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ANGIOGENESIS MODEL WITH ERLANG DISTRIBUTED DELAY IN VESSELS FORMATION

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ABSTRACT

We consider the model of angiogenesis process proposed by Bodnar and Foryś (2009) with time delay included into the vessels formation process, where delay is distributed according to the Erlang distribution.

INTRODUCTION

Angiogenesis is a process of formation of new vessels from pre-existing ones. It is a normal and vital process in growth and development of animal organisms, required during the repair mechanism of damaged tissues. On the other hand, it is essential in the transition of avascular forms of solid tumours into metastatic ones. When the tumour approaches 1-2 mm^3 of volume, necrotic core is formed and the growth process is slowed down [6]. Then, cancer cells start to secrete angiogenic factors yielding new vessels formation. The supply of nutrients allows cancer growth and help to remove the metabolism waste products. Understanding the mechanisms of angiogenesis might give a possibility to improve cancer treatment since good functioning blood vessels allow anti-cancer drugs to penetrate better the tumour structure, and hence reduce the tumour mass.

In this paper we consider the model of tumour angiogenesis proposed in [1] and studied in [4] (in the context of discrete delays) with the distributed delay of the vessels formation, assuming the Erlang distribution for stability analysis. Thus we consider the following system of the first order differential equations with distributed delay

$$\begin{aligned}
\dot{N}(t) &= \alpha N(t)\Big(1 - \frac{N(t)}{1 + f_1(E(t))}\Big),\\
\dot{P}(t) &= f_2(E(t))N(t) - \delta P(t),\\
\dot{E}(t) &= \left(\int_0^\infty k(s) f_3(P(t-s))ds - \alpha\Big(1 - \frac{N(t)}{1 + f_1(E(t))}\Big)\right) E(t),
\end{aligned} \tag{1}$$

where $N(t)$, $P(t)$, $E(t)$ and α describe the tumour size, the amount of regulating proteins, the effective vessel density, and the tumour proliferation rate respectively. It is assumed that 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 an increasing function such that $f_1(0) = 0$, $\lim_{E\to+\infty} f_1(E) = b_1 > 0$,

(A2) f_2 is a decreasing convex function with $f_2(0) = a_2 > 0$ and $\lim_{E\to+\infty} f_2(E) = 0$,
(A3) f_3 is an increasing function with $f_3(0) = -a_3 < 0$, $f_3(m_3) = 0$ and $\lim_{P\to+\infty} f_3(P) = b_3$.
For detailed derivation of the model described by (1) we refer to [1, 4]. We assume the function $k(s) : [0, \infty) \to [0, \infty)$ is a probability density with finite expectation, that is

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

To close the system we need to define initial conditions. Let $C = \mathbf{C}((-\infty, 0], \mathbb{R}^3)$ be the space of continuous functions defined on the interval $(-\infty, 0]$ with values in $\mathbb{R}^3$, and as C_+ we define the subspace of C that consist of the functions with non-negative values. Because our delay distribution has infinite support, we need to control the behaviour of the initial condition at the infinity (see [7]). To this end, let define a Banach space Φ,

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

and we consider the initial function from the set $\Phi_+ = \Phi \cap C_+$.

MODEL ANALYSIS

In this section we consider basic properties of system (1) for general kernel $k(s)$ and study stability in the case of Erlang distribution.

Theorem 1. *Let the functions f_i, $i = 1, 2, 3$, fulfil conditions* (A1)–(A3). *For an arbitrary initial function $\phi = (\phi_N, \phi_P, \phi_E) \in \Phi_+$ there exists unique solution in Φ_+ defined on $t \in [0, +\infty)$. Moreover, the following inequalities*

$$\begin{aligned} N_{\min} \le N(t) &\le N_{\max}, \\ 0 \le P(t) &\le \max\{\frac{a_2}{\delta} N_{\max}, \phi_2(0)\}, \\ 0 \le E(t) &\le \phi_3(0)\exp((b_3 + \alpha(N_{\max} - 1))t), \end{aligned} \tag{2}$$

hold for all $t \ge 0$, where

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

Proof. It is easy to show that the right-hand side of system (1) fulfils local Lipschitz condition, which yields the local existence of the solution to (1). Non-negativity follows easily from the form of the system (1).

The estimation of the solutions are obtained in the same way as in [4]. Then the global existence of the solutions can be proved by the use of Theorem 2.7 from [7, Chapter 2]. □

Analysis of the existence of steady states is the same as in [3]. We summarise the results shortly. The steady states

$$A = (0, 0, 0) \quad \text{and} \quad B = \left(1, \frac{a_2}{\delta}, 0\right)$$

always exist. 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 solutions of the equation

$$g(x) = f_2(x)(1 + f_1(x)) - \delta m_3 = 0. \tag{3}$$

The stability of the steady state A and B does not depend on time delay, as it was in the case of discrete delays, see [4]. We recall these results without a proof.

