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Maja Szlenk (Warsaw)
Marek Bodnar * (Warsaw)

Analysis of delay differential equations modelling tumor growth with angiogenesis

Abstract Angiogenesis is a crucial process for the survival of cancer cells. Due to the rapid growth of the tumor, blood vessels delivering oxygen become insufficient, which leads to hypoxic regions inside the tumor and therefore death of the cells. Cancer cells deal with this problem by stimulating the growth of new vessels, thus providing the necessary amount of oxygen. The understanding of this process allowed to develop antiangiogenic therapy, which attack tumor vasculature instead of the cells themselves. It is believed that an effective treatment combines antiangiogenic factors with radio- and chemotherapy. Our aim is to construct a mathematical model describing this process, which would further allow to select an optimal dosage. In this paper we propose a delay differential model of tumor growth and perform its preliminary analysis. We then introduce a method, which enables further study of this model. The results are illustrated by numerical simulations.

2010 Mathematics Subject Classification: Primary: 34D20; Secondary: 92C99.

Key words and phrases: angiogenesis, VEGF, antiangiogenic treatment, delay differential equations, stability analysis.

1. Introduction. Angiogenesis is the process of growing new blood vessels from pre-existing ones. Many proteins participate in this process, stimulating or inhibiting the growth. One of the key regulators of angiogenesis is the vascular endothelial growth factor (VEGF). As a result of its production, the cells on the tip of the vessel migrate and the cells in the stalk proliferate, causing the blood vessel to grow [4].

This process naturally occurs for example during healing wounds. However, it also becomes crucial in tumor growth. As the tumor volume increases rapidly, cancer cells struggle with oxygen shortage. Hypoxia is however one of the factors that causes angiogenesis. The proteins responsible for this process are hypoxia induced factors (HIF) [7], consisting of subunits HIFα and HIFβ. Their function is described in Fig. 1.

The understanding of this process is crucial to develop an effective antiangiogenic treatment as a less invasive alternative to radio- and chemotherapy. Instead of destroying cancer cells directly, one can destroy only the vasculature of a tumor or just inhibit the vessel growth, and therefore prevent the

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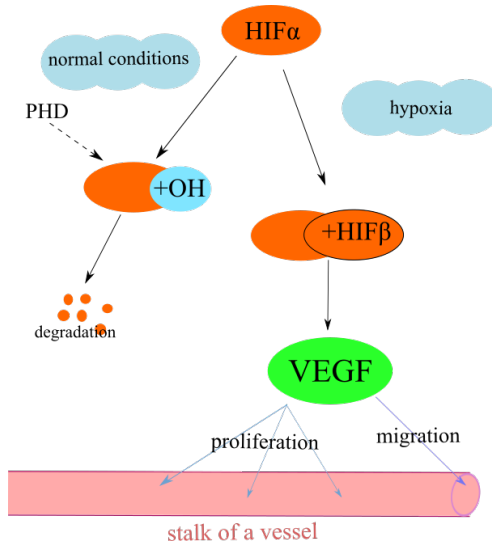

Figure 1: Schematic illustration of angiogenesis. At the normal oxygen level, HIFα gets hydroxylated by PHD proteins and then degraded. In case of the oxygen shortage, HIFα binds with HIFβ and activates proangiogenic factors, including VEGF. The latter causes the tip cells to migrate to hypoxic regions, while stimulating proliferation of the stalk cells.

tumor from growing. One of the used medicines is bevacizumab, which is an antibody to VEGF [8]. Other treatments include blocking angiogenic factors or activation of inhibitors.

