MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **10**, Number **1**, February **2013**

doi:10.3934/mbe.2013.10.19

pp. **19–35**

MODEL OF TUMOUR ANGIOGENESIS – ANALYSIS OF STABILITY WITH RESPECT TO DELAYS

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Abstract. In the paper we consider the model of tumour angiogenesis process proposed by Bodnar&Foryś (2009). The model combines ideas of Hahnfeldt et al. (1999) and Agur et al. (2004) describing the dynamics of tumour, angiogenic proteins and effective vessels density. Presented analysis is focused on the dependance of the model dynamics on delays introduced to the system. These delays reflect time lags in the proliferation/death term and the vessel formation/regression response to stimuli. It occurs that the dynamics strongly depends on the model parameters and the behaviour independent of the delays magnitude as well as multiple stability switches with increasing delay can be obtained.

1. **Introduction.** Angiogenesis is a process of new vessels formation from the pre-existing ones. It is a normal and vital process in growth and development of animal organisms. It is required during the repair mechanism of damaged tissues like wound healing processes. However, it is also an essential step in the solid tumours transition from the avascular forms to cancers that are able to metastase and cause lethal outcome of the disease. Clearly, when tumour approaches a size of 1-2 mm^3 the necrotic core formation in the centre of tumour and saturation of the growth process are observed. Next, cancer cells start to secrete number of angiogenic factors e.g. FGF, VEGF, VEGFR, Ang1 and Ang2, which promote proliferation and differentiation of endothelial cells, smooth muscle cells, fibroblasts initiating the process of new blood vessels formation. New vessels provide the nutrients for growing cancer mass and help to remove the methabolism waste products. Hence, angiogenesis promotes the cancer mass growth. On the other hand, one should keep in mind that angiogenesis might also give a possibility to improve the cancer treatment since good functioning blood vessels allow anti-cancer drugs better penetrate the tumour structure, and hence reduce the tumour mass.

One of the most well known models describing the influence of new blood vessels development on the tumour dynamics was proposed by Hahnfeldt et al. [15] and later studied in detail by d'Onofrio&Gandolfi [6]. The results of [6] were extended in [7] where the

2010 *Mathematics Subject Classification.* Primary: 34K11, 34K13, 34K18, 34K20, 49K25; Secondary: 92B05, 93C23.

Key words and phrases. Delay differential equations, stability analysis, Hopf bifurcation, angiogenesis, tumour growth.

M. J. Piotrowska's research was supported by Marie Curie European Reintegration Grant within the 7th European Community Framework Programme, grant agreement No. PERG03-GA-2008-230993. All the authors was supported by the Polish Ministry of Science and Higher Education, within the Iuventus Plus Grant: "Mathematical modelling of neoplastic processes" grant No. IP2011 041971.

effect of a class of antiangiogenic drugs that act by altering periodically the proliferation related parameters of the vascular cells was analysed. Moreover, recently the notation of generalised angiogenesis model taking into account anti-angiogenic therapy was introduced by d'Onofrio&Gandolfi in [8]. In [24] Piotrowska&Foryś considered the Hahnfeldt et al. model with two discrete delays in more general case, compare also [8]. Namely, the dynamics of the family of delayed models based on the Gompertz type description ([25]) of the tumour growth was studied. Additionally, within last years, different treatment protocols were introduced to the Hahnfeldt et al. model and the optimal control theory was applied, see e.g. [9], [22], [23] or [27].

Hence, among the models of angiogenesis, the Hahnfletd *et al.* model [15] can be considered as a classic one. However, global stability of a positive steady state is a weak point of it, since newly formed vessels usually have highly unstable structure. Moreover, feedback loops present in the system can lead to oscillatory dynamics, cf. e.g. [14]. To reflect the complex nature of the vessels formation process, Arakelyan *et al.* [3] proposed a very complex computer model, which was compared with implanted human ovarian carcinoma in [2]. Then, in the works by Agur *et al.* [1] and Fory *et al.* [12], that complex model was simplified to the system of three equations with two time delays. The main advantage of the simplified model comparing to the previous ones was introducing of the so-called effective vessel density, that is the amount of vessels supplying one unit volume tumour. The delays included into the model stand for the length of feedback loops described in details in the original computer model in [3]. In [1] the authors claimed that although the proposed model is simple, it can reflect complex dynamics of the vessels formation because of possible oscillations that appear due to a Hopf bifurcation. More precisely, in this paper it was checked that the assumptions of the Hopf bifurcation theorem (in the sense presented in [16]) with the delay as a bifurcation parameter are fulfilled. However, more detailed analysis of the model presented in [12] showed that independently of the magnitude of delays the positive steady state is always unstable and the model cannot reflect a stable behaviour of newly formed vessels that is observed for some less aggressive tumours (see eg. [18]). In [4], combining the ideas presented by Hahnfeldt *et al.* [15] and Agur *et al.* [1] we proposed a model of three differential equations with delays that can describe the process of formation of new vessels in tumour and reflect both stable and unstable structure of vessels observed in reality.

1.1. **Model presentation.** The three-variable model proposed by Agur et al. in [1] has the following form

$$\begin{aligned} \dot{N} &= f_1(E(t-\tau_1))N(t), \\ \dot{P} &= f_2(E(t))N(t) - \delta P(t), \\ \dot{E} &= \left(f_3(P(t-\tau_2)) - f_1(E(t-\tau_1))\right) E(t), \end{aligned} \tag{1.1}$$

where $N(t)$, $P(t)$, $E(t) = \frac{V(t)}{N(t)}$ and $V(t)$ describe the tumour size, the amount of regulating proteins, the effective vessel density and the total blood vessels volume, respectively. Moreover, $\tau_1, \tau_2 \geq 0$ denote the time delays in the proliferation/death and the vessel formation/regression response to stimuli, respectively. *Per capita* growth rates of tumour and vessels are described using switching functions f_1, f_3, respectively. We have $f_i(0) = -a_i < 0$, $f_i(x)$ are increasing and $f_i(x) \to b_i > 0$ as $x \to +\infty$, for $i = 1, 3$, with $x = E$ for $i = 1$, $x = P$ for $i = 3$. The protein production function f_2 is decreasing to 0 and parameter $\delta > 0$ describes the degradation of the angiogenic substance.

In [4] the constructive criticism of model (1.1) was pretended. As a result Bodnar&Foryś proposed the modified model of angiogenesis. This model has the following form

$$
\begin{aligned}
\dot{N} &= \alpha N(t)\Big(1 - \frac{N(t)}{1 + f_1(E(t-\tau_1))}\Big),\\
\dot{P} &= f_2(E(t))N(t) - \delta P(t),\\
\dot{E} &= \Big(f_3(P(t-\tau_2)) - \alpha\Big(1 - \frac{N(t)}{1 + f_1(E(t-\tau_1))}\Big)\Big)E(t),
\end{aligned}
\tag{1.2}
$$

where α is the proliferation rate and the variables and constants have the same meaning as for system (1.1). It is assumed that functions f_i, $i = 1, 2, 3$, are at least continuous and there exist positive constants a_2, a_3, b_1, b_3 and m_3 such that

(C1) f_1 is increasing, $f_1(0) = 0$ and $\lim_{E\to+\infty} f_1(E) = b_1 > 0$;
(C2) f_2 is decreasing and convex, $f_2(0) = a_2 > 0$ and $\lim_{E\to+\infty} f_2(E) = 0$;
(C3) f_3 is increasing, $f_3(0) = -a_3 < 0$, $f_3(m_3) = 0$ and $\lim_{P\to+\infty} f_3(P) = b_3$.