Proposition 2. *Let the functions $f_i \in C^1$, $i = 1, 2, 3$, fulfil conditions* (A1)–(A3). *Then the trivial steady state A of system* (1) *exists and is unstable independently of the model parameters. The semi-trivial steady state B of system* (1) *is locally asymptotically stable for $a_2 < \delta m_3$ and unstable for $a_2 > \delta m_3$.*

Stability of positive steady states

Local qualitative properties of the positive steady state $D_i = (\bar{N}_i; m_3; \bar{E}_i)$ of system (1) in the case of discrete delays have been studied in [3]. In this section, we focus on examining the stability and instability of the positive steady state D_i in the case of distributed delay. We consider Erlang probability distribution, which is a special type of Gamma distribution with the shape parameter being a natural number. The kernel of Erlang distribution is given by

$$k(s) = \begin{cases} \frac{a^n (s-\sigma)^{n-1}}{(n-1)!} \,\mathrm{e}^{-a(s-\sigma)}, & s \geq \sigma, \\ 0, & \text{otherwise}, \end{cases} \tag{4}$$

where $a, \sigma > 0$, and a is a scaling parameter. For the case $\sigma = 0$ we call this distribution the non-shifted Erlang distribution while, to the case $\sigma > 0$ we refer as to the shifted Erlang distribution. The mean value of the non-shifted Erlang distribution is given by $\frac{n}{a}$, while the variance is equal to $\frac{n}{a^2}$. Then, the average delay is equal to this mean and the deviation measures the degree of concentration of the delay about the average value. On the other hand, for the shifted Erlang distribution the mean value is $\sigma + \frac{n}{a}$, while the variance is the same as for non-shifted one. Taking the limit $n \to +\infty$ and keeping $n/a = \tau$ constant we obtain system (1) with discrete delay τ. By direct calculation, it is found that $\int_0^\infty k(s)\,\mathrm{e}^{-\lambda s}\,\mathrm{d}s = \frac{a^n}{(a+\lambda)^n}\,\mathrm{e}^{-\lambda\sigma}$.

The stability matrix of system (1) for the steady state D_i reads

$$M(\bar{N}, \bar{P}, \bar{E}) = \begin{bmatrix} -\alpha - \lambda & 0 & \alpha d_1 \\ f_2(\bar{E}_i) & -\delta - \lambda & -\bar{N}_i\, d_2 \\ b\alpha \bar{E}_i & \bar{E}_i d_3 \frac{a^n}{(a+\lambda)^n}\,\mathrm{e}^{-\lambda\sigma} & -\alpha b \bar{E}_i d_1 - \lambda \end{bmatrix},$$

where

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

Consequently, the characteristic quasi-polynomial has the form

$$W(\lambda) = \lambda^3 + (C_1 + C_3)\lambda^2 + (C_2 + \delta C_3)\lambda + \Big(C_4\lambda + \alpha C_4 - C_3 C_5\Big)\frac{a^n}{(a+\lambda)^n}\,\mathrm{e}^{-\lambda\sigma}, \tag{5}$$

where

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

Conditions (A1)–(A3) guarantee the positivity of $d_1,\ d_2,\ d_3,\ b$ and β. Consequently, $C_i > 0$ for $i = 1, 2, ..., 5$.

Theorem 3. *Let the functions $f_i \in C^1$, $i = 1, 2, 3$, fulfil conditions* (A1)–(A3). *If $g'(\bar{E}_i) > 0$, where g is given by* (3)*, then the positive steady state $D_i = (\bar{N}_i; m_3; \bar{E}_i)$ is unstable.*

Proof. We show that the characteristic function $W(\lambda)$ has at least one positive real root. The proof of Theorem 3.4 in [3] showed that the sign of $\alpha C_4 - C_3 C_5$ 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 $\lambda_0 > 0$ such that $W(\lambda_0) = 0$, and this implies that D_i is unstable. □

Note that if $\alpha C_4 \neq C_4 a + C_3 C_5$, then λ is zero of $W(\lambda)$ if and only if λ is zero of

$$W_1(\lambda) = (a+\lambda)^n\Big(\lambda^3 + (C_1 + C_3)\lambda^2 + (C_2 + \delta C_3)\lambda\Big) + a^n\Big(C_4\lambda + \alpha C_4 - C_3 C_5\Big)\mathrm{e}^{-\lambda\sigma}. \tag{6}$$

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) is equivalent to study zeros of the polynomial W_1 defined by (6).

