ANGIOGENESIS MODEL WITH ERLANG DISTRIBUTED DELAYS

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ABSTRACT. We consider the model of angiogenesis process proposed by Bodnar and Foryś (2009) with time delays included into the vessels formation and tumour growth processes. Originally, discrete delays were considered, while in the present paper we focus on distributed delays and discuss specific results for the Erlang distributions. Analytical results concerning stability of positive steady states are illustrated by numerical results in which we also compare these results with those for discrete delays.

1. **Introduction.** In this paper we focus on the process of angiogenesis, which means formation of new vessels from pre-existing ones. It is a normal and vital process in growth and development of animal organisms, but it is also essential in the transition of avascular forms of solid tumours into metastatic ones. Small tumours (less than 1–2 mm^3 of volume) receive nutrients from the outside by simple diffusion. Then necrotic core starts to grow, which is associated with the secretion of angiogenic factors by cancer cells. The supply of nutrients allows cancer to grow further, and moreover vessels form the path for spreading cancer cells in the organism.

Mathematical modelling of this process is inextricably linked with the idea of anti-angiogenic treatment first considered by Folkman in 1971 (c.f. [15]). However, as anti-angiogenic agents were not known that time, it took more than 20 years for the specific models of angiogenesis and anti-angiogenic treatment appear (c.f. [17] were one of the best known models of it has been proposed).

Various approaches were used to describe the angiogenesis process in mathematical language. The simplest approach is based on ordinary differential equations describing the dynamics of tumour and vasculature, like in the approach of Hahnfeldt et al. [17]. This idea was extended by many authors, including d'Onofrio and Gandolfi [14], Agur et al. [2], Bodnar and Foryś [8], Poleszczuk et al. [21], Piotrowska and Foryś [20, 16]. However, in many cases spatio-temporal dynamics of

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vessels and tumour structure is important. To reflect such a structure one can use the approach of partial differential equations. First models of that type was based on reaction-diffusion equations with the process of chemotaxis taken into account; cf. [12]. Many papers focusing on chemotaxis modelling was published by M. Chaplain and coauthors (cf. [12], [19] where also haptotaxis process was considered, [3] with the influence of external forces). Yet another approach is based on cellular automata. Models of that type was proposed by Rieger and coauthors (cf. [6, 23]), while Alarcón et al. [1] considered hybrid cellular automaton in the context of multiscale modelling. Very nice review of various types of spatio-temporal models of vasculogenesis and angiogenesis processes could be find in [22], where a list of many other references on that topic is available.

In this paper we consider the model of tumour angiogenesis proposed in [7] and studied in [9] in the context of discrete delays. However, discrete delays could be only an approximation of delays present in real life, and therefore, following [10] we decided to incorporate distributed delays and compare the results with those for the discrete case. We mainly focus on the Erlang distributions, however some results for general distributions are also obtained. Partial results for the distributed delay in the vessel formation process was presented in [5]. Here, we incorporate distributed delays both in the vessel formation and tumour growth processes. Thus we consider the following system of the first order differential equations with distributed delays

$$
\begin{aligned}
\dot{N}(t) &= \alpha N(t)\left(1 - \frac{N(t)}{1 + f_1(h_1(E_t))}\right), \\
\dot{P}(t) &= f_2(E(t))N(t) - \delta P(t), \\
\dot{E}(t) &= \left(f_3(h_2(P_t))ds - \alpha\left(1 - \frac{N(t)}{1 + f_1(h_1(E_t))}\right)\right)E(t),
\end{aligned}
\tag{1.1}
$$

where $N(t)$, $P(t)$, $E(t)$, α and δ describe the tumour size, the amount of regulating proteins, the effective vessel density, the tumour proliferation rate and the degradation of proteins, respectively. Both parameters could also include the influence of treatment.

The functions $h_i : \mathbf{C}((-\infty, 0], \mathbb{R})$, $i = 1, 2$, are defined as follows

$$
h_i(\phi) = \int_0^\infty k_i(s)\phi(-s)\,\mathrm{d}s,
$$

and we assume $k_i(s) : [0, \infty) \to [0, \infty)$ are probability densities with finite expectations, that is

$$
\int_0^\infty k_i(s)\,\mathrm{d}s = 1 \quad \text{and} \quad 0 < \int_0^\infty s k_i(s)\,\mathrm{d}s < \infty, \quad i = 1, 2.
$$

For any $\phi \in \mathbf{C}(\mathbb{R}, \mathbb{R})$, the function ϕ_t is defined as $\phi_t(s) = \phi(t+s)$ for $s \in (-\infty, 0]$.

Moreover, we assume that the functions f_i are locally Lipschitz and there exist positive constants A_2, A_3, B_1, B_3 and m_3 such that

(A1) f_1 is increasing, $f_1(0) = 0$ and $\lim_{E \to +\infty} f_1(E) = B_1 > 0$,
(A2) f_2 is decreasing and convex, $f_2(0) = A_2 > 0$ and $\lim_{E \to +\infty} f_2(E) = 0$,
(A3) f_3 is increasing, $f_3(0) = -A_3 < 0$, $f_3(m_3) = 0$ and $\lim_{P \to +\infty} f_3(P) = B_3$.

For detailed derivation of the model described by Eqs. (1.1) we refer to [7, 9].

To close the problem we need to define initial data. Let $\mathcal{C} = \mathbf{C}((-\infty, 0], \mathbb{R}^3)$ be the space of continuous functions defined on the interval $(-\infty, 0]$ with values in $\mathbb{R}^3$, and as $\mathcal{C}_+$ we define the subspace of $\mathcal{C}$ that consist of the functions with

non-negative values. Because the distributions of delays have infinite supports, we need to control the behaviour of initial functions at infinity (see [18]). To this end, let define a Banach space Φ in the following way

$$\Phi = \left\{ \phi \in \mathcal{C} : \lim_{s \to -\infty} \phi(s) \mathrm{e}^s = 0 \quad \text{and} \quad \sup_{s \in (-\infty, 0]} |\phi(s) \mathrm{e}^s| < \infty \right\},$$

$$\|\phi\|_\Phi = \sup_{s \in (-\infty, 0]} |\phi(s) \mathrm{e}^s|,$$

and we consider initial functions from the set $\Phi_+ = \Phi \cap \mathcal{C}_+$.