2. Model derivation. The idea is partially based on a model introduced by Hahnfeldt *et al.* [3] using concepts proposed in [1, 2]. We assume that the tumor growth rate depends on the effective vascular density, which reflects the availability of nutrients and oxygen. We limit our study to time when a necrotic core is not formed, however some tumor cells have insufficient oxygen supply and become hypoxic. Thus, we divide tumor cells into two populations: normal (we denote by P the size of this population) and hypoxic (the size of this population is H). We omit the inhibiting factors and assume that the change in the vasculature (denoted by Q) relies on the amount of hypoxic cells with some delay. We also suppose that existing vasculature is large enough to respond to angiogenic signals, and – in the absence of hypoxic cells – the vasculature does not change. We propose the following tumor dynamics

$$\begin{aligned}
\dot{P} &= \rho_P(E)P - f_1(E)P + f_2(E)H - s_P(t)P,\\
\dot{H} &= \rho_H(E)H + f_1(E)P - f_2(E)H - s_H(t)H,\\
\dot{Q} &= \frac{b}{1+u(t)}H(t-\tau) - s_Q(t)Q,
\end{aligned} \tag{1}$$

where $E = \frac{Q}{P+H}$ is understood as the efficiency of vasculature. Functions ρ_P and ρ_H are growth rates of hypoxic and normal cells, respectively. A function $u(t)$ models antiangiogenic treatment (decreasing the vasculature growth rate) while functions s_P, s_H and s_Q combine the influence of chemo- and radiotherapy and natural death rates of cancer and blood cells. Functions f_1 and f_2 describe the flux between normal and hypoxic cells, depending on the efficiency. As the tumor vasculature may become disorganized and ineffective [5], we assume the existence of an optimal vasculature efficiency $E_{\text{opt}} < \infty$. Thus we suppose f_1 and f_2 are continuous functions satisfying

- $f_1(0) = a_1 > 0$, $f_1(E_{\text{opt}}) = 0$, $\lim_{E\to\infty} f_1(E) \leq a_1$, f_1 is decreasing on $(0, E_{\text{opt}})$ and increasing on $(E_{\text{opt}}, +\infty)$,
- $f_2(0) = 0$, $f_2(E_{\text{opt}}) = a_2$, $\lim_{E\to\infty}$, $f_2(E) \leq a_2 > 0$, f_2 is increasing on $(0, E_{\text{opt}})$ and decreasing on $(E_{\text{opt}}, +\infty)$.

The examples of such functions are illustrated in Fig. 2.

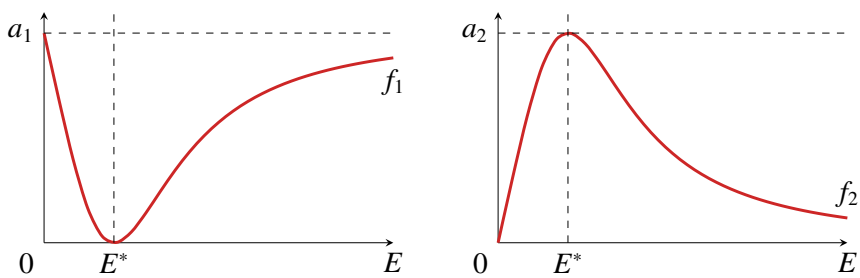

Figure 2: Examples of functions f_1 i f_2

In this paper we consider two simplifications of a general model (1). First, we analyse the model without treatment, we assume constant growth rates of P and H and zero death rates. Therefore, we study the following system of equations

$$\begin{aligned} \dot{P} &= \rho_P P - f_1(E)P + f_2(E)H, \\ \dot{H} &= \rho_H H + f_1(E)P - f_2(E)H, \\ \dot{Q} &= bH(t-\tau). \end{aligned} \tag{2}$$

We show that the dynamics of model (2) is quite complex and can substantially differ from the model in which the difference between hypoxic and non-hypoxic cells is not taken into account. We illustrate this considering another simplification of model (1) in which we do not distinguish between normal and hypoxic cells. We assume that the tumor growth rate is a continuous increasing function f such that $f(0) = 0$. Moreover, in this model we also include explicitly death of tumour cells and degradation of vessels with rates

a and μ, respectively. Then, we get the following system of equations

$$\begin{aligned} \dot{P} &= f(E)P - aP, \\ \dot{Q} &= bP(t-\tau) - \mu Q. \end{aligned} \tag{3}$$

3. Properties of solutions. First of all we prove that unique solutions to (2) exist and are non-negative for the non-negative initial function.