To close the system we define an initial condition of the following form

$$
N(t) = N_0(t) \geq 0, \quad P(t) = P_0(t) \geq 0, \quad E(t) = E_0(t) \geq 0, \quad \text{for} \quad t \in [-\tau_M, 0], \tag{1.3}
$$

where $\tau_M = \max\{\tau_1, \tau_2\}$, and $N_0, P_0, E_0 \in \mathbf{C}([-\tau_M, 0]; \mathbb{R}_{\geq 0})$.

2. **Basic properties of the model.**

Theorem 2.1. *Assume that N_0, P_0 and E_0 are non-negative and the functions f_i, $i = 1, 2, 3$, are continuous and fulfil conditions* (C1)–(C3). *Then solutions to problem* (1.2)–(1.3) *exist globally, are unique and non-negative. Moreover, the following inequalities*

$$
\begin{aligned}
N_{\min} &\leq N(t) \leq N_{\max}\,,\\
0 &\leq P(t) \leq \max\left\{\frac{a_2}{\delta}N_{\max}\,, P_0(0)\right\},\\
0 &\leq E(t) \leq E_0(0)\exp\left((b_3 + \alpha(N_{\max} - 1))\,t\right)
\end{aligned}
$$

hold for all $t \geq 0$, where

$$
N_{\min} = \min\{1, N_0(0)\}, \quad N_{\max} = \max\{N_0(0), 1 + b_1\} > 1\,.
$$

Proof. First notice that the non-negativity of existing solutions is obvious. Clearly, the first equation of system (1.2) can be rewritten as

$$
N(t) = N(0)\exp\left(\alpha\int_0^t \Big(1 - \frac{N(s)}{1 + f_1(E(s-\tau_1))}\Big)ds\right),
$$

and the same procedure can be applied to the third equation. This yields $N(t) \geq 0$ and $E(t) \geq 0$. Thus, the second equation can be estimated as $\dot{P}(t) \geq -\delta P(t)$ and non-negativity of $P(t)$ follows.

Since the function f_i, $i = 1, 2, 3$, are only assumed to be continuous, not necessarily Lipschitz continuous, hence we cannot use a general theorem of uniqueness. We use the step method to prove existence and uniqueness of solutions. Let $\tau_m = \min\{\tau_1, \tau_2\}$. Then for $t \in [0, \tau_m]$ system (1.2) is a non-autonomous system of differential equations. The first equation of (1.2) depends only on the first variable, because $E(t - \tau) = E_0(t - \tau)$ is a given continuous function on the considered time interval, and therefore the solution locally exists. Moreover, non-negativity yields $\dot{N} \leq \delta N$, that guarantees global existence on $[0, \tau_m]$. Next, after solving the first equation, similar arguments apply to the last equation of (1.2), and then to the second one. All solutions are unique due to the fact that the right-hand side of system (1.2) is locally Lipschitz continuous with respect to N, P, E.

Now, we give more strict estimates of the values of $N(t)$, $P(t)$ and $E(t)$. The first equation of (1.2) and condition (C1) imply inequalities

$$\alpha N(t)(1-N(t)) \le \dot{N}(t) \le \alpha N(t)\left(1-\frac{N(t)}{1+b_1}\right),$$

and thus

$$N_{\min} \le N(t) \le N_{\max}.$$

From the second equation of (1.2) and conditions (C1)–(C2) we have

$$-\delta P(t) \le \dot{P}(t) \le a_2 N_{\max} - \delta P(t) \implies 0 \le P(t) \le \max\left\{\frac{a_2}{\delta}N_{\max}, P_0(0)\right\}.$$

Due to condition (C3), the last equation of (1.2) can be estimated as follows

$$\dot{E}(t) \le (b_3 - \alpha + \alpha N_{\max})\, E(t) \implies E(t) \le E_0(0)\exp\left((b_3 + \alpha(N_{\max} - 1))\, t\right).$$

Thus, the step method yields global existence of unique solutions fulfilling the above estimates and the proof is completed. □

2.1. **Steady states.** The analysis of steady states existence is exactly the same as in [4]. However, due to some changes of notation we summarise it briefly.

From the first equation of (1.2) we have either $\bar{N} = 0$ or $\bar{N} = 1 + f_1(\bar{E})$. In the first case we immediately get $\bar{P} = 0$ and $\bar{E} = 0$ from the second and third equation of (1.2), respectively. If $\bar{N} = 1 + f_1(\bar{E})$, then the third equation gives two possibilities. Either $\bar{E} = 0$ and this implies $\bar{N} = 1$ and $\bar{P} = a_2/\delta$ or $\bar{E} \ne 0$. In the latter case we obtain $\bar{P} = m_3$, $\bar{N} = 1 + f_1(\bar{E})$ and $\bar{E}$ is a solution to $f_2(\bar{E})\big(1 + f_1(\bar{E})\big) = \delta m_3$. Hence, depending on the functions f_1 and f_2 there can exist zero, one or more positive steady states given by $(\bar{N}, m_3, \bar{E})$.

Concluding, we have at least two non-negative steady states

$$A = (0,0,0), \qquad B = (1, a_2/\delta, 0),$$

and the positive steady states $D_i = (\bar{N}_i, m_3, \bar{E}_i)$ do not necessarily exist.

2.1.1. *Existence of positive steady states.* As it was discussed in [4] the positive steady state D_i exists if and only if the auxiliary function

$$g(x) = f_2(x)(1 + f_1(x)) - \delta m_3 \tag{2.1}$$

has a positive root. Clearly, $g(0) = a_2 - \delta m_3$ and $g(+\infty) = -\delta m_3$. Thus, for $a_2 > \delta m_3$ there exists at least one positive root of $g(x)$. Therefore, there exists at least one positive steady state D_1 and in generic case the number of positive steady states is odd.

Let us assume that the functions f_1 and f_2 are differentiable. Differentiating the function g defined by (2.1) we obtain

$$g'(x) = f_2'(x)(1 + f_1(x)) + f_2(x) f_1'(x). \tag{2.2}$$

If the function f_1 increases slow enough, then $g'(x) < 0$ and there exists at most one steady state D_1. On the other hand, if $a_2 < \delta m_3$, then in generic case the number of positive states D_i is even, for details see [4].

Frequently the functions f_i, $i = 1, 2, 3$, used in the literature (e.g. [4, 1]) are Hill functions. In the following part of this section we show that there can exist at most three steady states in this case.

First notice, that the function f_3 does not have any influence on the number of steady states. Now, let us assume that $f_i \sim x^m/(1+x^n)$, $i = 1,2$. However, since f_2 is assumed to be convex we take $m = 0$, $n = 1$ for it. Thus, for the functions f_1 and f_2 of the form

$$f_1(x) = \frac{b_1 x^n}{c_1 + x^n}\,, \quad f_2(x) = \frac{a_2 c_2}{c_2 + x}\,, \quad n \in \mathbb{N},\ n \geq 1, \tag{2.3}$$

we may prove the following result.

Proposition 2.2. *Let f_1 and f_2 be given by (2.3) and denote*

$$\bar{x}_0 = \frac{c_1}{b_1+1}\left(\sqrt{b_1\left(\frac{c_2}{c_1}(b_1+1)-1\right)}-1\right). \tag{2.4}$$

(i) For $n = 1$ there can be at most two positive steady states of (1.2). If $a_2 > \delta m_3$, then there exist exactly one positive steady state of (1.2). If $a_2 < \delta m_3$, then if $c_1 > b_1 c_2$ or $g(\bar{x}_0) < 0$, then there exists no positive steady state, while if $g(\bar{x}_0) > 0$, then there exist exactly two positive steady states of (1.2).

(ii) For $n > 2$ there can be at most three positive steady states of (1.2).

Proof. Calculating the derivative of g one obtains

$$g'(x) = -a_2 c_2 \frac{(b_1+1)x^{2n} + c_1(b_1+2-nb_1)x^n - nb_1c_1c_2x^{n-1} + c_1^2}{(c_2+x)^2(c_1+x^n)^2}\,. \tag{2.5}$$

Now, we consider the case $n = 1$ and $n \geq 2$ separately.