2. **Analysis of the model.** In this section we consider basic properties of system (1.1) for general distributions $k_i(s)$ and study stability in the case of Erlang distributions. For all results presented here we assume the functions f_i, $i = 1, 2, 3$, fulfil conditions (A1)–(A3).

Theorem 2.1. *For any arbitrary initial function $\phi = (\phi_N, \phi_P, \phi_E) \in \Phi_+$ there exists a unique solution of system (1.1) in Φ_+ defined on $t \in [0, +\infty)$. Moreover, for all $t \geq 0$ any solution satisfies the following inequalities*

$$N_{\min} \leq N(t) \leq N_{\max},$$

$$0 \leq P(t) \leq \max\left\{ \frac{A_2}{\delta} N_{\max}, \phi_2(0) \right\}, \tag{2.1}$$

$$0 \leq E(t) \leq \phi_3(0) \exp\left((B_3 + \alpha(N_{\max} - 1))t \right),$$

where

$$N_{\min} = \min\left\{ 1, \phi_N(0) \right\}, \quad N_{\max} = \max\left\{ \phi_N(0), 1 + B_1 \right\}.$$

Proof. It is easy to see that the right-hand side of system (1.1) is locally Lipschitz, which yields local existence of the solution of (1.1). Non-negativity follows from the form of this right-hand side. Inequalities (2.1) could be obtained in the same way as in [9]. Then the global existence of the solutions can be proved by the use of Theorem 2.7 from [18, Chapter 2]. □

Now, we turn to steady states. It is obvious that there are at least two steady states

$$A = (0, 0, 0) \quad \text{and} \quad B = \left(1, \frac{A_2}{\delta}, 0 \right),$$

compare [9]. Moreover, there can exist positive steady states $D_i = (\bar{N}_i, m_3, \bar{E}_i)$, with $\bar{N}_i = 1 + f_1(\bar{E}_i)$, and $\bar{E}_i$ are zeros of the function

$$g(x) = f_2(x)(1 + f_1(x)) - \delta m_3. \tag{2.2}$$

Stability of the steady states A and B does not depend on time delays, as in the discrete case; c.f. [9]. We recall the results without the proof.

Proposition 2.2. *The trivial steady state A of system (1.1) exists and is unstable independently of the model parameters. The semi-trivial steady state B of system (1.1) is locally asymptotically stable for $A_2 < \delta m_3$ and unstable for $A_2 > \delta m_3$.*

2.1. **Stability of positive steady states.** In this section, we focus on examining the stability of the positive steady states D_i in the case of distributed delays. First, we give some general results regarding stability and later we consider Erlang probability distribution, which is a special type of Gamma distribution with the shape parameter being a natural number.

In the general case let us define

$$K_i(\lambda) = \int_0^\infty k_i(s)\mathrm{e}^{-\lambda s}\,\mathrm{d}s. \tag{2.3}$$

Then, the stability matrix of system (1.1) for the steady state D_i reads

$$M(\bar{N}, \bar{P}, \bar{E}) = \begin{pmatrix} -\alpha - \lambda & 0 & \alpha d_1 K_1(\lambda) \\ f_2(\bar{E}_i) & -\delta - \lambda & -\bar{N}_i\, d_2 \\ \alpha b\bar{E}_i & d_3 \bar{E}_i K_2(\lambda) & -\alpha b d_1 \bar{E}_i K_1(\lambda) - \lambda \end{pmatrix},$$

where

$$b = \frac{1}{1 + f_1(\bar{E}_i)}, \quad d_1 = f_1'(\bar{E}_i) > 0, \quad d_2 = -f_2'(\bar{E}_i) > 0, \quad d_3 = f_3'(m_3) > 0.$$

Hence, the characteristic quasi-polynomial has the form

$$\begin{aligned} W(\lambda) =&\lambda^3 + C_1\lambda^2 + C_2\lambda + (\lambda^2 + \delta\lambda)C_3 K_1(\lambda) + \\ &+ (\lambda + \alpha)C_4 K_2(\lambda) - C_3 C_5 K_1(\lambda)K_2(\lambda), \end{aligned} \tag{2.4}$$

with

$$C_1 = \alpha + \delta, \quad C_2 = \alpha\delta, \quad C_3 = \alpha\beta d_1, \quad C_4 = \frac{\beta d_2 d_3}{b^2}, \quad C_5 = \delta d_3 m_3, \quad \beta = b\bar{E}_i.$$

Conditions (A1)–(A3) guarantee positivity of b, β and d_i, $i = 1, 2, 3$. Consequently, $C_i > 0$ for $i = 1, \ldots, 5$.

Theorem 2.3. *If $g'(\bar{E}_i) > 0$, where g is given by (2.2), then the positive steady state $D_i = (\bar{N}_i, m_3, \bar{E}_i)$ is unstable.*

Proof. We show that the characteristic function (2.4) has at least one positive real root. In the proof of Theorem 3.4 in [9] it is shown that the sign of $W(0) = \alpha C_4 - C_3 C_5$ is reverse to the sign of $g'(\bar{E}_i)$. Therefore, the assumption $g'(\bar{E}_i) > 0$ implies that $W(0) < 0$. Further, it is easy to see that $W(\lambda) \to +\infty$ as $\lambda \to +\infty$. Then there exists at least one real positive eigenvalue, and this implies that D_i is unstable. $\qquad\square$

Now, we focus on the cases when only one of the considered processes is delayed and the other is instantaneous. First, we consider $k_2(s) = \delta_D(s)$, where δ_D means Dirac-delta distribution, that is only the first delay is present in the system.