THEOREM 3.1 If $f_1, f_2 \in C^1$, then for any initial function from $C([-\tau, 0], \mathbb{R}^3_+)$ there exists a unique non-negative solution to (2) defined for all $t \geq 0$.

PROOF The right-hand side of (2) is of C^1 class, thus unique solutions exist locally. On the other hand, the right-hand side of (2) is non-negative on the boundary of $\mathbb{R}^3_+$ and thus solutions are non-negative (see [6, Th. 3.4]). The global existence is easily proved by the step method. In fact, if the solution to system (2) is defined for $t \in [0, n\tau]$, then the function Q can be expressed as an integral of the known function H (we need value of H on the interval $[(n-1)\tau, n\tau]$) and it is bounded. Thus, the first two equations of system (2) can be treated as a system of non-autonomous ODEs. Because of assumptions on functions f_1 and f_2, the right hand side of this system is globally Lipschitz and thus its solutions are also well defined on the whole interval $[n\tau, (n+1)\tau]$. Thus, mathematical induction yields that we can extend the solutions for each $[n\tau, (n+1)\tau]$, for $n \in \mathbb{N}$. ∎

An analogous argument allows us to state

THEOREM 3.2 If $f \in C^1$, then for any initial function from $C([-\tau, 0], \mathbb{R}^2_+)$ there exists a unique non-negative solution to (3) defined for all $t \geq 0$.

3.1. The analysis of a simplified model. First, we analyze system (3).

PROPOSITION 3.3 If $\sup_{E \geq 0} f(E) < a$, then all solutions to system (3) with non-negative initial data converge to $(0, 0)$.

PROOF The inequality $\sup_{E \geq 0} f(E) < a$ implies that $\dot{P} < -\delta P$ for some $\delta > 0$. Thus, $P(t) < P(0)e^{-\delta t} \to 0$ as $t \to +\infty$. We can choose $\delta \neq \mu$. Then, for $t > \tau$ for the second equation of (3) we get

$$\begin{aligned} Q(t) &= Q(0)e^{-\mu t} + be^{-\mu t} \int_0^t e^{\mu s} P(s-\tau) ds \\ &= Q(0)e^{-\mu t} + be^{-\mu t} \int_0^\tau e^{\mu s} P(s-\tau) ds + be^{-\mu t} \int_\tau^t e^{\mu s} P(s-\tau) ds \\ &< Q(0)e^{-\mu t} + be^{\mu(\tau - t)} \int_{-\tau}^0 e^{\mu y} P(y) dy + \frac{bP(0)}{\mu - \delta} \left(e^{\delta(\tau - t)} - e^{\mu(\tau - t)} \right), \end{aligned}$$

therefore $Q(t) \to 0$ as $t \to +\infty$. ∎

Thus, we assume further that $\sup f(E) > a$. Besides from a non-generic situation where $f(\frac{b}{\mu}) = a$, system (3) does not have positive steady states. However, if we write an equation for E, then we may solve the first equation of (3) obtaining P as a function of E and then consider only the equation for E. It turns out, that this equation has a steady state E_*, and if E is equal to its value, then the cells grow exponentially with a rate $f(E_*) - a$. Calculating the derivative of E, we get

$$\dot{E} = b\frac{P(t-\tau)}{P(t)} - (\alpha + f(E))E, \tag{4}$$

where $\alpha = \mu - a$. Integrating the first equation of (3), we have

$$P(t) = P(0)\exp\left(\int_0^t \Big(f(E(s)) - a\Big)ds\right).$$

Introducing it into (4) we get

$$\dot{E} = b\exp\left(-\int_{t-\tau}^t \Big(f(E(s)) - a\Big)ds\right) - \big(\alpha + f(E)\big)E. \tag{5}$$

This equation is valid for $t \geq \tau$, as the function $P_{|[\tau,0)}$ is unknown.

Proposition 3.4 Equation (5) has exactly one positive steady state E_*, which satisfies

$$be^{-(f(E_*)-a)\tau} = (\alpha + f(E_*))E_* \tag{6}$$

Proof It follows immediately from the form of equation (5) that if E_* is a steady state of (5) then it solves equation (6). It remains to prove that equation (6) has exactly one positive solution.