If $n = 1$ the numerator of (2.5) is a quadratic polynomial

$$(b_1+1)x^2 + 2c_1 x + c_1\,(c_1 - b_1 c_2)\,. \tag{2.6}$$

Hence, if $b_1 < c_1/c_2$, then (2.6) is positive for any $x \geq 0$ and this implies that $g'(x) < 0$ for $x \geq 0$, so g is decreasing and the steady state exists if $g(0) > 0$, that is $a_2 > m_3\delta$. On the other hand, if $b_1 > c_1/c_2$, then (2.6) has exactly one positive root $\bar{x}_0$ given by (2.4). Thus, the function g is increasing on $(0, \bar{x}_0)$ and decreasing for greater x. Thus, if $g(0) = a_2 - \delta m_3 < 0 < g(\bar{x}_0)$, then there exist exactly two positive steady states D_i, $i = 1,2$, and if $g(0) = a_2 - \delta m_3 > 0$, then there exists exactly one positive steady state D_1. This completes the proof in case $n = 1$.

If $n \geq 2$, we use the Descartes' rule of signs. Notice that the coefficient of x^{2n}, as well as the free term, are positive, while the sign of the coefficient of x^{n-1} is negative. Hence, independently of the sign of the coefficient of x^n, there are always two changes of sign. Thus, by the Descartes' rule of signs, $g'(x)$ has two or zero positive roots. Therefore, we have one of the following possibilities: either g is decreasing (so there exists one positive steady state if $a_2 > \delta m_3$) or there exist $\bar{x}_{0,1}$ and $\bar{x}_{0,2}$ such that g is decreasing on $(0, \bar{x}_{0,1}) \cup (\bar{x}_{0,2}, \infty)$ and increasing on $(\bar{x}_{0,1}, \bar{x}_{0,2})$. Then, depending on the values δm_3, $g(\bar{x}_{0,1})$ and $g(\bar{x}_{0,2})$ there can be up to three positive steady states D_i. □

3. **Analysis of steady states stability.** Under our assumptions the functions f_i, $i = 1,2,3$, are continuous. However, standard local asymptotic stability analysis is easier to perform for differentiable functions f_i, compare the text-books on DDEs [16, 17, 20]. On the other hand, since one of our goals is to investigate a Hopf bifurcation, an additional smoothness is required. These assumptions do not limit our results a lot because functions that typically appear in applications have desired smoothness properties. Moreover, we focus on generic cases in our analysis, so only strict inequalities on parameters are of our interest.

In the following, to shorten the notation, we use the notion of stability meaning local asymptotic stability.

Characteristic function for a general steady state $(\bar{N}, \bar{P}, \bar{E})$ has the form

$$W(\lambda) = -\det\Big(M(\bar{N}, \bar{P}, \bar{E})\Big),$$

where

$$M(\bar{N}, \bar{P}, \bar{E}) = \begin{bmatrix} \alpha\left(1 - \frac{2\bar{N}}{1+f_1(\bar{E})}\right) - \lambda & 0 & \frac{\alpha\bar{N}^2}{(1+f_1(\bar{E}))^2} f_1'(\bar{E})\mathrm{e}^{-\lambda\tau_1} \\ f_2(\bar{E}) & -\delta - \lambda & f_2'(\bar{E})\bar{N} \\ \frac{\alpha\bar{E}}{1+f_1(\bar{E})} & f_3'(\bar{P})\bar{E}\mathrm{e}^{-\lambda\tau_2} & m_{330} - \frac{\alpha\bar{N}\bar{E}}{(1+f_1(\bar{E}))^2} f_1'(\bar{E})\mathrm{e}^{-\lambda\tau_1} - \lambda \end{bmatrix} \tag{3.1}$$

with

$$m_{330} = f_3(\bar{P}) - \alpha\left(1 - \frac{\bar{N}}{1 + f_1(\bar{E})}\right).$$

Proposition 3.1. *Let the functions $f_i \in \mathbf{C}^1$, $i = 1, 2, 3$, fulfil conditions* (C1)–(C3). *Then the trivial steady state $A = (0, 0, 0)$ of system* (1.2) *exists and is unstable independently of the model parameters.*

Proof. For $\tau_j = 0$, $j = 1, 2$, the trivial steady state of system (1.2) is unstable as it was proved in [4]. Consider system (1.2) for $\tau_j > 0$, $j = 1, 2$. For the trivial steady state the matrix M reads

$$M(0, 0, 0) = \begin{bmatrix} \alpha - \lambda & 0 & 0 \\ a_2 & -\delta - \lambda & 0 \\ 0 & 0 & -a_3 - \alpha - \lambda \end{bmatrix}$$

and it does not depend on the delays present in the model. Hence, delays have no influence on the stability, and thus $A = (0, 0, 0)$ is unstable. □

Proposition 3.2. *Let functions $f_i \in \mathbf{C}^1$, $i = 1, 2, 3$, fulfil conditions* (C1)–(C3). *Then the semi-trivial steady state $B = (1, a_2/\delta, 0)$ of system* (1.2) *exists and is stable for $a_2 < \delta m_3$ and unstable for $a_2 > \delta m_3$.*

Proof. As showed in [4] the semi-trivial steady state $B = (1, a_2/\delta, 0)$ exists and is stable or unstable depending on the sign of expression $a_2 - \delta m_3$. The matrix M defined by (3.1) has the following form

$$M(1, a_2/\delta, 0) = \begin{bmatrix} -\alpha - \lambda & 0 & \alpha f_1'(0)e^{-\lambda\tau_1} \\ a_2 & -\delta - \lambda & f_2'(0) \\ 0 & 0 & f_3\left(\frac{a_2}{\delta}\right) - \lambda \end{bmatrix}$$

for the semi-trivial steady state. Hence, calculating the characteristic quasi-polynomial we arrive at

$$W(\lambda) = -(\alpha + \lambda)(\delta + \lambda)\left(f_3(\frac{a_2}{\delta}) - \lambda\right).$$

Therefore, again, the delays have no influence on the stability of this state, and $B = (1, a_2/\delta, 0)$ is stable for $a_2 < m_3\delta$ and unstable for $a_2 > m_3\delta$. □

Stability analysis for the positive steady state(s) of system (1.2) for $\tau_j = 0$, $j = 1$, 2, was presented in [4]. It implies that the number of positive steady states and theirs stability strongly depends on the model parameters and the properties of the function g given by (2.1). We only present the summarising lemma below.

Lemma 3.3. *Assume that the functions $f_i \in \mathbf{C}^1$, $i = 1, 2, 3$, fulfil conditions* (C1)–(C3) *and let $\tau_j = 0$, $j = 1, 2$, and m_3 be the zero of the function f_3 and g be given by* (2.1).

