Analysis of the family of angiogenesis models with distributed time delays

Bodnar, M.?1 & Piotrowska, M.J.?2

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

1mbodnar@mimuw.edu.pl, 2monika@mimuw.edu.pl

Research Article

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Abstract

In the presented paper a family of angiogenesis models, that is a generalisation of Hahnfeldt et al. model is proposed. Considered family of models is a system of two differential equations with distributed time delays. The global existence and the uniqueness of the solutions are proved. Moreover, the stability of the unique positive steady state is examined in the case when delay distributions are Erlang or piecewise linear distributions. Theorems guaranteeing the existence of stability switches and occurrence of the Hopf bifurcation are proved. Theoretical results are illustrated by numerical analysis performed for parameters estimated by Hahnfeldt et al. (Cancer Res., 1999).

Keywords: delay differential equations, distributed delay, stability analysis, the Hopf bifurcation, angiogenesis

1 Introduction

Angiogenesis is a very complex process which accompanies us through our whole life starting from the development of the embryo and ending with wound healing in advanced age since it is process of
blood vessels formation from the pre-existing ones. Clearly, it is often considered as a vital process involved in organism growth and development. On the other hand, it can also be a pathological process since it may promote the growth of solid tumours. Indeed, in the first stage of solid tumour development cells create multicellular spheroid (MCS) — a small spherical aggregation. For a fast growing tumour (comparing to the healthy tissue) tumour’s cells located in the centre of MCS receive less and less nutrients (such as glucose and oxygen) since they are supplied through the diffusion of that substances from the external vessels only. Hence, when MSCs reach a certain size (usually around 2–3 mm in diameter, [1,2]) two processes are observed: saturation of growing cellular mass, and the necrotic core formation in the centre of MCSs. The tumour cells that are poorly nourished secrete number of angiogenic factors, e.g. FGF, VEGF, VEGFR, Ang1 and Ang2, which promote the proliferation and the differentiation of endothelial cells, smooth muscle cells, fibroblasts and also stabilise new created vessels initiating the process of the angiogenesis. From that point of view, angiogenesis can be also considered as an essential step in the tumours transition from the less harm for hosts avascular forms to cancers that are able to metastasise and finally cause the lethal outcome of the disease.

In [1] Folkman showed that growth of solid tumours strongly depends on the amount of blood vessels that are induced to grow by tumours. He summarised that, if the tumour could be stopped from its own blood supply, it would wither and die, and nowadays he is considered as a father of the anti-angiogenic therapy the approach that aims to prevent the tumour from developing its own blood supply system.

On the other hand, angiogenesis has also the essential role in the tumours treatment during chemotherapy since the anti-cancer drugs distributed with blood need to be delivered to the tumour and the efficiently working vessels net allows the drugs to penetrate the tumour structure better. One also need to take into account fact that the vessel’s net developed due to the angiogenesis initiated by tumour cells is not as efficient as the net in the healthy tissue e.g. consists loops. That causes large difficulties during the treatment of tumours because drugs transport is often ineffective.

Because of the reasons explained above, the process of angiogenesis is very important for solid tumour growth and also for anti-tumour treatment. Hence, a number of authors described that process using various mathematical models: macroscopic [3–11], individual-based models [12,13] or hybrid models [14,15]. One of the most well recognised angiogenesis models was proposed by Hahnfeldt et al. [11] later on studied in [8]. Among others, models with discrete delays describing the same angiogenesis process were recently considered in [16] and [5]. Models investigating the tumour development and angiogenesis process in the context of anti-angiogenic therapy, chemotherapy or radiotherapy were also considered in [17–23], in the context of optimal treatment schedules [24–29] or in context of the vessels maturation in [30,31].

Let consider the family of the angiogenesis models that consists of two differential equations in the following form

\[
\frac{dp}{dt} = rp(t)h\left(\frac{p(t-\tau_1)}{q(t-\tau_1)}\right), \quad (1.1a)
\]

\[
\frac{dq}{dt} = q(t)\left(b\left(\frac{p(t-\tau_2)}{q(t-\tau_2)}\right)^\alpha - a_Hp^{2/3}(t)-\mu\right), \quad (1.1b)
\]