The left-hand side of (6) is a positive decreasing function of E_*. On the other hand, the right-hand side is increasing, it is equal to 0 for $E_* = 0$ and tends to $+\infty$ as $E_* \to +\infty$. Therefore, there exists exactly one E_* satisfying (6). ∎

Now we prove that the unique steady state of (5) is locally asymptotically stable.

Theorem 3.5 If $f \in C^1$, the steady state E_* of (5) is locally asymptotically stable for all $\tau \geq 0$.

Proof For $\tau = 0$, equation (5) takes the form

$$\dot{E} = b - (\alpha + f(E))E. \tag{7}$$

Because $\alpha + f(E_*) > 0$ and f is increasing, the right-hand of (7) is positive for $E < E_*$ and it is negative for $E > E_*$. Thus, the steady state is stable.

For $\tau > 0$ we linearise (5) around the steady state E^*. Substituting $\tilde{E} = E - E_*$, then expanding the right-hand side of (5) into a Taylor series around E_*, and omitting higher order terms we get

$$\dot{\tilde{E}} = be^{-(f(E_*)-a)\tau}\left(1 - f'(E_*)\int_{t-\tau}^{t}\tilde{E}ds\right) - (\alpha + f(E_*))E_* - (\alpha + f'(E_*))\tilde{E}.$$

Using (6), we can write the equation for $\dot{\tilde{E}}$ as

$$\dot{\tilde{E}} = -a_0\int_{t-\tau}^{t}\tilde{E}ds - a_1\tilde{E},$$

where $a_1 = \alpha + f(E_*) + f'(E_*)E_*$ and $a_0 = f'(E_*)(\alpha + f(E_*))E_*$. By putting $\tilde{E}(t) = \tilde{E}(0)e^{\lambda t}$, we get the characteristic function

$$W(\lambda) = \lambda + a_1 + \frac{a_0}{\lambda}(1 - e^{-\lambda\tau}).$$

We show that the stability change is not possible. If the steady state is unstable for some $\tau > 0$, then there would exist $\omega > 0$ such that $\lambda = i\omega$ would be a zero of the characteristic function W.

For $\omega > 0$, the equation $W(i\omega) = 0$ is equivalent to

$$-\omega^2 + ia_1\omega + a_0 = a_0e^{-i\omega\tau}.$$

By taking modulus of both sides and dividing by ω^2, we get

$$\omega^2 = 2a_0 - a_1^2 = -f'(E_*)^2E_*^2 - (\alpha + f(E_*))^2 < 0.$$

Hence, there is no solution for ω, therefore critical τ does not exist and a unique steady state is stable for all $\tau \geq 0$. ∎

3.2. Asymptotic dynamics of system (2). System (2) has only one non-negative steady state $(0, 0, 0)$. This trivial steady state is unstable. Indeed, as $\frac{d}{dt}(P + H) = \rho_P P + \rho_H H$, the sum of $P + H$ is a strictly increasing function unless both variables are zero. Moreover, Q is also strictly increasing unless $H(t - \tau) = 0$. Thus, we proceed here as in the case of system (3) to eliminate variable P. First, we change variables taking $E = \frac{Q}{P+H}$ and $r = \frac{H}{P+H}$. We have

$$\begin{aligned}\dot{r} &= \frac{\dot{H}P - \dot{P}H}{(P+H)^2}\\ &= \frac{\left(\frac{r}{1-r}\rho_H + f_1(E) - \frac{r}{1-r}f_2(E)\right)P^2 - \left(\rho_P - f_1(E) + \frac{r}{1-r}f_2(E)\right)P\frac{r}{1-r}P}{\frac{P^2}{(1-r)^2}}\\ &= r(1-r)(\rho_H - \rho_P) + ((1-r)^2 + r(1-r))f_1(E) - (r(1-r) + r^2)f_2(E).\end{aligned}$$

and

$$\dot{E} = \frac{\dot{Q}(P+H) - (\dot{P}+\dot{H})Q}{(P+H)^2}$$
$$= \frac{b\frac{r(t-\tau)}{1-r(t-\tau)}P(t-\tau)}{\frac{P(t)}{1-r(t)}} - \frac{\left(\rho_P + \frac{r}{1-r}\rho_H\right)P}{\frac{P}{1-r}}E$$