1. *If $a_2 < \delta m_3$ and $g'(E_i) \neq 0$, then there exists odd number (possibly 0) of steady states $D_i = (\bar{N}_i, m_3, \bar{E}_i)$ and steady states with odd indexes are stable, while those with even indexes are unstable.*
2. *If $a_2 > \delta m_3$ and $g'(E_i) \neq 0$, then there exists even number of steady states $D_i = (\bar{N}_i, m_3, \bar{E}_i)$ and steady states with even indexes are stable, while those with odd indexes are unstable.*

The matrix M defined by (3.1) has the following form

$$M(\bar{N}_i, m_3, \bar{E}_i) = \begin{bmatrix} -\alpha - \lambda & 0 & \alpha f_1'(\bar{E}_i)\mathrm{e}^{-\lambda\tau_1} \\ f_2(\bar{E}_i) & -\delta - \lambda & f_2'(\bar{E}_i)\bar{N}_i \\ \frac{\alpha \bar{E}_i}{1+f_1(\bar{E}_i)} & f_3'(m_3)\bar{E}_i\mathrm{e}^{-\lambda\tau_2} & -\frac{\alpha\bar{E}_i}{1+f_1(\bar{E}_i)} f_1'(\bar{E}_i)\mathrm{e}^{-\lambda\tau_1} - \lambda \end{bmatrix}$$

for positive steady state(s) $D_i = (\bar{N}_i, m_3, \bar{E}_i)$ (if any exists). The characteristic quasi-polynomial reads

$$W(\lambda) = \lambda^3 + C_1\lambda^2 + C_2\lambda + (\lambda^2 + \delta\lambda)C_3\mathrm{e}^{-\lambda\tau_1} + (\lambda + \alpha)C_4\mathrm{e}^{-\lambda\tau_2} - C_3C_5\mathrm{e}^{-\lambda(\tau_1+\tau_2)}, \quad (3.2)$$

where

$$\begin{aligned} &C_1 = \delta + \alpha, \quad C_2 = \alpha\delta, \quad C_3 = \alpha\beta d_1, \quad C_4 = a^2\beta d_2 d_3, \quad C_5 = \delta d_3 m_3, \\ &a = 1 + f_1(\bar{E}), \quad d_1 = f_1'(\bar{E}), \quad d_2 = -f_2'(\bar{E}), \quad d_3 = f_3'(m_3), \quad \beta = \frac{\bar{E}}{1 + f_1(\bar{E})}. \end{aligned} \quad (3.3)$$

Due to assumptions (C1)–(C3) we have $d_1, d_2, d_3, c_2, \beta > 0$. Hence, $C_i > 0$ for $i = 1, ..., 5$.

Theorem 3.4. *Let the functions $f_i \in \mathbf{C}^1$, $i = 1, 2, 3$, fulfil conditions* (C1)–(C3) *and $D_i = (\bar{N}_i, m_3, \bar{E}_i)$ be a positive steady state of system* (1.2)*. If $g'(E_i) > 0$, where the function g is given by* (2.1)*, then the steady state D_i is unstable for all $(\tau_1, \tau_2) \in (\mathbb{R}^+)^2 \setminus \{(\tau_1^*, \tau_2^*) : \exists\, \omega > 0\,,\ W(i\omega) = 0\}$, where W is the characteristic function given by* (3.2)*.*

Proof. Case $\tau_1 = \tau_2 = 0$ was studied in [4]. Let us briefly repeat the argument. In this case the characteristic function $W(\lambda)$ given by (3.2) is a polynomial with all coefficients, except the free term, positive. The free term reads $\alpha C_4 - C_3C_5$. Using definitions (3.3) as well as the identity $\delta m_3 = f_2(\bar{E}_i)(1 + f_1(\bar{E}_i))$ we derive the following equality

$$\begin{aligned} \alpha C_4 - C_3C_5 =& \alpha\beta d_3\left(a^2 d_2 - \delta m_3 d_1\right) \\ =& -\alpha\beta d_3\left(1 + f_1(\bar{E}_i)\right)\left(\left(1 + f_1(\bar{E}_i)\right)f_2'(\bar{E}_i) + f_1'(\bar{E}_i)f_2(\bar{E}_i)\right). \end{aligned}$$

Notice that the expression in the last parenthesis is equal to the derivative $g'(\bar{E}_i)$ (compare (2.2)):

$$\alpha C_4 - C_3C_5 = -\alpha\beta d_3\left(1 + f_1(\bar{E}_i)\right)g'(\bar{E}_i)\,. \quad (3.4)$$

Thus, the sign of $\alpha C_4 - C_3C_5$ is reverse to the sign of $g'(\bar{E}_i)$. Therefore, it is clear that if $g'(\bar{E}_i) > 0$, then $W(\lambda)$ has a real positive root, so the steady state D_i is unstable for $\tau_1 = \tau_2 = 0$.

In order to prove that the steady state D_i is unstable for $\tau_1 \geq 0$, $\tau_2 \geq 0$, $\tau_1 + \tau_2 > 0$, we use the Mikhailov criterion (see [11]). We show that the change of the argument of $W(i\omega)$ as ω varies from 0 to $+\infty$ is different than $\frac{3\pi}{2}$. To this end we need to calculate

$$\begin{aligned} \Re\mathrm{e}(W(i\omega)) =& -(C_1 + C_3\cos(\omega\tau_1))\,\omega^2 + \omega\,(\delta C_3\sin(\omega\tau_1) + C_4\sin(\omega\tau_2)) + \\ &+ \alpha C_4\cos\omega\tau_2 - C_3C_5\cos\omega(\tau_1+\tau_2)\,, \\ \Im\mathrm{m}(W(i\omega)) =& -\omega^3 + \omega^2 C_3\sin(\omega\tau_1) + \omega(C_2 + \delta C_3\cos(\omega\tau_1) + C_4\cos(\omega\tau_2)) - \\ &- \alpha C_4\sin\omega\tau_2 + C_3C_5\sin\omega(\tau_1+\tau_2)\,. \end{aligned} \quad (3.5)$$

Thus,

$$\sin(W(i\omega)) = \frac{\Im\mathfrak{m}(W(i\omega))}{\sqrt{(\Re\mathfrak{e}(W(i\omega)))^2 + (\Im\mathfrak{m}(W(i\omega)))^2}} \xrightarrow{\omega\to+\infty} -1,$$
$$\cos(W(i\omega)) = \frac{\Re\mathfrak{e}(W(i\omega))}{\sqrt{(\Re\mathfrak{e}(W(i\omega)))^2 + (\Im\mathfrak{m}(W(i\omega)))^2}} \xrightarrow{\omega\to+\infty} 0,$$

and hence $\lim_{\omega\to\infty} W(i\omega) = 3\pi/2 + 2k\pi$ for some $k \in \mathbb{Z}$.

On the other hand, $W(0) = \alpha C_4 - C_3C_5$ and due to the assumption of Theorem as well as (3.4) we have $W(0) < 0$. Thus, the change of the argument of $W(i\omega)$ as ω varies from 0 to $+\infty$ is equal to $\pi/2 + 2k\pi$ for some $k \in \mathbb{Z}$ and it is different from $\frac{3\pi}{2}$. Hence, (3.2) has roots in the right hand-side of complex plane.

Clearly, there can exist values (τ_1^*, τ_2^*) for which there is ω_0 such that $W(i\omega_0) = 0$. In such case we cannot use neither the Mikhailov criterion nor the linearisation theorem. However, the set $\{(\tau_1^*, \tau_2^*) : \exists\omega > 0\,,\ W(i\omega) = 0\}$ has zero measure in the space $(\mathbb{R}^+)^2$, and hence it is not a generic case. □

In the case of non-negative delays the analysis of stability of steady states D_i that are stable for $\tau_1 = \tau_2 = 0$ is more complicated. Here, we restrict our analysis to two cases presented below.

3.1. **Case $\tau_1 = 0$ and $\tau_2 > 0$.** For $\tau_1 = 0$, characteristic quasi-polynomial (3.2) has the following form

$$W_1(\lambda) = \lambda^3 + (C_1 + C_3)\lambda^2 + (C_2 + \delta C_3)\lambda + (C_4\lambda + \alpha C_4 - C_3C_5)e^{-\lambda\tau_2}. \tag{3.6}$$

Theorem 3.5. *Let the functions $f_i \in \mathbf{C}^1$, $i = 1, 2, 3$, fulfil conditions* (C1)–(C3)*, $\tau_1 = 0$ and $D_i = (\bar{N}_i, m_3, \bar{E}_i)$ be a positive steady state of system* (1.2) *such that $g'(\bar{E}_i) < 0$, where g' is given by* (2.2)*. Then there exists $\tau_{2,0}$ such that*

(i) the steady state D_i is stable for $\tau_2 < \tau_{2,0}$;
(ii) the steady state D_i is unstable for $\tau_2 > \tau_{2,0}$.