In the theorem presented below we shall use the following auxiliary polynomials and positive zeros of these polynomials. Let us define

$$w_1(\omega) = -\omega^3 - C_3\omega^2 + (C_2 + C_4 - \delta C_3)\omega - C_3 C_5, \tag{2.5}$$

$$w_3(\omega) = -(C_1 + C_3)\omega^2 - \delta C_3\omega + \alpha C_4 - C_3 C_5, \tag{2.6}$$

and

$$w_4(\omega) = -(C_1 - C_3)\omega^2 + \delta C_3\omega + \alpha C_4 + C_3 C_5. \tag{2.7}$$

To obtain positive zeros of w_1 one needs to assume $C_2 + C_4 - \delta C_3 > 0$. Moreover, the value at positive extremum, that is at $P_{\max} = \frac{-2C_3 + \sqrt{4C_3^2 + 12(C_2 + C_4 - \delta C_3)}}{6}$, must be positive. Hence, it is necessary that $w_1(P_{\max}) > 0$. In such a case

there exist two positive zeros $P_1 < P_2$ of w_1. Next, we easily see that if $g'(\bar{E}_i)$ < 0, that is $\alpha C_4 - C_3 C_5 > 0$, then w_3 has exactly one positive zero $P_3 = \frac{-\delta C_3 + \sqrt{\delta^2 C_3^2 - 4(C_1+C_3)(\alpha C_4 - C_3 C_5)}}{2(C_1+C_3)}$. Similarly, if $C_1 > C_3$, then w_4 has exactly one positive zero

$$P_4 = \frac{\delta C_3 + \sqrt{\delta^2 C_3^2 + 4(C_1 - C_3)(\alpha C_4 + C_3 C_2)}}{2(C_1 - C_3)}.$$

In the following, we require $P_1 < P_3$ and $P_4 < P_2$.

Theorem 2.4. *Assume that $g'(\bar{E}_i) < 0$ and $D_i = (\bar{N}_i, m_3, \bar{E}_i)$ is a positive steady state of system* (1.1). *Assume also that the delay distribution k_2 is concentrated at zero, that is $k_2(s) = \delta_D(s)$. If*

(i) *$\beta d_1 < 1$ and*

$$\frac{2\alpha^2 b}{d_2 \bar{E}_i} < d_3 < \min\left\{\frac{b}{2 d_2 \bar{E}_i}\left(\delta^2 - \alpha^2\left(\beta^2 {d_1}^2 - 1\right)\right), \frac{\delta}{2\beta^2 {d_1}^2 m_3}\left(1 - \beta^2 {d_1}^2\right)\right\},$$

   or

(ii) *$C_1 > C_3$, $w_1(P_{\max}) > 0$ and $w_1(P_i) > 0$ for $i = 3, 4$, where w_1 is defined by* (2.5) *and P_3, P_4 are positive zeros of* (2.6) *and* (2.7), *respectively,*

then D_i is locally asymptotically stable for any distribution k_1.

Proof. The steady state D_i is stable in the case without delay for $g'(\bar{E}_i) < 0$. Hence, we need to show that the characteristic function has no purely imaginary zeros. Therefore, we investigate the behaviour of $W(i\omega)$.

Let

$$K_1(i\omega) = \eta_1 - i\zeta_1, \quad \eta_1 = \int\limits_0^\infty k_1(s)\cos(\omega s)\,\mathrm{d}s, \quad \zeta_1 = \int\limits_0^\infty k_1(s)\sin(\omega s)\,\mathrm{d}s.$$

Thus

$$W(i\omega) = -i\omega^3 - C_1\omega^2 + i(C_2 + C_4)\omega + ((-\omega^2 + i\delta\omega)C_3 - C_3 C_5)(\eta_1 - i\zeta_1) + \alpha C_4,$$

and we have

$$\begin{aligned}
\mathfrak{Re}(W(i\omega)) &= -C_1\omega^2 + \alpha C_4 - C_3(\omega^2 + C_5)\eta_1 + \delta C_3\omega\zeta_1, \\
\mathfrak{Im}(W(i\omega)) &= -\omega^3 + (C_2 + C_4)\omega + \delta C_3\omega\eta_1 + C_3(\omega^2 + C_5)\zeta_1.
\end{aligned} \tag{2.8}$$

Assume that there exists $\omega > 0$ such that $W(i\omega) = 0$, then

$$\begin{aligned}
\left(-C_1\omega^2 + \alpha C_4\right)^2 + \left(-\omega^3 + (C_2 + C_4)\omega\right)^2 &= \\
\left(-C_3(\omega^2 + C_5)\eta_1 + \delta C_3\omega\zeta_1\right)^2 &+ \left(\delta C_3\omega\eta_1 + C_3(\omega^2 + C_5)\zeta_1\right)^2.
\end{aligned} \tag{2.9}$$

For Eq. (2.9) we have

$$\begin{aligned}
L.H.S &= \omega^6 + \left(C_1^2 - 2(C_2 + C_4)\right)\omega^4 + \left((C_2 + C_4)^2 - 2\alpha C_1 C_4\right)\omega^2 + \alpha^2 C_4^2, \\
R.H.S &= C_3^2\left(\omega^4 + \left(\delta^2 + 2C_5\right)\omega^2 + C_5^2\right)\left(\zeta_1^2 + \eta_1^2\right).
\end{aligned}$$

Schwarz inequality yields

$$\left(\int\limits_0^\infty \cos(\omega s)k_1(s)\,\mathrm{d}s\right)^2 = \left(\int\limits_0^\infty \cos(\omega s)\,\mathrm{d}\left(\int_0^s k_1(u)\,\mathrm{d}u\right)\right)^2$$

$$\leq \int\limits_0^\infty \cos^2(\omega s)\,\mathrm{d}\left(\int_0^s k_1(u)\,\mathrm{d}u\right)\int\limits_0^\infty \mathrm{d}\left(\int_0^s k_1(u)\,\mathrm{d}u\right)$$

$$= \int\limits_0^\infty \cos^2(\omega s)k_1(s)\,\mathrm{d}s,$$

$$\left(\int\limits_0^\infty \sin(\omega s)k_1(s)\,\mathrm{d}s\right)^2 \leq \int\limits_0^\infty \sin^2(\omega s)k_1(s)\,\mathrm{d}s.$$

Consequently, $\zeta_1^2 + \eta_1^2 \leq 1$. Then, ω satisfying $W(i\omega) = 0$ should fulfil

$$0 = L.R.S. - R.H.S.$$

$$\omega^6 + \left(C_1^2 - 2\tilde{C}_{2,4}\right)\omega^4 + \left(\left(\tilde{C}_{2,4}\right)^2 - 2\alpha C_1 C_4\right)\omega^2 +$$

$$+ \alpha^2 C_4^2 - C_3^2 \left(\omega^4 + \left(\delta^2 + 2C_5\right)\omega^2 + C_5^2\right),$$

where $\tilde{C}_{2,4} = C_2 + C_4$. Let us denote $y = \omega^2$ and define the auxiliary function

$$F(y) = y^3 + \left(C_1^2 - 2\tilde{C}_{2,4} - C_3^2\right)y^2 + \left(\left(\tilde{C}_{2,4}\right)^2 - 2\alpha C_1 C_4 - C_3^2\left(\delta^2 - 2C_5\right)\right)y +$$

$$+ \alpha^2 C_4^2 - C_3^2 C_5^2,$$

Existence of purely imaginary eigenvalue requires $F(y) \leq 0$ for some positive y. However, all coefficients of this polynomial are positive under the assumptions, and then purely imaginary eigenvalue $i\sqrt{y}$ does not exist.