Finally, we get

$$\begin{aligned}
\dot{P} &= G(r,E)P,\\
\dot{r} &= (1-r)f_1(E) - rf_2(E) - \rho_\Delta r(1-r),\\
\dot{E} &= b\frac{r(t-\tau)(1-r(t))}{1-r(t-\tau)}\frac{P(t-\tau)}{P(t)} - (\rho_P - \rho_\Delta r)E,
\end{aligned} \tag{8}$$

where $G(r,E) = \rho_P - f_1(E) + f_2(E)\frac{r}{1-r}$, $\rho_\Delta = \rho_P - \rho_H > 0$. By integrating the equation for P, we get

$$P(t) = P(0)\exp\left(-\int_0^t G(r(s),E(s))ds\right),$$

and introducing it into the last equation of system (8) we get for $t \geq \tau$

$$\begin{aligned}
\dot{r} &= (1-r)f_1(E) - rf_2(E) - \rho_\Delta r(1-r),\\
\dot{E} &= b\frac{r(t-\tau)(1-r(t))}{1-r(t-\tau)}\exp\left(-\int_{t-\tau}^t G(r,E)ds\right) - (\rho_P - \rho_\Delta r)E.
\end{aligned} \tag{9}$$

3.2.1. Existence of steady states. If (r_*, E_*) is a steady state of system (9), then it satisfies

$$f_1(E_*)(1-r_*) - \rho_\Delta r_*(1-r_*) - f_2(E_*)r_* = 0, \tag{10}$$

and

$$E_* = \frac{br_*e^{-(\rho_P - \rho_\Delta r_*)\tau}}{\rho_P - \rho_\Delta r_*}. \tag{11}$$

We can determine the existence of steady states under some constraints on f_1 and f_2.

THEOREM 3.6 If $f_1(E) + f_2(E) = 1$ for all $E \geq 0$, then there exists a steady state of system (9). Moreover, if $\frac{b}{\rho_H}\exp(-\rho_H\tau) \leq E_{\text{opt}}$, the steady state (r_*, E_*) is unique.

PROOF If $f_1(E) + f_2(E) = 1$, then (10) is equivalent to

$$f_2(E_*) - (1-r_*)(1-\rho_\Delta r_*) = 0. \tag{12}$$

Let E_* be a function of r_*, defined by (11). It is obvious that this function is continuous. For $r_* = 0$ the left-hand side of (12) is negative. Indeed, we have

$$f_2\big(E_*(0)\big) - (1 - r_*)(1 - \rho_\Delta r_*) = f_2(0) - 1 = -1.$$

On the other hand, $E_*(1) > 0$, thus for $r_* = 1$ we get

$$f_2\big(E_*(1)\big) - (1 - r_*)(1 - \rho_\Delta r_*) = f_2\big(E_*(1)\big) > 0.$$

Hence, there exists at least one solution to (12) and thus at least one positive steady state of (9).

Note that for $G_* = G(r_*, E_*)$,

$$\frac{d}{dr_*} E_* = b \frac{e^{-G_*\tau}(1 + \rho_\Delta \tau r_*)G_* + \rho_\Delta r_* e^{-G_*\tau}}{G_*^2} > 0,$$

therefore E_* is an increasing function of r_*. If $E_*(1) = \frac{be^{-\rho_H \tau}}{\rho_H} < E_{\text{opt}}$, then $f_2(E_*)$ is increasing for $0 < r_* < 1$. In this case $f_2(E_*)$ crosses $(1 - r_*)(1 - \rho_\Delta r_*)$ at exactly one point, which gives a unique steady state of (9). ∎

