)}$ for $V \to 0$, while for $p = 0$ there is $K = \frac{b}{d}\frac{\beta+1}{a(\beta+1)+I} V^{1/3}$.

Thus, we can deduce that the null-cline for V is below the null-cline for K for small V and above this null-cline for large V. Therefore, to determine the dynamics of Eqs. (10) we have to determine the number of intersections between both null-clines in $\mathcal{D}$, this is to calculate the number of steady states. The equality $K(V) = V$ yields

$$\alpha V^{p+2/3} + \alpha(\beta + \vartheta) V^{2/3} - V^p - \beta = 0, \tag{11}$$

where $\alpha = \frac{ad}{b}$ and $\vartheta = I/a$. To determine a number of positive solutions to Eq. (11) we use Descartes' rule of signs. Although the rule can be applied only for polynomials it can be used for Eq. (11) for any $p = k/(3n)$, $k, n \in \mathbb{N}$, since then the left-hand side of Eq. (11) is a polynomial of $x = V^{1/(3n)}$, and by a continuity argument the result can be extended for any $p \geq 0$. For $p = 0$ the coefficients have signs: $++-$ and for $p \in (0, 2/3)$: $++--$, thus Descartes' rule of signs implies that there exists exactly one positive solution to Eq. (11). If $p > 2/3$, then we have to change the places of the second and the third term in the left-hand side of Eq. (11) and therefore, the sings are as follows: $+-+-$. This implies that Eq. (11) can have either three or one positive solution. In the case $p = 2/3$, the signs can be $++-$ (if $\beta + \vartheta > 1$) or $+--$ (if $\beta + \vartheta < 1$), but this means one change of sings of the coefficients and therefore there exists exactly one positive solution to Eq. (11). Now, we consider $p > 2/3$ and give a sufficient condition for the existence of a unique positive solution to Eq. (11). This condition guarantees monotonicity of the left-hand side of Eq. (11). Differentiating with respect to V one gets

$$\alpha\left(p + \frac{2}{3}\right) V^{p-1/3} + \frac{2\alpha}{3}(\beta + \vartheta)V^{-1/3} - pV^{p-1} \tag{12}$$

Positivity of the derivative (12) for $V > 0$ is equivalent to the inequality

$$g(V) = \alpha\left(p + \frac{2}{3}\right) V^{2/3} + \frac{2\alpha}{3}(\beta + \vartheta)V^{2/3-p} > p\,, \quad V > 0\,.$$

Now, we find the minimum of the function g. Calculating the derivative of g and letting it to be zero we find the point V_0 at which g reaches its minimum

$$V_0 = \left(\frac{\left(p - \frac{2}{3}\right)(\beta + \vartheta)}{\left(p + \frac{2}{3}\right)}\right)^{1/p}$$

The condition $g(V_0) > p$ guarantees the monotonicity of the left-hand side of Eq. (11) and thus existence of a unique positive solution to Eq. (11). We can rewrite the inequality $g(V_0) > p$ and formulate

Lemma 3.1. *If $p \in [0, \frac{2}{3}]$ or $p > \frac{2}{3}$ and the inequality*

$$I > a\left(\left(\frac{b}{ad}\right)^{\frac{3p}{2}}\left(\frac{p - \frac{2}{3}}{p + \frac{2}{3}}\right)^{1-\frac{3p}{2}} - \beta\right) \tag{13}$$

holds, then there exists a unique steady state of Eqs. (10) in $\mathcal{D}$.

We want to emphasize that Ineq. (13) is only the sufficient condition for the existence of a unique positive steady state. If this condition is not fulfilled it can also happen that the positive steady state is unique. It should be also marked that to have Ineq. (13) satisfied the positivity of the expression in the brackets is necessary and it depends on the parameter values. Consider the simplified case $a = \beta = 1$. Then there should be

$$\left(\frac{b}{ad}\right)^{\frac{3p}{2}}\left(\frac{p - \frac{2}{3}}{p + \frac{2}{3}}\right)^{1-\frac{3p}{2}} > 1$$

and this can be satisfied only for $b > ad$.