Clearly, the free term is positive due to $g'(\bar{E}_i) < 0$. Moreover, inequalities (i) are equivalent to

$$\beta d_1 < 1, \quad \alpha^2 < \frac{\beta\,d_2 d_3}{2b^2} \quad \text{and}$$

$$\delta > \max\left\{\sqrt{\alpha^2(\beta^2 d_1{}^2 - 1) + \frac{2\beta\,d_2 d_3}{b^2}}, \frac{2\beta^2 d_1{}^2 d_3 m_3}{1 - \beta^2 d_1{}^2}\right\}.$$

Therefore,

$$C_1^2 - 2(C_2 + C_4) - C_3^2 = \delta^2 - \alpha^2\left(\beta^2 d_1{}^2 - 1\right) - \frac{2\beta\,d_2 d_3}{b^2} > 0,$$

$$(C_2 + C_4)^2 - 2\alpha C_1 C_4 - \delta^2 C_3^2 - 2C_3^2 C_5 =$$

$$\left(\alpha\,\delta + \frac{\beta\,d_2 d_3}{b^2}\right)^2 - \frac{2\alpha\,(\delta + \alpha)\,\beta\,d_2 d_3}{b^2} - \delta^2\alpha^2\beta^2 d_1{}^2 - 2\alpha^2\beta^2 d_1{}^2\delta\,d_3 m_3 =$$

$$\left(\left(1 - \beta^2 d_1{}^2\right)\alpha^2\delta - 2\alpha^2\beta^2 d_1{}^2 d_3 m_3\right)\delta + \frac{\beta\,d_2 d_3}{b^2}\left(\frac{\beta\,d_2 d_3}{b^2} - 2\alpha^2\right) > 0.$$

Due to the continuous dependance of eigenvalues on the model parameters this completes the proof of the first part.

For the proof of the second part, notice that (2.8) implies

$$\mathfrak{Re}(W(i\omega)) \geq -(C_1 + C_3)\omega^2 - \delta C_3\omega + \alpha C_4 - C_3 C_5,$$
$$\mathfrak{Re}(W(i\omega)) \leq -(C_1 - C_3)\omega^2 + \delta C_3\omega + \alpha C_4 + C_3 C_5,$$
$$\mathfrak{Im}(W(i\omega)) \geq -\omega^3 - C_3\omega^2 + (C_2 + C_4 - \delta C_3)\omega - C_3 C_5.$$

It is clear that,

$$\mathfrak{Re}(W(i\omega)) > 0 \text{ for } \omega \in [0, P_3), \quad \text{and} \quad \mathfrak{Im}(W(i\omega)) > 0 \text{ for } \omega \in (P_1, P_2),$$
$$\mathfrak{Re}(W(i\omega)) < 0 \text{ for } \omega \in (P_4, \infty).$$

Inequalities $w_1(P_i) > 0$ for $i = 3, 4$, imply $P_1 < P_3$ and $P_2 > P_4$. Moreover, $w_3(0) < w_4(0)$ and $w_3'(\omega) < w_4'(\omega)$ for $\omega > 0$. Therefore $P_3 < P_4$ and there is no $\omega \geq 0$ such that $W(i\omega) = 0$. This completes the proof of the theorem. $\qquad\square$

Remark 1. If the second condition of assumption (i) of Theorem 2.4 is satisfied, then

$$\delta^2 > 3\alpha^2.$$

If this inequality holds, we can choose sufficiently small d_1 and later we can take a proper value of d_3 such that the condition (i) of Theorem 2.4 holds.

In the following, we shall consider Erlang distributed delays. The density of Erlang distribution is given by

$$k(s) = \begin{cases} \dfrac{a^m (s-\sigma)^{m-1}}{(m-1)!} \mathrm{e}^{-a(s-\sigma)}, & s \geq \sigma, \\ 0, & \text{otherwise,} \end{cases} \tag{2.10}$$

where $a, \sigma > 0$, and a is a scaling parameter. To the case $\sigma = 0$ we refer as to the non-shifted Erlang distribution, while to the case $\sigma > 0$ we refer as to the shifted one. The mean value of the non-shifted Erlang distribution is given by $\frac{m}{a}$ and the variance is equal to $\frac{m}{a^2}$. The average delay is equal to this mean, obviously, and the deviation measures the concentration of the delay about the average value. For the shifted Erlang distribution the mean value is $\sigma + \frac{m}{a}$ and the variance is the same as for the non-shifted one. On the other hand, taking the limit $m \to +\infty$ and keeping $m/a = \tau$ constant we obtain system (1.1) with discrete delay τ. By direct calculation, it is found that $\int_0^\infty k(s)\mathrm{e}^{-\lambda s}\,\mathrm{d}s = \frac{a^m}{(a+\lambda)^m}\mathrm{e}^{-\lambda\sigma}$.

Now, let us consider the first distribution to be Erlang, $k_1(s) = k(s)$, while the other is still $k_2(s) = \delta_D(s)$. In this case, if $C_5 \neq a(a - \delta)$, then the characteristic function (2.4) could be replaced by

$$W_I(\lambda) = (a+\lambda)^m \left(\lambda^3 + C_1\lambda^2 + (C_2 + C_4)\lambda + \alpha C_4\right) + \\ + a^m \left(C_3\lambda^2 + \delta C_3\lambda - C_3 C_5\right)\mathrm{e}^{-\lambda\sigma}. \tag{2.11}$$

As the case $C_5 = a(a - \delta)$ is non-generic, in the following we assume $C_5 \neq a(a - \delta)$, and consider the simplest possible Erlang distribution with $m = 1$ and $\sigma = 0$.