4. Numerical simulations and conclusions. We study the qualitative differences of solutions to system (9) and equation (5) comparing the dynamics of vasculature efficiency E. In the simulations we choose the value of the parameter b as in Hahnfeldt et al.(1999). The solution to (5) is oscil-

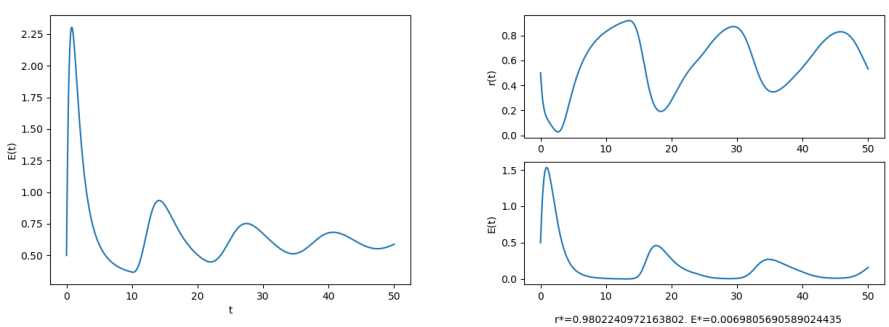

Figure 3: Simulations of (5) and (9) for $a = \mu = 0.5$, $b = 5.85$, $\tau = 10$ and $\rho_P = 1$, $\rho_\Delta = 0.3$. In this case both solutions for E tend to their stationary states.

lating around the steady state E_* with amplitude converging to 0, compare left-hand side panel of Fig. 3. On the other hand, the dynamics of (9) is richer and the behaviour of solutions depends strongly on the model's parameters. The solution to (9) may oscillate around the steady state with damping amplitude and converges eventually to the steady state (compare the right-hand side panel of Fig. 3). However, for other sets of parameters solutions might

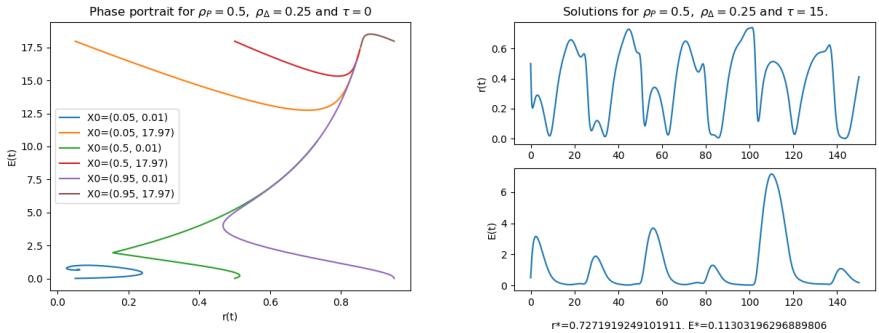

Figure 4: For $\rho_P = 0.5$ and $\rho_\Delta = 0.25$ we have two locally stable steady states for $\tau = 0$ and one unstable state for $\tau = 15$.

exhibit non-vanishing and irregular oscillations, compare the right-hand side panel of Fig. 4.

The dynamics of the system (9) changes significantly with increasing τ. Theorem 3.6 implies that if the system has multiple steady states for $\tau = 0$, they stick together into a unique steady state for sufficiently large τ. Fig. 4 and 5 illustrate different behaviours of solutions to system (9). In Fig. 4 we can see a situation, where there are two locally stable steady states for $\tau = 0$ and one unstable state for large τ. In Fig. 5 w can compare the phase portrait for $\tau = 0$ with the solutions for nonzero delay.