where variables \( p(t) \) and \( q(t) \) represent the tumour volume at time \( t \), and the maximal tumour size for which tumour cells can be nourished by the present vasculature. Thus, the ratio \( \frac{p}{q} \) is interpreted as the measure of vessels density. The function \( h \) reflects dependence of tumour growth rate on the vascularisation. We assume \( h \) is decreasing. In the literature, in the context of model \( (1.1) \), it is usually assumed that the tumour growth is governed by logistic and generalised logistic (see [8–10]) or by Gompertzian (see [8,11]) law. The parameter \( r \) reflects the maximal tumour growth rate. The delays \( \tau_1 \) and \( \tau_2 \) present in the system represent time lags in the processes of the tumour growth and the vessels formation, respectively. Moreover, it is assumed that the population of the endothelial cells...
depends on both: the stimulation process initiated by poorly nourished tumour cells and the inhibiting factors secreted by tumour cells causing the vessels lost. The parameter $\alpha$ reflects the strength of the dependence of the vessels dynamics on the ratio $\tilde{q}$. Parameters $a_H$ and $b$ are proportionality parameters of inhibition and stimulation of the angiogenesis process, respectively. In the case when two processes, from which one appears on the surface of a sphere and other the inside the sphere, are considered one due to the spherical symmetry assumption has the ratio of the tumour surface to its volume represented by the exponent $2/3$. Thus, the term $-a_H q(t)\tilde{q}^{2/3}$ appears in the Eq. (1.1b) in model (1.1) the spontaneous loss of functional vasculature is represented by the term $-\mu q(t)$. In (1.1), the parameter $\mu$ was estimated to be equal to zero. On the other hand, the term $-\mu q(t)$ for $\mu > 0$ can be also interpreted as a constant continuous anti-angiogenic treatment, hence it is also considered in the presented study. For detailed derivation of system (1.1) without delays and with logarithmic function $h$ from a reaction-diffusion system see [11].

The model (1.1) with $\alpha = 1$, Gompertzian tumour growth, and without time delays was firstly proposed by Hahnfeldt \textit{et al.} in [11]. The modification of the Hahnfeldt \textit{et al.} model was considered by various authors. d’Onofrio and Gandolfi [8] proposed system of ordinary differential equations (ODEs) based on Hahnfeldt \textit{et al.} idea but with $h$ being linear or logarithmic function, and with $\alpha = 0$, that is when the dynamics of the second variable of the model does not depend on the vascularisation of the tumour. Later in [32] Bodnar and Forys introduced discrete time delays into the model with Gompertzian tumour growth and the family of models for parameter $\alpha$ from the interval $[0, 1]$ was considered. The analysis was later extended in [17]. In the same time, d’Onofrio and Gandolfi in [10] studied the model for $\alpha = 0$ with discrete time delays and different functions $h$. The analysis of the family of models with discrete delays was extended in [33–34] where the directions of the existing Hopf bifurcations were studied.

However, in all these papers only the discrete time delays were considered. Of course, in reality delay is somehow distributed around some average value. Thus, in this paper we will study the modification of the family of models (1.1) in which the delays are distributed around their average values $\tau_1$ and $\tau_2$ instead of being concentrated in these points. Up to our knowledge such modification of the family of models has not been considered yet. We are also not aware of any result considering linear systems similar to the linearised system of the model with distributed delays considered in this paper. In fact known analytical results regarding the stability of trivial steady state for linear equations with distributed delays are rather limited, see e.g. [35] and references therein. Most results concern single equation (see [35, 38], and references therein). In some papers second order equation or system of equations with distributed delays are considered (see [39] for the second order linear equation, and [40] for the Lotka-Volterra system). However, in these two cases time delays are only finite and delayed terms do not appear on the diagonal of the stability matrix, and hence these results can not be applied directly to the system considered in this paper. The single infinite distributed time delay is considered in [41] for the model of immune system–tumour interactions, however in that paper only an exponential distribution is considered and the linear chain trick that reduce the system with infinite delay to a larger system of ODEs is used.

A part of our results is based on application of the Mikhailov Criterion, which generalised version is formulated and proved in the Appendix. This generalisation plays an essential role in studying local stability of the steady state with certain distributed delays.

We formulate, the considered in this paper, model with the distributed delays, including the definition of the proper space and initial conditions, in the next section.

The paper is organised as follows: in Section 2 considered family of angiogenesis models with distributed delays is proposed. In Section 3 the mathematical analysis including the global existence and uniqueness of solutions, stability of existing steady state of considered family of models for different types of considered delay distributions is presented. In that section we also discuss possibilities of stability changes of a positive steady state. Next, our stability results are illustrated and extended by the numerical simulations. In Section 5 we discuss and summary our results. Finally, for com-
pleteness in the A we formulate generalized Mikhailov Criterion used in the paper and we prove it.