Theorem 2.5. *If $m = 1$, $\sigma = 0$ and $g'(\bar{E}_i) < 0$, then the positive steady state D_i is locally asymptotically stable.*

Proof. For this case the characteristic function W_I simplifies to

$$W_I(\lambda) = (a+\lambda)\left(\lambda^3 + C_1\lambda^2 + (C_2 + C_4)\lambda + \alpha C_4\right) + a\left(C_3\lambda^2 + \delta C_3\lambda - C_3 C_5\right).$$

The Routh-Hurwitz Criterion for W_I reads

$$q_1 q_2 q_3 > q_3^2 + q_1^2 q_4, \qquad (2.12)$$

where

$$q_1 = a + C_1, \quad q_2 = a(C_1 + C_3) + \eta_2, \quad q_3 = a(\eta_2 + \delta C_3) + \alpha C_4, \quad q_4 = a\eta_4,$$

and

$$\eta_2 = C_2 + C_4, \quad \eta_4 = \alpha C_4 - C_3 C_5,$$

Notice that inequality (2.12) is equivalent to

$$P(a) = a_3 a^3 + a_2 a^2 + a_1 a + a_0 > 0,$$

where

$$a_3 = (C_1 + C_3)(\eta_2 + \delta C_3) - \eta_4,$$
$$a_2 = \alpha C_4(C_1 + C_3) + C_2(\eta_2 + \delta C_3) + C_1(C_1 + C_3)(\eta_2 + \delta C_3)$$
$$\quad + C_4(\eta_2 + \delta C_3) - (\eta_2 + \delta C_3)^2 - 2C_1\eta_4,$$
$$a_1 = C_1(\eta_2^2 + \alpha C_3 C_4 + \delta C_3 \eta_2) - \alpha C_4(\eta_2 + 2\delta C_3) + C_1^2 C_3 C_5,$$
$$a_0 = \alpha C_4(C_1\eta_2 - \alpha C_4).$$

Due to the definitions of C_1 and η_i we have:

$$a_0 = \alpha C_4\Big((\delta + \alpha)(C_2 + C_4) - \alpha C_4\Big) = \alpha C_4\Big((\delta + \alpha)C_2 + \delta C_4\Big) > 0,$$

$$a_1 = (\alpha + \delta)\Big((C_2 + C_4)^2 + \alpha C_3 C_4 + \delta C_3(C_2 + C_4)\Big) - \alpha C_4(C_2 + C_4) +$$
$$\quad - 2\alpha\delta C_3 C_4 + C_1^2 C_3 C_5$$
$$= \alpha\Big(\eta_2 C_2 + \alpha C_3 C_4 + \delta C_2 C_3\Big) + \delta\eta_2\big(\eta_2 + \delta C_3\big) > 0,$$

$$a_2 = \alpha C_4 C_3 + C_2(\eta_2 + \delta C_3) + (C_1(\alpha + \delta) + C_1 C_3)(\eta_2 + \delta C_3) + C_4(\eta_2 + \delta C_3) +$$
$$\quad - (\eta_2 + \delta C_3)^2 - \alpha C_1 C_4 + 2C_3 C_5,$$
$$= \alpha C_4 C_3 + (\delta C_1 + (\alpha + \delta)C_3)(\eta_2 + \delta C_3) + \alpha C_1(C_2 + \delta C_3) +$$
$$\quad - \delta C_2 C_3 - \delta C_4 C_3 - \delta^2 C_3^2 + 2C_3 C_5,$$
$$= \alpha C_4 C_3 + (\delta C_1 + \alpha)C_3(\eta_2 + \delta C_3) + \alpha C_1(C_2 + \delta C_3) + 2C_3 C_5 > 0,$$

$$a_3 = (\delta + \alpha + C_3)(C_2 + C_4 + \delta C_3) - \alpha C_4 + C_3 C_5$$
$$= (\delta + C_3)(C_2 + C_4 + \delta C_3) + \alpha(C_2 + \delta C_3) + C_3 C_5 > 0.$$

Hence, $P(a) > 0$ for every positive a. This means that the condition of stability is always satisfied. $\qquad \square$

Remark 2. Although Theorem 2.4 gives condition guaranteeing stability of the positive steady state for any delay distribution, Theorem 2.5 says that the positive steady state, if it is stable for the case without delay, cannot lose stability when the tumour growth process is delayed according to the Erlang distribution.

Now, we switch to the case when $k_1(s) = \delta_D(s)$, while the second distribution is Erlang, that is $k_2(s) = k(s)$ described by Eq. (2.10). Note that if $\alpha C_4 \neq C_4 a + C_3 C_5$, then λ is the eigenvalue defined by (2.4) if and only if λ is zero of

$$W_{II}(\lambda) = (a + \lambda)^m\Big(\lambda^3 + (C_1 + C_3)\lambda^2 + (C_2 + \delta C_3)\lambda\Big) +$$
$$\quad + a^m\Big(C_4\lambda + \alpha C_4 - C_3 C_5\Big)e^{-\lambda\sigma}. \qquad (2.13)$$

Again, because the case $\alpha C_4 = C_4 a + C_3 C_5$ is non-generic, we do not consider it here, and in the following we assume $\alpha C_4 \neq C_4 a + C_3 C_5$. Thus, studying the stability of the positive steady states D_i of system (1.1) is equivalent to study zeros of the polynomial W_{II} defined by (2.13). Below, we again study the simplest case of Erlang distribution with $m = 1$ and $\sigma = 0$.

Proposition 2.6. *If $m = 1$, $\sigma = 0$, $g'(\bar{E}_i) < 0$ and $Q_1 Q_2 Q_3 > Q_3^2 + Q_1^2 Q_4$, where*

$$Q_1 = C_1 + C_3 + a, \qquad Q_2 = C_2 + \delta C_3 + a(C_1 + C_3),$$
$$Q_3 = a(C_2 + C_4 + \delta C_3), \quad Q_4 = a(\alpha C_4 - C_3 C_5),$$

then the positive steady state D_i is locally asymptotically stable.