Proposition 4. *Assume that the functions* $f_i \in C^1$, $i = 1, 2, 3$, *fulfil conditions* (A1)–(A3). *If* $n = 1$, $\sigma = 0$, $g'(\bar{E}_i) < 0$, *and* $Q_1 Q_2 Q_3 > Q_3^2 + Q_1^2 Q_4$, *where*

$$Q_1 = C_1 + C_3 + a,\ \ Q_2 = C_2 + \delta C_3 + a(C_1 + C_3),\ \ Q_3 = a(C_2 + \delta C_3 + C_4),\ \ Q_4 = a(\alpha C_4 - C_3 C_5), \quad (7)$$

then the positive steady state D_i *is locally asymptotically stable.*

Proof. For $n = 1$ and $\sigma = 0$, the polynomial W_1 reads

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

and the assertion of the proposition comes directly from the Routh-Hurwitz Criterion. □

Now, we try to answer the question when the assumptions of Proposition 4 are satisfied. To simplify calculations, let us denote

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

Under the assumptions of Proposition (4) we have $\eta_4 > 0$, which suggest stability for sufficiently large a due to continuous dependance.

With this notation we have

$$Q_1 = \eta_1 + a, \quad Q_2 = \eta_2 + a\eta_1, \quad Q_3 = a(\eta_2 + C_4), \quad Q_4 = a\eta_4, \quad Q_i > 0 \ \text{for} \ i = 1, \dots, 4.$$

Now, the R-H condition reads

$$a(\eta_1 + a)(\eta_2 + a\eta_1)(\eta_2 + C_4) > a^2(\eta_2 + C_4)^2 + a\,(\eta_1 + a)^2\eta_4. \quad (8)$$

Since $a > 0$ we can divide both sides of (8) by a, obtaining equivalent condition

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

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

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

Because the coefficient of a^2 is positive, 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) $\eta_4 < \eta_2(\eta_2 + C_4)/\eta_1$, and $\eta_4 > (\eta_2 + C_4)(\eta_1^2 - C_4)/(2\eta_1)$ and the discriminant of the quadratic polynomial is positive — there exists two critical values of a;

(3) $\eta_4 < \eta_2(\eta_2 + 1)/\eta_1$, and either $\eta_4 < (\eta_2 + C_4)(\eta_1^2 - C_4)/(2\eta_1)$ 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

$$\Big((\eta_2 + C_4)(\eta_1^2 - C_4) - 2\eta_1\eta_4\Big)^2 - 4\eta_1\Big(\eta_2(\eta_2 + C_4) - \eta_1\eta_4\Big)\Big(\eta_1(\eta_2 + C_4) - \eta_4\Big) > 0, \quad (9)$$

together with

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

Inequality (9) is equivalent to

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

and dividing by $\eta_2 + C_4$ and collecting terms with $\eta_1^2 - C_4$ we obtain

$$(\eta_2 + C_4)(\eta_1^2 - C_4)^2 - 4\eta_1\eta_4(\eta_1^2 - C_4) + 4\eta_1\Big(\eta_4(\eta_2 + \eta_1^2) - \eta_1\eta_2(\eta_2 + C_4)\Big) > 0. \quad (10)$$

Notice that the free and linear terms of (10) are positive under the assumption

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

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 $d_2 d_3$.

Eventually, two stability switches are possible under the assumptions

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

Proposition 5. *Let the functions* $f_i \in C^1$, $i = 1,2,3$, *fulfil conditions* (A1)–(A3). *If*

(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_1 given by (6), we define the auxiliary function

$$F(\omega) = \omega^2(a^2+\omega^2)^n\left(\omega^4 + ((C_1+C_3)^2 - 2(C_3\delta + C_2))\omega^2 + (C_3\delta + C_2)^2\right) - \\ - a^{2n}C_4^2\omega^2 - a^{2n}(C_4\alpha - C_3C_5)^2.$$

Notice, that

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

Using this equality and substituting $y = \omega^2$ we get

$$F(y) = y(a^2+y)^n\left(y^2 + (\alpha^2(1+\beta d_1)^2 + \delta^2)y + (C_3\delta + C_2)^2\right) - a^{2n}C_4^2 y - a^{2n}(C_4\alpha - C_3C_5)^2$$

Clearly, $F(y)$ has at least one positive root, since the coefficient of y with the highest power is positive, while the free term is negative. We show that this roost is a 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 [5], completes the proof. □