2 Family of angiogenesis models with distributed delays

The effect of the tumour stimulation of the vessels growth as well as the positive influence of the vessel network on the tumour dynamics is neither instantaneous nor delayed by some constant value. Hence, to reflect reality better, instead of constant delays considered earlier in [8], [33] or [34] we consider the delays that are distributed around some mean value and their distributions are given by the general probability densities $f_i$. We study the following system

\[
\frac{d}{dt} p(t) = r p(t) h \left( \int_0^\infty f_1(\tau) \frac{p(t-\tau)}{q(t-\tau)} \, d\tau \right),
\]

\[
\frac{d}{dt} q(t) = q(t) \left( b \int_0^\infty f_2(\tau) \left( \frac{p(t-\tau)}{q(t-\tau)} \right)^{\alpha} \, d\tau - a H p^{2/3}(t) - \mu \right),
\]

where $f_i(s) : [0, \infty) \to \mathbb{R}^+$ are delay distributions with the following properties:

(\textbf{H1}) $\int_0^\infty f_i(s) \, ds = 1, i = 1, 2$ and

(\textbf{H2}) $0 \leq \int_0^\infty s f_i(s) \, ds < \infty, i = 1, 2$.

Throughout this paper we would refer to distributions $f_i$ as kernels. Moreover, we assume that the function $h$ has the following properties:

(\textbf{P1}) $h : (0, \infty) \to \mathbb{R}$ is a continuously differentiable decreasing function;

(\textbf{P2}) $h(1) = 0$;

(\textbf{P3}) $h'(1) = -1$.

Note, the properties (\textbf{P2}) and (\textbf{P3}) do not make our studies less general as a proper rescaling and a suitable choice of parameter $r$ always allows us to arrive to the case when $h(1) = 0$ and $h'(1) = -1$. Note, that any probability distribution defined on $[0, +\infty)$ with a finite expectation fulfils our assumptions (\textbf{H1}) and (\textbf{H2}) made on kernels.

It should be mentioned that the distributed delays are thought to be more realistic but on the other hand they might be more difficult to work with. Moreover, sometimes the particular forms of kernels may be difficult to estimate from the experimental data.

To close the model (2.1) we need to define the initial conditions. We consider the continuous initial functions $\phi : (-\infty, 0] \to \mathbb{R}^2$. For infinite delays we need to regulate the behaviour of functions as $t$ tends to $-\infty$. To this end we introduce a suitable space. Let us denote as $C = C((-\infty, 0], \mathbb{R}^2)$ a space of continuous functions defined on the interval $(-\infty, 0]$ with the values in $\mathbb{R}^2$. For an arbitrary chosen non-decreasing continuous function $\eta : (-\infty, 0] \to \mathbb{R}^+$ such that $\lim_{\theta \to -\infty} \eta(\theta) = 0$, we define the Banach space

$$\mathcal{K}_\eta = \left\{ \varphi \in C : \lim_{\theta \to -\infty} \varphi(\theta) \eta(\theta) = 0 \quad \text{and} \quad \sup_{\theta \in (-\infty, 0]} |\varphi(\theta)\eta(\theta)| < \infty \right\},$$

with a norm

$$\|\varphi\|_\eta = \sup_{\theta \in (-\infty, 0]} |\varphi(\theta)\eta(\theta)|, \quad \text{for any} \quad \varphi \in \mathcal{K}_\eta.$$
We need initial functions $\phi$ to be in $\mathcal{K}_{\eta}$ for some arbitrary non-decreasing continuous function $\eta$ that tends to 0 for arguments tending to $-\infty$ (see [12]). If the delay is finite, that is if supports of $f_1$ and $f_2$ are compact, we suppose initial functions $\phi \in C([-\tau_{\text{max}}, 0], \mathbb{R}^2)$, where the interval $[-\tau_{\text{max}}, 0]$ contains supports of $f_i$, $i = 1, 2$. However, this is equivalent to consider the space $\mathcal{K}_{\eta}$ with any $\eta$ being equal to 1 on $[-\tau_{\text{max}}, 0]$ and decreasing to 0 in $-\infty$. If the support of the kernel is unbounded and the initial function $\phi$ is also unbounded, then we need to choose an appropriate function $\eta$ (which in turn implies a choice of the phase space $\mathcal{K}$). The function $\eta$ must be chosen to control the behaviour of the initial function in $-\infty$. However, due to biological interpretation of the model parameter, it is reasonable to restrict our analysis to the globally bounded initial functions. Thus, we can chose any positive continuous non-decreasing function $\eta$ that $\eta(\theta) \rightarrow 0$ for $\theta \rightarrow -\infty$ for example $\eta = e^\theta$.