Proof. For $m = 1$ and $\sigma = 0$, the polynomial W_{II} defined by (2.13) reads

$$W_{II}(\lambda) = \lambda^4 + (C_1 + C_3 + a)\lambda^3 + (C_2 + \delta C_3 + a(C_1 + C_3))\lambda^2 +$$
$$+ a(C_2 + C_4 + \delta C_3)\lambda + a(\alpha C_4 - C_3 C_5),$$

and the assertion of the proposition comes directly from the Routh-Hurwitz Criterion. $\square$

Now, we try to answer the question when the assumptions of Proposition 2.6 are satisfied. To simplify calculations and shorten notation, let us denote

$$\eta_1 = C_1 + C_3, \quad \eta_2 = C_2 + \delta C_3, \quad \eta_4 = \alpha C_4 - C_3 C_5.$$

With this notation we have

$$Q_1 = \eta_1 + a, \quad Q_2 = \eta_2 + a\eta_1, \quad Q_3 = a(\eta_2 + C_4), \quad Q_4 = a\eta_4,$$

$$Q_i > 0 \quad \text{for} \quad i = 1, \dots, 4.$$

Now, the Routh-Hurwitz condition is equivalent to

$$a^2\Big(\eta_1\big(\eta_2 + C_4\big) - \eta_4\Big) + a\Big(\big(\eta_2 + C_4\big)\big(\eta_1^2 - C_4\big) - 2\eta_1\eta_4\Big) + \qquad (2.14)$$
$$+ \eta_1\Big(\eta_2\big(\eta_2 + C_4\big) - \eta_1\eta_4\Big) > 0.$$

Notice that the coefficient of a^2 is positive. Clearly, using the definitions of η_1, η_4 and C_1 we have

$$\eta_1\big(\eta_2 + C_4\big) - \eta_4 = \eta_1\eta_2 + (\alpha + \delta + C_3)C_4 - \alpha C_4 + C_3 C_5 = \eta_1\eta_2 + (\delta + C_3)C_4 + C_3 C_5 > 0.$$

Now, we have only three possibilities:

1. $\eta_2(\eta_2 + C_4) < \eta_1\eta_4$ – there exists exactly one critical value of a, below which the steady state is unstable and above which it is stable (average delay is $1/a$ in this case);
2. $\big(\eta_2 + C_4\big)\big(\eta_1^2 - C_4\big)/2 < \eta_1\eta_4 < \eta_2(\eta_2 + C_4)$ and the discriminant of the quadratic polynomial is positive – there exist two critical values of a;
3. $\eta_1\eta_4 < \eta_2(\eta_2 + 1)$ and either $\eta_1\eta_4 < \big(\eta_2 + C_4\big)\big(\eta_1^2 - C_4\big)/2$ or the discriminant of the quadratic polynomial is negative – the steady state is stable for all a.

To obtain two changes of stability, we need to have

$$\Big(\big(\eta_2 + C_4\big)\big(\eta_1^2 - C_4\big) - 2\eta_1\eta_4\Big)^2 > 4\eta_1\Big(\eta_2\big(\eta_2 + C_4\big) - \eta_1\eta_4\Big)\Big(\eta_1\big(\eta_2 + C_4\big) - \eta_4\Big), \quad (2.15)$$

together with

$$\frac{(\eta_1^2 - C_4)(\eta_2 + C_4)}{2} < \eta_1\eta_4 < \eta_2(\eta_2 + C_4).$$

Inequality (2.15) is equivalent to

$$\left(\eta_2 + C_4\right)\left(\eta_1^2 - C_4\right)^2 - 4\eta_1\eta_4\left(\eta_1^2 - C_4\right) - 4\eta_1^2\eta_2\left(\eta_2 + C_4\right) + 4\eta_1\eta_2\eta_4 + 4\eta_1^3\eta_4 > 0,$$

and collecting terms with $\eta_1^2 - C_4$ we obtain

$$\left(\eta_2 + C_4\right)\left(\eta_1^2 - C_4\right)^2 - 4\eta_1\eta_4\left(\eta_1^2 - C_4\right) + 4\eta_1\left(\eta_4\left(\eta_2 + \eta_1^2\right) - \eta_1\eta_2\left(\eta_2 + C_4\right)\right) > 0. \quad (2.16)$$

Notice that the free and linear terms of (2.16) are positive under the assumption

$$\eta_4 > \frac{\eta_1\eta_2\left(\eta_2 + C_4\right)}{\eta_2 + \eta_1^2} \quad \text{and} \quad \eta_1^2 < C_4.$$

We have $\eta_1^2 - C_4 = (\alpha + \delta + \alpha\delta)^2 - \beta d_2 d_3/b^2$, and it is negative for sufficiently large $d_2 d_3$ or sufficiently small b.

Eventually, two stability switches are possible under the assumptions

$$\frac{\eta_1\eta_2\left(\eta_2 + C_4\right)}{\eta_2 + \eta_1^2} < \eta_4 < \frac{\eta_2(\eta_2 + C_4)}{\eta_1} \quad \text{and} \quad \eta_1^2 < C_4.$$

Proposition 2.7. *If $g'(\bar{E}_i) \neq 0$ and*

(i) D_i *is unstable for $\sigma = 0$, then it is unstable for all $\sigma > 0$;*

(ii) D_i *is stable for $\sigma = 0$, then there exists $\sigma_0 > 0$, such that D_i is stable for $\sigma < \sigma_0$, and D_i is unstable for $\sigma > \sigma_0$. Furthermore, if $f_i \in \mathbf{C}^2, i = 1, 2, 3$, then Hopf bifurcation occurs at σ_0.*

Proof. For the characteristic function W_{II} given by (2.13), we define the auxiliary function

$$F(y) = y\left(a^2 + y\right)^m \left(y^2 + ((C_1 + C_3)^2 - 2(C_3\delta + C_2))y + (C_3\delta + C_2)^2\right) -$$
$$- a^{2m}C_4^2 y - a^{2m}(C_4\alpha - C_3 C_5)^2,$$

where $y = \omega^2$. Notice, that

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

Clearly, F has at least one positive zero, since the coefficient of y with the highest power is positive, while the free term is negative. We show that this is the unique simple positive root. Note, that all coefficients of F are positive with the exception of the free term which is negative and the coefficient of y, which sign is not determined. However, in both cases, there exists exactly one change of sign in the coefficients of the polynomial F, and the Descartes' Rule of Signs implies that F has a unique and simple positive root. This, together with Theorem 1 from [13], completes the proof. $\qquad\square$

Eventually, we consider both distributions to be Erlang with the same parameters.