From the treatment point of view it is also of great interest to know the dependence of steady state values on the magnitude of drug dosage I. We obviously

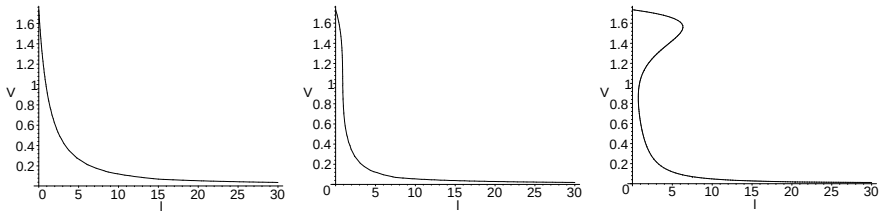

FIGURE 1. Dependence of the steady state tumor volume V on I for different values of the Hill coeffcient: $p = 0$ in the left, $p = 4$ in the middle and $p = 10$ in the right-hand graph.

have $\bar{V} = \bar{K}$ at the steady state $(\bar{V}, \bar{K})$. Therefore, we can consider only the dependence $\bar{V}(I)$. Rewriting Eq. (11) one gets $\left(\alpha V^{2/3} - 1\right)(V^p + \beta) + \alpha \frac{I}{a} V^{2/3} = 0$ which yields $\bar{V}(I) < \bar{V}(0) = \alpha^{-3/2}$. If there exists unique steady state $\bar{V}$ we expect that it decreases with increasing I, while for three steady states we expect that the smallest and the largest one decrease and the middle steady state increases with I. In Fig. 1 we present the dependence of the tumour volume $\bar{V}$ on the magnitude of drug dosage for the parameter values from Hahnfeldt et al [21] and $a = \beta = 1$. We see that the shape of graphs confirms our expectations.

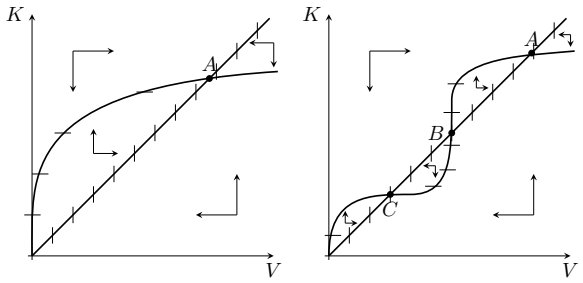

FIGURE 2. A sketch of the phase space portrait of Eqs. (10). On the left-hand side the case with one positive steady state, and on the right-hand side the case when three steady states exist.

From the phase space portrait (see Fig. 2) it can be deduced that the largest positive steady state (A) is always a stable node and so the smallest positive steady state (C), if it exists. The middle steady state, if exists, is a saddle point.

Moreover, we can formulate the following

Theorem 3.2. *If the positive steady state for Eqs.* (10) *is unique in* $\mathcal{D}$*, then it is globally stable in* $\mathcal{D}$*.*

Proof. In fact, studying the phase-space portraits for Eqs. (10) we see that every solution is bounded. Therefore, according to the Poincare – Bendixson theorem any solution tends to either a steady state or to a closed orbit. However, due to the Dulac – Bendixson criterion there is no close orbit in $\mathcal{D}$. Indeed, taking $B(V, K) = \frac{1}{VK}$

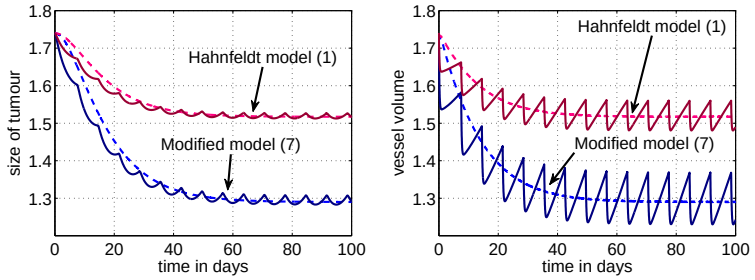

FIGURE 3. Comparison of solutions to the Hahnfeldt et al. model (1) and the modified model (8) for daily dose 0.05. Solid line — the solution for a dose is applied once a week, dotted line — a dose is applied every hour.

one gets

$$\frac{\partial}{\partial V}\left(-\frac{\lambda_1}{K}\ln\frac{V}{K}\right)+\frac{\partial}{\partial K}\left(\frac{b}{K}\frac{\beta+V^p}{I+a(\beta+V^p)}-dV^{-1/3}\right)=$$
$$=-\frac{\lambda_1}{KV}-\frac{b(\beta+V^p)}{K^2(I+a(\beta+V^p))}<0$$

which implies that there is no closed orbit in $\mathcal{D}$. □

At the end of this section we would like to mark that Eqs. (8) and (10) have been proposed and studied for the general form of the treatment. However, if we require in the absence of treatment that Eqs. (8) becomes the Hahnfeldt et al. model, then the number of parameters descreases, because the identity $b\frac{(\beta+V^p)}{a(\beta+V^p)+I(t)}\Big|_{I\equiv 0}=b$ must hold. This yields $a=1$.