Moreover, if $f_i \in \mathbf{C}^2$, $i = 1, 2, 3$, then Hopf bifurcation occurs at $\tau_2 = \tau_{2,0}$, that implies periodic solutions occurrence.

Proof. As it was proved in [4] condition $g'(\bar{E}_i) < 0$ implies that steady state D_i is stable for $\tau_1 = \tau_2 = 0$. We show that there exists $\tau_{2,0} > 0$ for which there is a pair of purely imaginary roots of W_1, this is $W_1(\pm i\omega) = 0$ for some $\omega > 0$. Re-writing (3.6) we obtain

$$W_1(\lambda) = P_1(\lambda) + Q_1(\lambda)e^{-\lambda\tau_2} = 0,$$

where

$$P_1(\lambda) = \lambda^3 + (C_1 + C_3)\lambda^2 + (C_2 + \delta C_3)\lambda, \quad \text{and} \quad Q_1(\lambda) = C_4\lambda + \alpha C_4 - C_3C_5. \tag{3.7}$$

Characteristic quasi-polynomial (3.2) has a pair of purely imaginary roots $\pm i\omega$, $\omega > 0$, if and only if

$$P_1(i\omega) = -Q_1(i\omega)e^{-i\omega\tau_{2,0}}.$$

This condition implies that there exist positive zeros of the auxiliary function $G_1(\omega) = |P_1(i\omega)|^2 - |Q_1(i\omega)|^2 = F_1(\omega^2)$, cf. [5] for detailed description of relations between this auxiliary function and the eigenvalues. Substituting $x = \omega^2$ we obtain

$$F_1(x) = x^3 + x^2((C_1 + C_3)^2 - 2(C_2 + \delta C_3)) + x((C_2 + \delta C_3)^2 - C_4^2) - (\alpha C_4 - C_3C_5)^2. \tag{3.8}$$

The coefficient of x with the highest power is positive, while the free term is negative. This implies that (3.8) has at least one positive real root. We show that this root is unique. To this end we calculate the derivative of F_1:

$$F_1'(x) = 3x^2 + 2x((C_1 + C_3)^2 - 2(C_2 + \delta C_3)) + (C_2 + \delta C_3)^2 - C_4^2.$$

Notice that the sign of the coefficient of the linear term of F_1' is positive. Indeed,

$$(C_1 + C_3)^2 - 2(C_2 + \delta C_3) = \alpha^2(1 + \beta d_1)^2 + \delta^2 > 0\,.$$

Hence, we have two possibilities. If $F_1'(0) = (C_2 + \delta C_3)^2 - C_4^2 > 0$, then $F_1'(x) > 0$ for all $x \geq 0$ and a positive root x_0 of F_1 is unique. On the other hand, if $F_1'(0) < 0$, then there exists a unique positive root $\bar{x}$ of F_1' such that the function F_1 is decreasing on $(0, \bar{x})$ and increasing for $x > \bar{x}$. Because $F_1(0) < 0$, the above arguments imply that $F_1(\bar{x}) < 0$ and there exists a unique positive root x_0 again. Moreover, in both cases, we can easily see that $F_1'(x_0) > 0$. Thus, using Proposition 1 from [5] we obtain

$$\operatorname{sgn}\left(\frac{d\Re\mathrm{e}\lambda(\tau)}{d\tau}\bigg|_{\tau=\tau_{2,0}}\right) = \operatorname{sgn}\left(\frac{d}{d\omega}G_1(\omega)\bigg|_{\omega=\sqrt{x_0}}\right) = \operatorname{sgn}\left(\frac{d}{dx}F_1(x)\bigg|_{x=x_0}\right) > 0.$$

Hence, roots of characteristic quasi-polynomial cross the imaginary axis from left to right with increasing bifurcation parameter τ_2 and the proof is completed. □

3.2. **Case $\tau_1 > 0$ and $\tau_2 = 0$.** For $\tau_1 > 0$ and $\tau_2 = 0$ characteristic quasi-polynomial (3.2) has the following form

$$W_2(\lambda) = \lambda^3 + C_1\lambda^2 + \lambda(C_2 + C_4) + \alpha C_4 + (C_3\lambda^2 + \delta C_3\lambda - C_3C_5)\mathrm{e}^{-\lambda\tau_1}. \tag{3.9}$$

As in the previous subsection, defining the auxiliary function we obtain

$$F_2(x) = x^3 + \alpha_2 x^2 + \alpha_1 x + \alpha_0\,, \tag{3.10}$$

where

$$\alpha_2 = C_1^2 - 2(C_2 + C_4) - C_3^2\,,\ \alpha_1 = (C_2 + C_4)^2 - 2\alpha C_1 C_4 - C_3^2\left(\delta^2 + 2C_5\right),\ \alpha_0 = \alpha^2 C_4^2 - C_3^2 C_5^2.$$

Theorem 3.6. *Let the functions $f_i \in \mathbf{C}^1$, $i = 1, 2, 3$, fulfil conditions* (C1)–(C3), $\tau_2 = 0$, $\bar{x}_1 = \frac{1}{3}\left(\sqrt{\alpha_2^2 - 3\alpha_1} - \alpha_2\right)$ *and D_i is stable for $\tau_j = 0$, $j = 1, 2$.*

(i) If one of the conditions
- *(a) $\alpha_1 > 0$ and $\alpha_2 > 0$;*
- *(b) $\alpha_1 > 0$ and $\alpha_2^2 < 3\alpha_1$;*
- *(c) $\alpha_1 > 0$ and $\alpha_2 < 0$ and $\alpha_2^2 > 3\alpha_1$ and $F_2(\bar{x}_1) > 0$;*
- *(d) $\alpha_1 < 0$ and $F_2(\bar{x}_1) > 0$*

holds, then the steady state D_i is stable for all $\tau_1 \geq 0$.

(ii) If one of the conditions
- *(a) $\alpha_1 < 0$ and $F_2(\bar{x}_1) < 0$;*
- *(b) $\alpha_1 > 0$, $\alpha_2 < 0$ and $\alpha_2^2 > 3\alpha_1$ and $F_2(\bar{x}_1) < 0$*

holds, then there exists $\tau_{1,c}$ such that for $\tau_1 \in (0, \tau_{1,c})$ the state D_i is stable. If $f_i \in \mathbf{C}^2$, $i = 1, 2, 3$, then Hopf bifurcation occurs at $\tau_1 = \tau_{1,c}$.

Remark. Notice that the conditions in the part (i) of Theorem 3.6 are equivalent to $\alpha_2^2 < 3\alpha_1$ or $\bar{x}_1 < 0$ or $F_2(\bar{x}_1) > 0$, while the conditions in the part (ii) of Theorem 3.6 are equivalent to $\alpha_2^2 > 3\alpha_1$ and $\bar{x}_1 > 0$ and $F_2(\bar{x}_1) < 0$.

Proof. Let us recall that stability of D_i for $\tau_1 = \tau_2 = 0$ implies $\alpha_0 > 0$ in generic cases. Hence, $\alpha_0 > 0$ is assumed in this proof. Notice also that if $\bar{x}_1$ is a real number, then F_2 has a local minimum at $\bar{x}_1$.