Proposition 2.8. *If $m = 1$, $\sigma = 0$, $g'(\bar{E}_i) < 0$, $q_{11}q_{22}q_{33} > q_{33}^2 + q_{11}^2 q_{44}$ and*

$$(q_{11}q_{44} - q_{55})(q_{11}q_{22}q_{33} - q_{33}^2 - q_{11}^2 q_{44}) > q_{55}(q_{11}q_{22} - q_{33})^2 + q_{11}q_{55}^2,$$

where

$$q_{11} = C_1 + 2a, \quad q_{22} = C_2 + 2a\,C_1 + a^2 + aC_3,$$
$$q_{33} = 2a\,C_2 + a^2 C_1 + a^2 C_3 + aC_3\delta + aC_4,$$
$$q_{44} = a^2 C_2 + a^2 C_3\delta + a^2 C_4 + aC_4\alpha, \quad q_{55} = a^2 C_4\alpha - a^2 C_3 C_5,$$

then the positive steady state D_i is locally stable.

Proof. For $m = 1$ and $\sigma = 0$, the characteristic function (2.4) reads

$$W(\lambda) = \frac{1}{(a+\lambda)^2}\Big(\left(\lambda^3 + C_1\lambda^2 + C_2\lambda\right)(a+\lambda)^2 + a(\lambda^2 + \delta\lambda)C_3(a+\lambda) +$$
$$+ \quad a(\lambda + \alpha)C_4(a+\lambda) - a^2 C_3 C_5\Big).$$

Hence, we need to study roots of the polynomial

$$\lambda^5 + (C_1 + 2a)\lambda^4 + (C_2 + 2a\,C_1 + a^2 + aC_3)\lambda^3 + (2a\,C_2 + a^2 C_1 + a^2 C_3 + aC_3\delta + aC_4)\lambda^2 +$$
$$+ (a^2 C_2 + a^2 C_3\delta + a^2 C_4 + aC_4\alpha)\lambda + a^2 C_4\alpha - a^2 C_3 C_5 = 0.$$

A direct application of the Routh-Hurwitz Criterion completes the proof. $\qquad\square$

3. **Numerical simulations.** For the numerical simulations we choose functions f_i and parameters values proposed in [9], that is

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

and

$$a_2 = 0.4, \quad a_3 = 1, \quad b_1 = 2.3, \quad b_3 = 1, \quad c_1 = 1.5, \quad c_2 = 1, \quad \alpha = 1, \quad \delta = 0.34. \quad (3.1)$$

For these values of parameters there exist three positive steady states:

$$D_1 \approx (1.04, 1.05, 0.17), \quad D_2 \approx (1.37, 1.05, 0.54), \quad D_3 \approx (2.67, 1.05, 1.99).$$

Now, we can influence the model dynamics changing the value of δ. This parameter could reflect an application of some treatment that blocks VEGF activation, which can be modelled by the increase of clearance rate. Then the steady state D_1 exists for $0.331 < \delta < 0.381$, D_3 for $\delta < 0.368$ and D_2 for $0.331 < \delta < 0.368$. The steady state D_2 is unstable, while D_1 and D_3 are stable for the case without time delay. In Table 1 we presented critical values of delay at which the steady states D_1

TABLE 1. Critical values of τ at which the positive steady state loses stability.

	steady state D_1					steady state D_3				
δ	0.332	0.346	0.36	0.368	0.378	0.3	0.332	0.346	0.36	0.368
discrete	66.7	33.4	29.3	43.6	182	4.49	5.89	7.53	13.0	94.0
$m = 1$	steady state does not lose stability									
$m = 2$	176	54.7	69.1	106.1	460	5.58	9.36	14.4	32.2	284
$m = 5$	89.9	29.6	37.4	56.6	234	4.03	5.97	8.34	16.6	135

and D_3 lose their stability, for some values of parameter δ, in the case of discrete delay, as well as the critical average delay at which the steady states D_1 and D_3 lose their stability for the case of the Erlang delay distribution, both in the vessel formation process, while the process of tumour growth is instantaneous. The average delay is calculated as m/a. These results are also illustrated in Fig. 1. Numerical simulations suggest that if δ converges to the limits of the interval of the existence of the steady state D_1, (average) critical value of delay tends to $+\infty$. Similar behaviour is observed for critical value of time delay for the steady state D_3, however for this state the interval of existence is bounded only from the right-hand side. It can be also noticed that for $m = 1$, the positive steady states do not change their
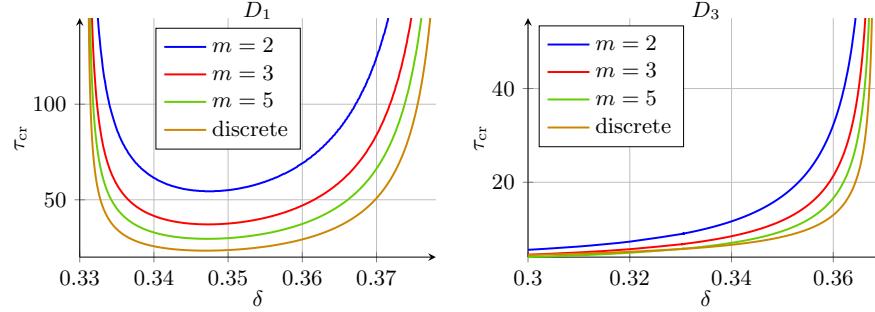
FIGURE 1. Critical average delay, that is m/a_{cr} for various values of m in the dependance on δ in the case when only the process of tumour growth is delayed; left – graphs for the steady state D_1, right – graphs for the steady state D_3.

stability, and this result is similar to those obtained when the tumour growth is delayed according to the Erlang distribution with $m = 1$. However, in the latter case the stability does not depend on other model parameters, while in the first case it depends on the model parameters. Numerical simulations suggest that for δ close to 0.346 the critical value of delay for the steady state D_1 is the smallest one while it is larger for other δ. The regions below the curves in Fig. 1 are stability regions. For the state D_1 stability regions for Erlang distributions is larger than in the discrete case, and decreases with increasing m. On the other hand, for the steady state D_3, the critical value of delay seems to be an increasing function of δ. For some values of δ the region of stability in the case of $m = 2$ is more than twice as large as in the discrete case. However, numerical simulations suggest, that for δ close to 0.3, the stability region for the Erlang distribution with $m = 5$ is smaller than for the discrete case, and this is somehow unexpected result.