4. **Numerical simulations.** To illustrate the behavior of solutions to Eqs. (8) with the pharmacokinetic function I given by Eq. (9) we perform some numerical simulation. We have taken the model parameters from Hahnfeldt et al. [21] rescaled as in [7]. Thus, we use the following values of parameters:

$$\lambda_1=0.192\,,\quad \lambda_2=0\,,\quad b=5.85\,,\quad d=4.052\,,\quad a=1\,,\quad g=0.1\,,\quad \beta=1\quad \gamma=1\,.$$

The daily dose of drug D_d is changing. In fact, we use $D=D_d/n$, where n is the number of doses applied each day. If the drug is applied every k-th day, then $n=1/k$. For chosen parameters' values there exists a unique positive steady state of Eqs. (10).

In order to compare the treatment that is considered in [21] with the treatment proposed in this paper we use exactly the same pharmacokinetic function. We have compared the solution to the original Hahnfeldt et al. model with the modified model for different values of p, that is for $p=1$ (see Figs. 3, 5, 7), $p=2$ and $p=0$ (see Figs. 4, 6, 8).

If the treatment is applied rarely, oscillations due to application of the drug can be observed (see Figs. 3, 4, 5, 6, 7, 8). If the daily dose is small, the size of tumor in the steady state is smaller for the modified model than for the Hahnfeldt et al. model and deceases with decreasing p (see Fig. 3, 4 and 9). If the daily dose is larger, the size of tumor in the steady state becomes smaller with increasing p (see Fig. 5, 6 and 9). For daily dose large enough (larger then 0.5), the size of tumor in

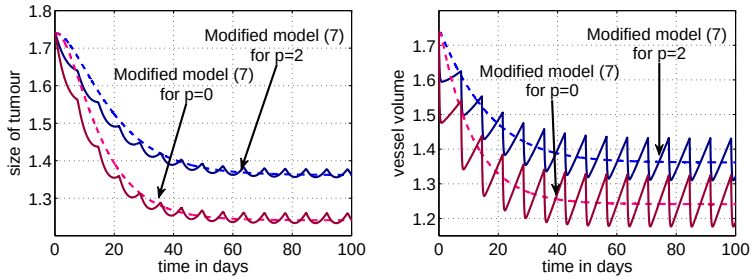

FIGURE 4. Comparison of solutions to the modified model (8) for daily dose 0.05 for different values of p. Solid line — the solution for a dose applied once a week, dotted line — a dose applied every hour.

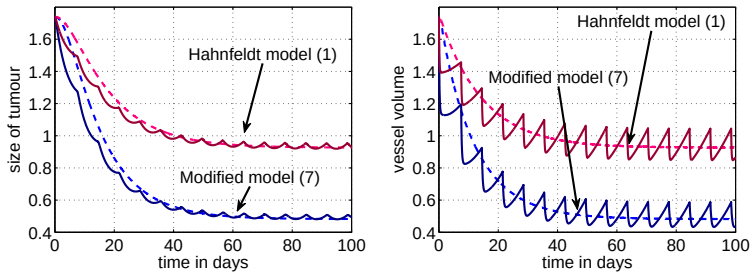

FIGURE 5. Comparison of solutions to the Hahnfeldt et al. model (1) and the modified model (8) for daily dose 0.2. Solid line — the solution for a dose applied once a week, dotted line — a dose applied every hour.

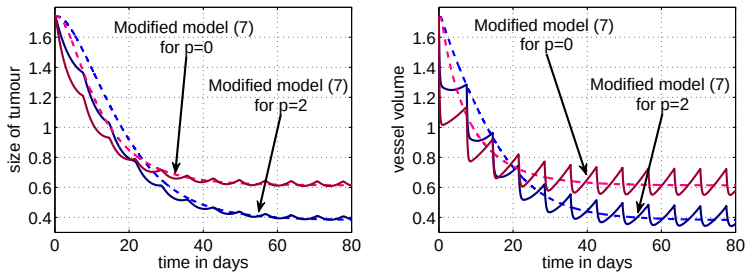

FIGURE 6. Comparison of solutions to the modified model (8) for daily dose 0.2 for different values of p. Solid line — the solution for a dose applied once a week, dotted line — a dose applied every hour.

the steady state becomes smaller for the Hahnfeldt et al. model (see Fig. 7, 8 and 9).

We have not observed any significant difference in mean values of solutions for different treatment regimes when mean values was calculated over the interval equal to the time between doses' applications.