Part (i). We need to show that there does not exist $\tau_{1,0} > 0$ for which there is a pair of purely imaginary roots of W_2. Clearly, if the condition (a) or (b) holds, then $F_2'(x) > 0$ for all $x \geq 0$, and therefore F_2 is increasing for $x \geq 0$. Hence, the inequality $\alpha_0 > 0$ implies that F_2 has no positive root. If the condition (c) or (d) holds, then F_2 is first increasing and then decreasing (if (c) holds) or only decreasing (if (d) holds) on $[0, \bar{x}_1)$ reaching its local minimum at x_1. Since $F_2(0) = \alpha_0 > 0$ and $F_2(\bar{x}_1) > 0$ the function $F_2(x)$ is positive for all $x \geq 0$. Hence, no stability switches occur.

Part (ii). We show that there exists $\tau_{1,0} > 0$ for which there is a pair of purely imaginary roots of W_2, i.e. $\omega_0 > 0$ such that $W_2(\pm i\omega_0) = 0$. Assumptions yield $\bar{x}_1 > 0$ and $F_2(\bar{x}_1) < 0$. Continuity of F_2 and the fact that $F_2(0) = \alpha_0 > 0$ imply that there exist $x_{0,0} < \bar{x}_1 < x_{0,1}$ such that $F_2(x_{0,j}) = 0$, $j = 1, 2$. Moreover, we have $F_2'(x_{0,0}) < 0$ and $F_2'(x_{0,1}) > 0$. Hence, at least one stability switch is possible for some value of $\tau_{1,c}$ and Hopf bifurcation occurs at this point. □

Proposition 3.7. *Let the functions $f_i \in \mathbf{C}^1$, $i = 1, 2, 3$, fulfil conditions* (C1)–(C3), $\tau_2 = 0$ *and $D_i = (\bar{N}_i, m_3, \bar{E}_i)$ be a positive steady state of system* (1.2) *such that $g'(\bar{E}_i) < 0$, where g' is given by* (2.2). *Then if*

$$\begin{aligned} \left|f_2'(E_i)\right| f_3'(m_3) &< \frac{\delta^2}{2(1+f_1(E_i))E_i}, \\ f_1'(\bar{E}_i) &< \frac{1+f_1(E_i)}{E_i} \cdot \min\left\{1, \sqrt{\frac{\delta^2 - 2(1+f_1(\bar{E}_i))\bar{E}_i\left|f_2'(\bar{E}_i)\right| f_3'(m_3)}{\delta(2m_3 f_3'(m_3)+\delta)}}\right\}, \end{aligned} \tag{3.11}$$

then the steady state D_i is stable for all $\tau_1 \geq 0$.

Proof. The technique of this proof is very similar to the one of Theorem 3.5. Clearly, the steady state D_i is stable for $\tau_1 = \tau_2 = 0$. We show the change of its stability is impossible.

Assume that there exists a pair of purely imaginary roots of characteristic quasi-polynomial (3.9), this is there exists $\omega_0 > 0$ such that $W(\pm i\omega_0) = 0$. We consider the auxiliary function F_2 defined by (3.10).

Notice that since the sign of $C_3C_5 - \alpha C_4$ is the same as the sign of the derivative $g(E_i)$, then we have $\alpha_0 > 0$ if the steady state D_i is stable for $\tau_1 = 0$. We derive conditions under which α_1 and α_2 are also positive. Using (3.3) we obtain

$$\alpha_2 = \alpha^2\left(1 - \beta^2 d_1^2\right) + \delta^2 - 2a^2\beta d_2 d_3.$$

It is easy to see that condition (3.11) implies

$$d_1 = f_1'(E_i) < \frac{1+f_1(E_i)}{E_i} = \frac{1}{\beta} \quad \text{and} \quad d_2 d_3 = \left|f_2'(E_i)\right| f_3'(m_3) < \frac{\delta^2}{2(1+f_1(E_i))E_i} = \frac{\delta^2}{2a^2\beta}.$$

Hence, $\alpha_2 > 0$. Again, using (3.3) we calculate

$$\alpha_1 = a^4\beta^2 d_2^2 d_3^2 + \alpha^2\left(-\beta^2\delta(2m_3d_3+\delta)d_1^2 + \delta^2 - 2a^2\beta d_2 d_3\right). \tag{3.12}$$

It can be easily seen that if (3.11) holds, then conditions

$$d_2 d_3 < \frac{\delta^2}{2a^2\beta} \quad \text{and} \quad d_1 < \frac{1}{\beta}\sqrt{\frac{\delta^2 - 2a^2\beta d_2 d_3}{\delta(2m_3d_3+\delta)}} \tag{3.13}$$

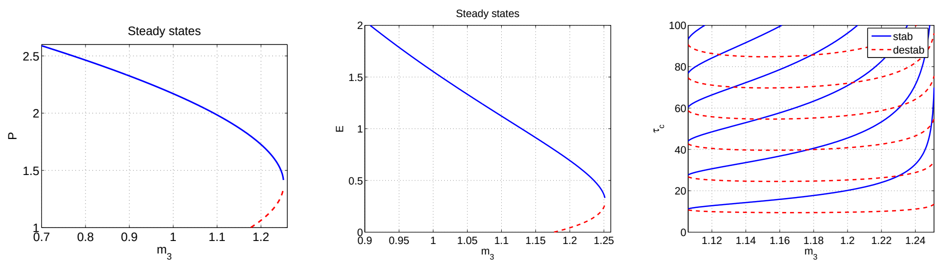

FIGURE 1. Here $n = 1$ and f_j, $j = 1, 2$, are Hill functions defined by (2.3) with $a_2 = 0.4$, $b_1 = 2.3$, $c_1 = 1.5$, $c_2 = 1$. In the left hand-side and middle graphs the dependence of the first and last coordinate of the positive steady state, respectively, on the parameter m_3 is presented. Solid and dashed lines denote stable (for $\tau_1 = \tau_2 = 0$) and unstable steady state, respectively. In the right-hand graph the dependence of critical values of τ_1 on the parameter m_3 for the positive steady state is presented. Dashed lines denote values for which eigenvalue crosses imaginary axis from left to right and the solid line – from right to left. We see that if m_3 is small enough, then multiple stability switches are possible. Other model parameters are: $\delta = 0.34$, $\alpha = 1$, $a_3 = b_3 = 1$.

are fulfilled yielding $\alpha_1 > 0$. Since α_0, α_1 and α_2 are all positive, by the rule of signs, $F_2(x)$ has no real roots and this contradicts the assumption that W_2 has a purely imaginary root. □

4. **Numerical simulations.** In this section we illustrate the theoretical results obtained above by numerical simulations. For these simulations we consider almost the same specific functions as in [4]. Namely, we take

$$f_1(E) = \frac{b_1 E^n}{c_1 + E^n}, \qquad f_2(E) = \frac{a_2 c_2}{c_2 + E}, \qquad f_3(P) = \frac{b_3(P^2 - m_3^2)}{\frac{m_3^2 b_3}{a_3} + P^2}.$$

Clearly, depending on the model parameters we have from zero up to three positive steady states (compare Proposition 2.2). We consider two cases $n = 1$ and $n = 2$, fix parameters:

$$\begin{aligned} a_2 &= 0.4, \quad a_3 = 1, \quad b_1 = 2.3, \quad b_3 = 1, \\ c_1 &= 1.5, \quad c_2 = 1, \quad \alpha = 1, \quad \delta = 0.34, \end{aligned} \tag{4.1}$$

and study the behaviour of the system depending on m_3, τ_1 and τ_2.

We are motivated by the number of recent studies on the different kinds of anti-angiogenic treatment applied to vascular tumours, [19, 23, 28, 26, 10]. We have decided to investigate the influence of m_3 parameter on the model dynamics since, together with a_3 and b_3, it characterises the *per capita* growth of vessels described by the function f_3, compare with (C3) assumption.