NUMERICAL SIMULATIONS AND DISCUSSION

For the numerical simulation we choose functions f_i and parameters values proposed in [3], that is

$$f_1(E) = \frac{b_1E^n}{c_1+E^n}, \qquad f_2(E) = \frac{a_2c_2}{c_2+E}, \qquad f_3(P) = \frac{b_3(P^2-m_3^2)}{\frac{m_3^2b_3}{a_3}+P^2},$$

and

$$a_2 = 0.4, \quad a_3 = 1, \quad b_1 = 2.3, \quad b_3 = 1, \quad c_1 = 1.5, \quad c_2 = 1, \quad \alpha = 1, \quad \delta = 0.34. \tag{11}$$

For these values of parameters there exist three positive steady states: $D_1 \approx (1.04, 1.05, 0.17)$, $D_2 \approx (1.37, 1.05, 0.54)$ and $D_3 \approx (2.67, 1.05, 1.99)$. 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 $0.331 < \delta < 0.381$, C_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 the case of discrete delay, the steady state D_1 loses its stability for: $\tau \approx 3.09$ for $\delta = 0.331$, $\tau \approx 3.37$ for $\delta = 0.34$, and $\tau \approx 6.00$ for $\delta = 0.38$, while for the steady state D_3 critical values are $\tau \approx 2.24$ for $\delta = 0.3$, $\tau \approx 2.27$ for $\delta = 0.34$, and $\tau \approx 2.39$ for $\delta = 0.36$. In Fig. 1 we have presented the values of critical average delay for Erlang distribution with various m. The average delay is calculated as m/a. For the case $m = 1$ stability change does not occur for these values of parameters. For the steady state D_3, the critical average delay is about 4 for $m = 5$ and $\delta = 0.3$ (that is almost twice as in the discrete case), and 7.07 for $\delta = 0.34$. The region below the curves are stability regions. Notice that this delays are much larger than for the discrete case.

In Fig. 2 we have shown exemplary solution of system (1) for parameters given by (11) and $\tau = 10$. It can be seen that for $m = 1$ the solution converges to the steady state very fast, while for $m = 5$ it seems that oscillations are sustained.

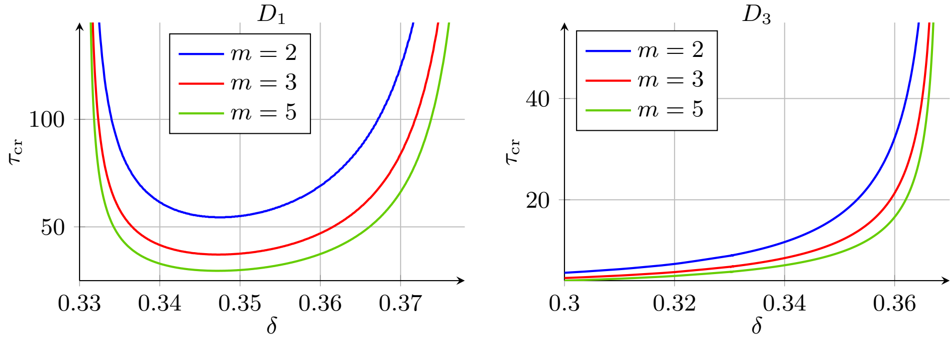

Figure 1. Critical average delay, that is $m/a_{\rm cr}$ for various values of m in dependance on δ. In the left-hand side panel the graphs for the steady state D_1 are presented, while in the right-hand side panel for the steady state D_3.

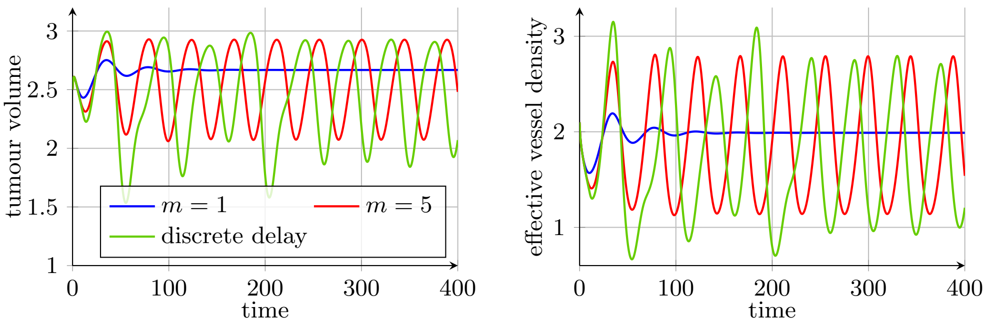

Figure 2. Solution of system (1) for parameters given by (11) and $\tau = 10$.

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