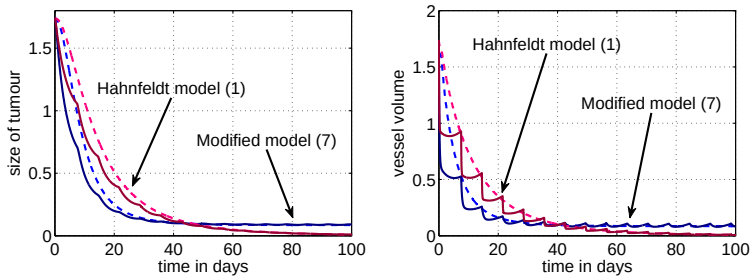

FIGURE 7. Comparison of solutions to the Hahnfeldt et al. model (1) and the modified model (8) for daily dose 0.7. Solid line — the solution for a dose applied once a week, dotted line — a dose applied every hour.

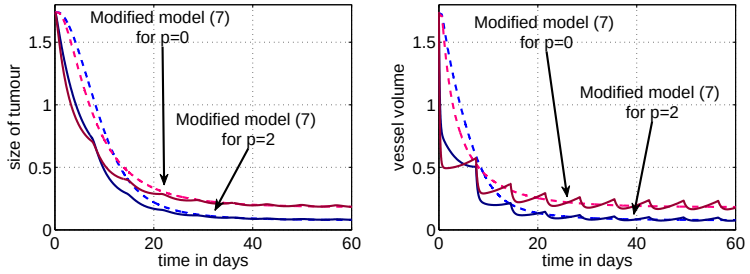

FIGURE 8. Comparison of solutions to the modified model (8) for daily dose 0.7 for different values of p. Solid line — the solution for a dose applied once a week, dotted line — a dose applied every hour.

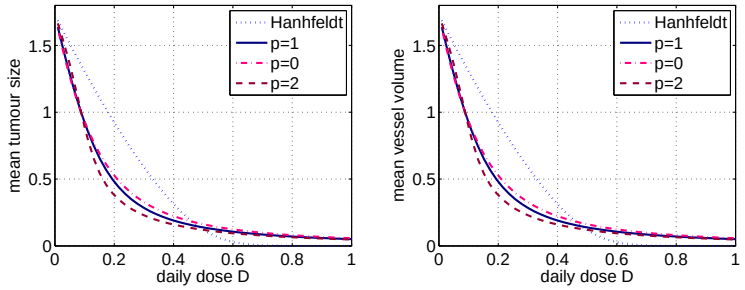

FIGURE 9. Comparison of the mean values of solutions to the Hahnfeldt et al. model (1) (dotted line) and the modified model (8) (solid line) in the steady state (after long time) depending on daily dose

5. **Summary.** In the paper we have described a new approach to antiangiogenic treatment. Typically, such treatment is described as a separate term in the equation describing the dynamics of vessels' volume, as in the case of the classical Hahnfeldt et al. model [21]. In our opinion such term reflects antivascular treatment, while

antiangiogenic treatment occurs on the level of the angiogenic signaling. We have considered such type of drugs which acts on the stimulators of angiogenesis and therefore, basing on the Hahnfeldt et al. ideas [21] we have modified the term describing stimulation of angiogenesis.

As it can be expected, the dynamics of both considered models is completely different. Starting the research on antiangiogenic treatment Folkman [15] believed that this should lead to complete recovery from cancer disease. Therefore, there were such requirements for the Hahnfeldt et al. model that it should reflect complete recovery for sufficiently high drug dosage. Now, after many years of experiments we know that generally it is not true. This is reflected in our modified model. We have studied the dynamics of the modified model in the case of constant treatment. We know that for the original Hahnfeldt et al. model the complete recovery is guaranteed under the assumption of sufficiently high drug dosage. For the modified model we have shown that complete recovery is impossible independently of the magnitude of this dosage (this phenomenon was recently noticed in [11, 13]. This suggest that using only antiangiogentic treatment we are not able to cure cancer. However, using antiangiogenic treatment we are able to decrease both cancer and vessels' volume and normalize vasculature such that chemotherapy can better penetrate tumor mass. This is now the main goal of antiangiogenic treatment.

We have performed a series of numerical simulations using non-constant treatment, described as an application of drug *as boli*. As for the constant treatment, the application of the same doses of drugs give different results depending on the Hill coefficient p. In our opinion, experiments with different doses of different drugs should be performed in order to check which model is better for the description of the specific drug.

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E-mail address: j.poleszczuk@mimuw.edu.pl
E-mail address: mbodnar@mimuw.edu.pl
E-mail address: urszula@mimuw.edu.pl