In Fig. 2 we see exemplary solutions of system (1.1) for parameters given by (3.1) and $\tau = 10$. For $m = 1$ the solution converges to the steady state very fast, while for $m = 5$ it seems that oscillations are sustained.
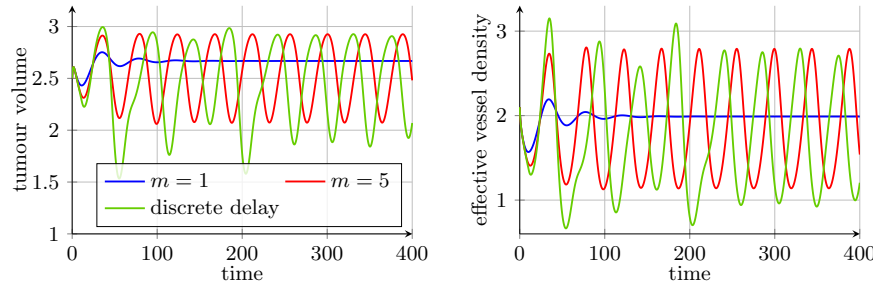

FIGURE 2. Solutions of system (1.1) for parameters given by (3.1) and $\tau = 10$, with time delay present only in the vessel formation term.

For comparison, we present solutions of system (1.1) with Erlang distributed delay with parameters $m = 1$ and $\sigma = 0$ or discrete delay present only in the tumour growth process. In this case Theorem 2.5 shows that the steady state is

stable independently of the model parameters. This is seen in Fig. 3. Eventually, we present the case of both processes delayed with the same Erlang distribution in Fig. 4.
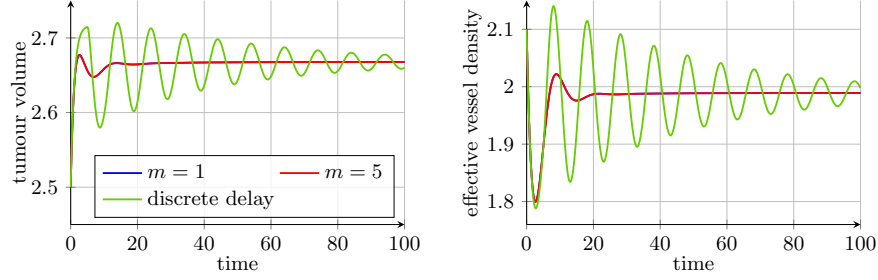

FIGURE 3. Solutions of system (1.1) for parameters given by (3.1) and $\tau = 10$, with time delay present only in the tumour growth term. Here, for Erlang distribution, the steady state is stable, and solutions for $m = 1$ and $m = 5$ are almost identical.
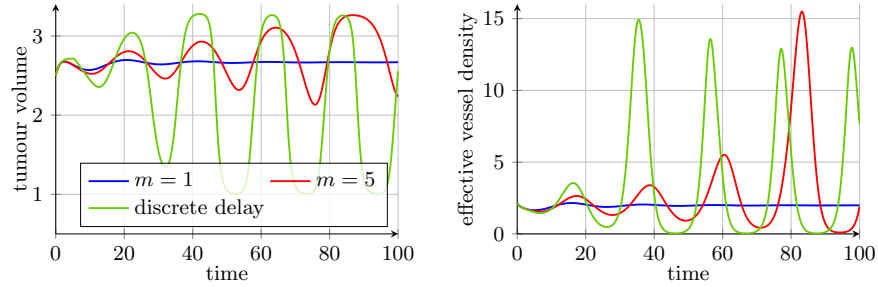

FIGURE 4. Solutions of system (1.1) for parameters given by (3.1) and $\tau = 5$, with time delay present in both terms.

From our numerical analysis it is clear that the most robust is the model with Erlang distribution with $m = 1$, while the most sensitive is the model with discrete delays. Moreover, in the case when the delay is present only in the tumour growth process, the influence of the magnitude of m is almost not visible. As we expect, for both delays being present, the behaviour of solutions is much more unpredictable. However, the result for $m = 1$ seems to be optimistic. Clearly, Erlang distribution with $m = 1$ is the most reasonable, and therefore this means that in reality oscillatory behaviour should be exception not rule.

4. **Conclusions and discussion.** In this paper a model of tumour angiogenesis with distributed delays was considered. We proved basic mathematical properties of the model showing that solutions are unique, non-negative and well defined on the whole positive half-line. We formulated conditions on the model parameters that guarantee lack of change of local stability of a steady state for any distribution of delays. On the other hand, we proved condition under which stability change can take place and Hopf bifurcation occurs. We gave more strict conditions in the case when delays are distributed according to Erlang distributions. Our results indicate that the model with distributed delays is more stable than with discrete ones. In

particular, we observe stabilisation of the solution in a steady state value for some delay distributions while in the same time solutions of the model with discrete delays exhibit oscillations. In the case of Erlang distributions we observe that the behaviour of the solution for large shape parameter is closer to the behaviour of the solution to the model with discrete delays.

The model considered in this paper is an extension of the model proposed earlier by Agur et. al. [2]. In this paper Agur et al. tried to simplified more complex computer model of angiogenesis process proposed in [4]. However, this model always exhibits oscillatory dynamics, which is not realistic. On the other hand, according to the data presented in [4], such type of the dynamics should be also present in the model, and therefore they included time delays into their model. Our idea was to combine the properties of the Hahnfeldt et al. model with the properties of the one presented in [2]. Here we decided to use distributed delays instead of discrete ones in order to make the model more realistic comparing to the previous discrete case [7]. Our results show that both type of the model dynamics could be observed for the model with delays distributed according to Erlang distributions, depending on the shape parameter, which is good from the point of view of potential applications. Although we have not validated our model with experimental data, it is done for a small modification of this model and the results should be published shortly; cf. [11].

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