In Fig. 1 (left and middle graphs) the dependence of the number of positive steady states and their local stability on m_3 for system (1.2) with $n = 1$ and $\tau_1 = \tau_2 = 0$ is presented. For sufficiently small m_3 there exists exactly one steady state, while for larger values there exist two steady states: stable and unstable one. Clearly, for $\tau_1 = 0$ a single Hopf bifurcation takes place and no other stability switches are possible. On the other hand, for $\tau_2 = 0$, according to Theorem 3.6, we might expect multiple stability switches of the positive steady state that is stable without delays. On the other hand, Theorem 3.4 implies

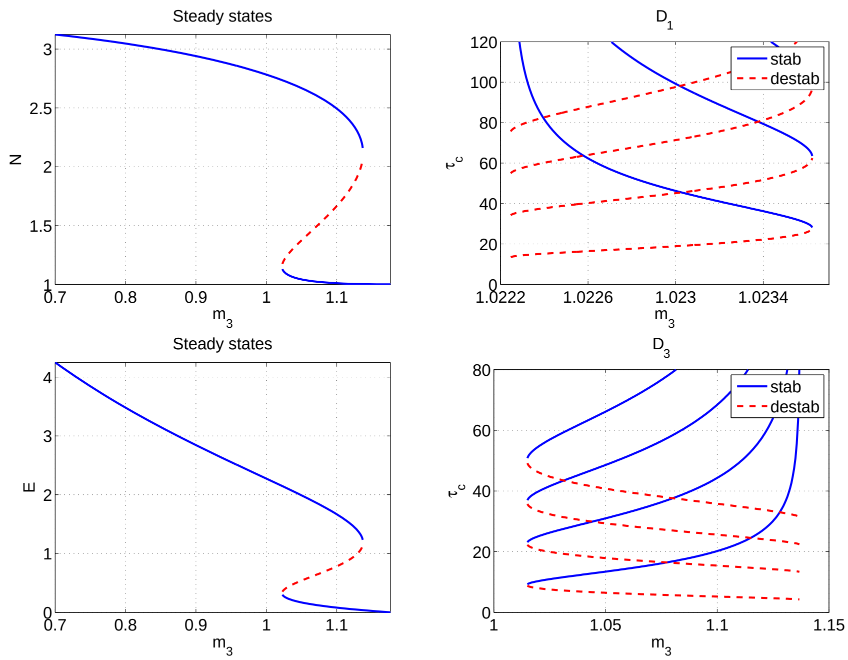

FIGURE 2. Here $n = 2$ and f_j, $j = 1, 2$, are Hill functions defined by (2.3) with $a_2 = 0.4$, $b_1 = 2.3$, $c_1 = 1.5$, $c_2 = 1$. In the left hand-side panel the dependence of the first and last coordinate of the positive steady states on the parameter m_3 is presented. Solid and dashed lines denote stable (for $\tau_1 = \tau_2 = 0$) and unstable steady states, respectively. In the right-hand panel the dependence of critical values of τ_1 on the parameter m_3 for the positive steady states is presented. Dashed lines denote values for which eigenvalues cross imaginary axis from left to right, while solid lines – from right to left. We see that if m_3 is small enough, then multiple stability switches are possible. Other model parameters are: $\delta = 0.34$, $\alpha = 1$, $a_3 = b_3 = 1$.

that the unstable positive steady state for system (1.2) without delays remains unstable for almost all positive delays. In Fig. 1 (right graph) the plot of critical values of the bifurcation parameter (τ_1) is presented. Dashed lines indicate the values of τ_1 for which the eigenvalues cross the imaginary axis from left to right in the complex plane. Solid lines stand for the values of bifurcation parameter for which we observe the movement in the opposite direction when τ_2 increases. For example, for $m_3 = 1.2$ only three stability switches are possible, while for $m_3 = 1.14$ there are 7 stability switches. Moreover, the number of stability switches decreases with increasing m_3.

For the same set of parameters (4.1) and for $n = 2$ we have from one to three positive steady states, as presented in left panel in Fig. 2. For $\tau_1 = \tau_2 = 0$ and small or large enough values of m_3 parameter there exists exactly one stable steady state. For the intermediate vales of m_3 parameter we have bistable model, i.e there exist two stable steady states and one unstable, and we observe the hysteresis phenomenon which was described in more details in [4]. In this case, for fixed parameters, the behaviour of solutions depends on the initial conditions. In Fig. 3 (left graph) we present the basins of attraction of stable steady states D_1 and D_3, while in Fig. 3 (right graph) the separating surface (so called separatrix)

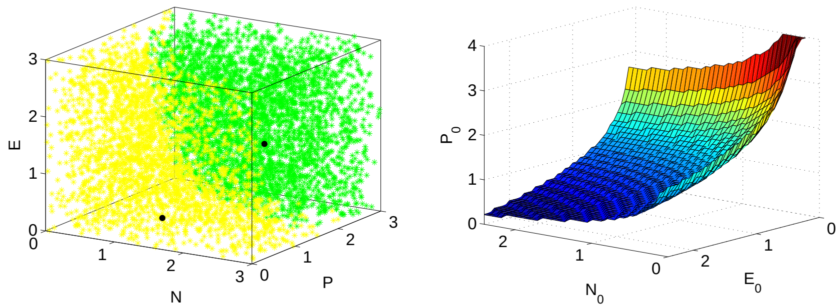

FIGURE 3. Left: basins of attraction for both non-negative locally stable steady states $D_1 = (1.009762, 1.1, 0.079959)$ and $D_3 = (2.493861, 1.1, 1.667231)$ (denoted by black dots) for $\tau_1 = \tau_2 = 0$, $n = 2$, f_j $j = 1, 2$, Hill functions defined by (2.3) with $a_2 = 0.4$, $b_1 = 2.3$, $c_1 = 1.5$, $c_2 = 1$, $\delta = 0.34$, $\alpha = 1$, $a_3 = b_3 = 1$ and $m_3 = 1.1$, are presented. Lighter (darker) stars indicate initial values for which solutions tend to D_1 (D_3). Right: the separatrix for the same set parameters is plotted.

is plotted. Clearly, the shape of this surface indicates that for $\tau_1 = \tau_2 = 0$ there is no possibility to start in the neighbourhood of tumour free state, i.e. $N_0 \approx 0$, and reach D_3 steady state. For positive delays the situation is again similar to case $n = 1$: the middle steady state remains unstable independently of the model parameters and for odd steady states we observe a Hopf bifurcation, compare with the right panel in Fig. 2. For example, for the largest positive steady state D_3 (right bottom graph) and $m_3 = 1.06$ only three stability switches are possible, while for $m_3 = 1.02$ we observe 11 stability switches. For this steady state the number of stability switches decreases with increasing m_3, while for the smallest one, that is D_1, that number increases, see right top graph in Fig. 2.

In Fig. 4, for the same set of parameters and particular delays values $\tau_1 = 18$ and $\tau_2 = 0$, the plots of solution as a function of time in different time intervals are presented. Here we observe an interesting long time behaviour. First, the solution reaches the neighbourhood of the stable steady state D_1 and after some time oscillations of the solution are observed.

As it is mentioned before, we are interested in the influence of the anti-angiogenic treatment, hence in Fig. 5 we present an example of simulations run for the same fixed set of parameters excluding delays and the parameter m_3. For these simulations the parameter m_3 is treated as a continuous slowly oscillating function of time and the delay values are varied. Clearly, for all cases the change in m_3 function forces that change in solutions behaviour. However, while for zero delays there is no oscillation corresponding to the constant parts of m_3 function and we observe typical hysteresis effect in switching the steady state attracting the solution, when we perturbed delays (as indicated in the plots titles) sometimes we observe the oscillatory behaviour.