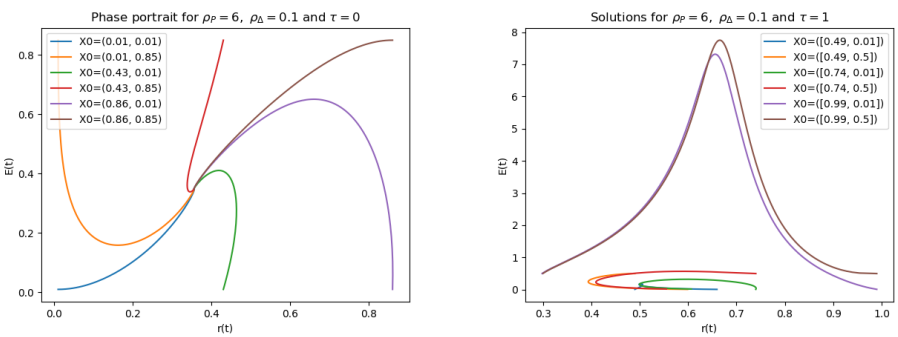

Figure 5: Differences in the dynamics of (9) with $\tau = 0$ and $\tau = 1$.

In this paper we studied models of tumor growth that was constructed on the basis of ideas proposed by Hahnfeldt et al.(1999). We compared the dynamics of the model in which we distinguished hypoxic cells with a simplified model in which we did not consider two tumor cell populations. It turns out that solutions to the simplified model converge to a unique steady state, while the other model exhibits much richer dynamics. There may exist multiple steady states, their existence and stability depend also on the delay

parameter. The division rates of the cell population play a significant role for the model dynamics. Further analysis of the model will enable us to partially determine the conditions for stability of the steady states of system (9).

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Analiza układu równań różniczkowych z opóźnieniem modelującego nowotwór z uwzględnieniem procesu angiogenezy

Maja Szlenk, Marek Bodnar

Streszczenie Angiogeneza jest procesem szczególnie istotnym w przypadku komórek nowotworowych. Na skutek gwałtownego wzrostu objętości guza, naczynia krwionośne zaopatrujące nowotwór stają się niewystarczające. Powoduje to tworzenie się niedotlenionych obszarów wewnątrz guza, a w konsekwencji obumarcie komórek. Komórki rakowe przeciwdziałają temu problemowi, stymulując rozrost nowych naczyń krwionośnych i zapewniając tym samym dopływ tlenu. Poznanie tego procesu pozwoliło na opracowanie terapii antyangiogenicznej, atakującej naczynia zaopatrujące nowotwór zamiast samych komórek. W tym artykule proponujemy model różniczkowy z opóźnieniem opisujący wzrost guza, uwzględniający proces angiogenezy. Przeprowadzamy jego wstępną analizę oraz formułujemy kilka wniosków dot. stabilności rozwiązań. Numerycznie symulacje ilustrują uzyskane wyniki.

Klasyfikacja tematyczna AMS (2010): 34D20; 92C99.

Słowa kluczowe: angiogeneza, VEGF, komórki rakowe, leczenie antyangiogeniczne, równania różniczkowe z opóźnieniem, analiza stabilności.

Maja Szlenk studiuje matematykę na wydziale Matematyki, Informatyki i Mechaniki Uniwersytetu Warszawskiego. W swojej pracy magisterskiej analizuje układ równań różniczkowych z opóźnieniem, modelujący wzrost guza nowotworowego. Jej zainteresowania naukowe obejmują zastosowania równań różniczkowych w naukach przyrodniczych i medycynie.

Marek Bodnar[a] pracuje na Wydziale Matematyki, Informatyki i Mechaniki Uniwersytetu Warszawskiego w Zakładzie Biomatematyki i Teorii Gier. Od ponad 15 lat zajmuje się modelowaniem matematycznym procesów biologicznych i medycznych ze szczególnym uwzględnieniem procesów nowtworowych. Badane modele są przeważnie układami nieliniowych równań różniczkowych z opóźnieniem.

[a] His research papers are listed in zbMath under ai:Bodnar.Marek, in MathSciNet under ID:663971.

Maja Szlenk
University of Warsaw
Faculty of Mathematics, Informatics and Mechanics
University of Warsaw, Banacha 2, Warsaw 02-097
E-mail: ms360364@student.mimuw.edu.pl

Marek Bodnar
University of Warsaw
Faculty of Mathematics, Informatics and Mechanics
University of Warsaw, Banacha 2, Warsaw 02-097
E-mail: mbodnar@mimuw.edu.pl

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