5. **Summary and conclusions.** The model of tumour angiogenesis studied in this paper includes two time delays reflecting the time needed for maturation/stabilisation of blood vessels τ_1 and angiogenic proteins production τ_2. We presented analysis of existence and stability of steady states with respect to the magnitude of delays. In the general form the right-hand side of the system is described by three functions reflecting the tumour

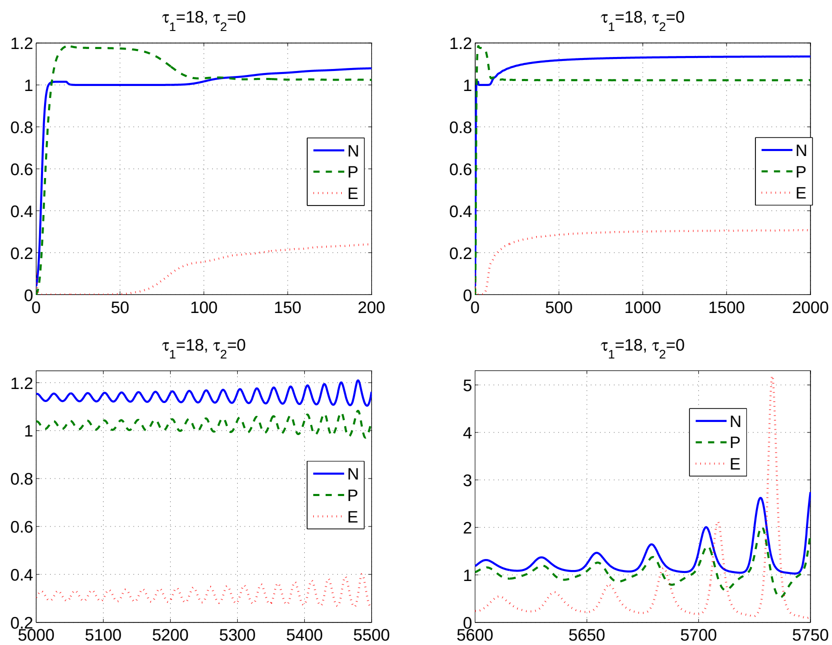

FIGURE 4. Solution to system (1.2) for $n = 2$ and f_j, $j = 1, 2$, are Hill functions defined by (2.3) with $a_2 = 0.4$, $b_1 = 2.3$, $c_1 = 1.5$, $c_2 = 1$, $\delta = 0.34$, $\alpha = 1$, $a_3 = b_3 = 1$, $m_3 = 1.0225$ and $\tau_1 = 18$, $\tau_2 = 0$. In this case there exist three positive steady states. The steady states D_1 and D_2 are unstable, while D_3 is stable. Initial functions are constant with $N_0 \equiv 0.04$, $P_0 \equiv 0$ and $E_0 \equiv 0.1$. Similar type of the behaviour was observed for various initial data.

carrying capacity depending on the amount of vessels f_1, angiogenic proteins production f_2 and stimulation of tumour vessels production f_3. These functions have some specific properties that are satisfied by some type of Hill functions. The analysis performed in the general case showed that apart the trivial and semi-trivial steady states there can be an arbitrary number of positive steady states and the model dynamics strongly depends both on the model parameters and the magnitude of delays. We focused on the cases in which one of the delays is positive and the other is zero. It occurred that multiple stability switches and periodic orbits arising due to a Hopf bifurcation are possible even under this simplifying assumption. Moreover, choosing the simplest Hill functions we were able to illustrate this theoretical result numerically. It should be noticed that, as showed in [24], for the d'Onofrio&Gandolfi and Hahnfeldt et al. models with single delay or two equal delays stability switches are not possible. On the other hand, although the dynamics of the Hahnfeldt et al. model with more than one delay included into it can also exhibit such properties like multiple stability switches, compare [24], hysteresis effect is not present in that model because only one positive steady state exists. Clearly, in [4] we showed that there can exist more than one positive steady state and for some parameter values the hysteresis loop and cusp catastrophe occur. Due to such effects as well as possible stability switches due to the increasing delay found in the present paper, small changes in parameter values can cause huge changes in the solution dynamics. Hence, we can conclude that such small changes of parameters can reflect instability described in [1, 3]. On the other hand,

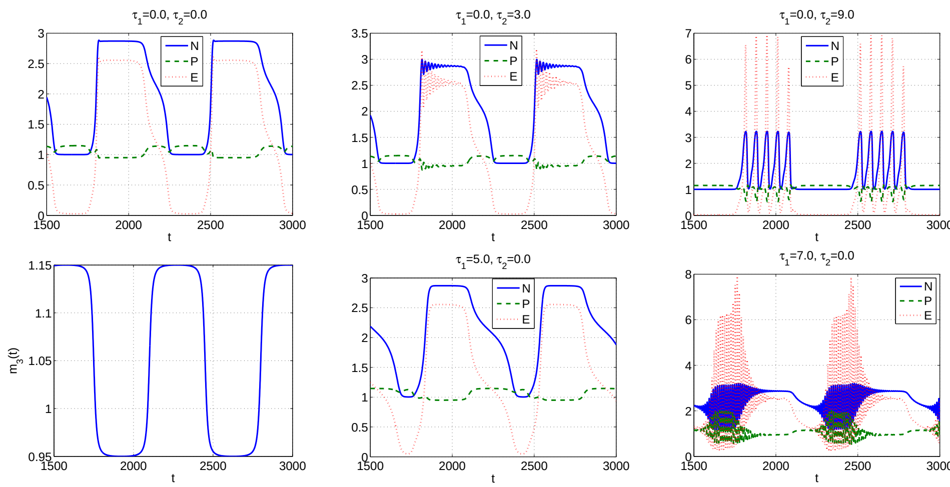

FIGURE 5. Solutions to system (1.2) for $n = 2$ and f_j, $j = 1, 2$, are Hill functions defined by (2.3) with $a_2 = 0.4$, $b_1 = 2.3$, $c_1 = 1.5$, $c_2 = 1$, $\delta = 0.34$, $\alpha = 1$, $a_3 = b_3 = 1$ and slowly varying, periodic m_3, and different values of time delays. The graph of $m_3(t)$ is presented in the left-hand side panel (bottom graph). A change of the behaviour is observed when m_3 changes from the values for which only D_1 exists to the values with only D_3 existing.

similar behaviour as observed due to the cusp catastrophe was described in [21, 13] as "sneaking through" mechanism. This mechanism is described as the possibility of change of the attractor of the model from the steady state with small tumour volume (less harm to the host) to the other with large one (much more dangerous) when some model parameters admit little changes. Therefore, the dynamics of our simple model can cover the behaviour observed for many other models that can be found in the literature.

Moreover, comparing to the Agur et al. model dynamics [1], we get possibility of stabilisation of tumour structure on some level which is impossible in the original model. In that model the only positive steady state of the system is a saddle in the case without delay and oscillatory dynamics that appear due to a Hopf bifurcation with increasing delay cannot be stable; we always observe oscillations increasing in time. Therefore, the changes we proposed in the original structure of the Agur at al. model [1] seem to be necessary to get biologically relevant model dynamics. Moreover, as we can see in numerical simulations presented in this paper, our model admits really complex dynamics that can be comparable with the results for real carcinoma studied using the complex numerical model in [3]. On the other hand, it can be very difficult to fit solutions of such simplified system to real data, as done in [3]. However, in our future work we plan to estimate our model parameters to fit as well as it is possible the dynamics of human ovarian carcinoma from [3]. It will allow us to bring closer to reality and make more useful predictions from the model dynamics.

Acknowledgments. M. J. Piotrowska's research was supported by Marie Curie European Reintegration Grant within the 7th European Community Framework Programme, grant agreement No. PERG03-GA-2008-230993.

All the authors was supported by the Polish Ministry of Science and Higher Education, within the Iuventus Plus Grant: "Mathematical modelling of neoplastic processes" grant No. IP2011 041971.

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Received March 15, 2012; revised September 03, 2012.

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