Nevertheless, because such assumption would not make theorems’ formulation simpler, we decided to present and prove theorems for arbitrary initial functions and not to assume a particular form of the function $\eta$.

3 Mathematical analysis of the family of angiogenesis models with distributed delays

Since the kernels used in (2.1) are probability distributions and due to property (P2) of the function $h$ the steady states of system (2.1) are the same as for Hahnfeldt et al. and d’Onofrio-Gandolfi models without delays or with discrete delays. Thus, system (2.1) has a unique positive steady state $(p_e, q_e)$, where $p_e = q_e = \left(\frac{b-\mu}{\alpha_{\eta_{\mu}}}\right)^\frac{1}{2}$ (compare e.g. [33]) if and only if $b > \mu$. Hence, in the rest of the paper we assume that $b > \mu$ holds.

Note, that solution to the both equations defined by (2.1) can be written in the exponential form. Thus, using the same argument as in [10] or in [33] (for the discrete delay cases), we deduce that $\mathbb{R}^2_+$ is the invariant set for system (2.1).

Note, that in system (2.1) terms with delay are of the form $p/q$. This, together with the invariance of $\mathbb{R}^2_+$ suggests the following change of variables

$$x = \ln\left(\frac{p}{p_e}\right), \quad y = \ln\left(\frac{pq_e}{qp_e}\right)$$

obtaining

$$\frac{dx(t)}{dt} = rh\left(\int_0^{\infty} f_1(\tau) e^{q(t-\tau)} \, d\tau\right),$$
$$\frac{dy(t)}{dt} = rh\left(\int_0^{\infty} f_1(\tau) e^{q(t-\tau)} \, d\tau\right) - b \int_0^{\infty} f_2(\tau) e^{qy(t-\tau)} \, d\tau + \left(b - \mu\right) e^{x(t)} + \mu. \quad (3.1)$$

Newly introduced variable $y$ allow us to consider system where only one variable ($y$) has delayed argument, whereas in system (2.1) we have both variables with delayed arguments. Clearly, the steady state for the re-scaled system (3.1) is $(x_e, y_e) = (0, 0)$.

It should be mentioned here that the scaling procedure transforms $\mathbb{R}^2_+$ into the whole $\mathbb{R}^2$, so space $\mathcal{K}_{\eta}$ is the appropriate phase space for the model (3.1).

3.1 Existence and uniqueness of solutions

**Theorem 3.1** Let $\eta: (-\infty, 0] \rightarrow \mathbb{R}^+$ be a continuous, non-decreasing function such that $\lim_{\theta \rightarrow -\infty} \eta(\theta) = 0$, let functions $f_i$ fulfil (H1)–(H2), and let function $h$ fulfils (P1)–(P3). For any initial functions $\phi = (\phi_1, \phi_2) \in \mathcal{K}_{\eta}$ there exists $t_0 > 0$ such that system (3.1) with initial condition $x(t) = \phi_1(t)$, $y(t) = \phi_2(t)$ for $t \in (-\infty, 0]$, has a unique solution in $\mathcal{K}_{\eta}$ defined on $t \in [0, t_0]$. 

Proof: The right-hand side of system (3.1) fulfils local Lipschitz condition. In fact, the assumption (P1) implies that derivative of $h$ is bounded on any compact set of $(0, +\infty)$. Thus, the function $h$ is locally Lipschitz function as well as all functions on the right-hand side of (3.1). This implies that the Lipschitz condition is fulfilled for any bounded set in $K_n$. Hence, there exists a unique solution to the system (3.1) defined on $t \in [0, t_0)$ (see [42, Chapter 2, Theorem 1.2]).

Theorem 3.2 (global existence) If assumption of Theorem 3.1 are fulfilled and if the kernel functions $f_i$ and initial conditions are globally bounded, then solutions to (3.1) are defined for all $t \geq 0$.

Proof: The right-hand side of (3.1) can be written in a functional form as

$$\frac{d}{dt} x(t) = G_1(x, y), \quad \frac{d}{dt} y(t) = G_2(x, y),$$

with

$$G_1(x, y) = rh \left( \int_0^\infty f_1(\tau) e^{\phi_1(\tau)} \, d\tau \right),$$

$$G_2(x, y) = rh \left( \int_0^\infty f_1(\tau) e^{\phi_1(\tau)} \, d\tau \right) - b \int_0^\infty f_2(\tau) e^{\phi_2(\tau)} \, d\tau + (b - \mu) e^{\beta \phi_1(0)} + \mu,$$

for $(\phi_1, \phi_2) \in C$. Note that due to (P1) we have $|G_1(\phi_1, \phi_2)| \leq rh(\exp(-\|\phi_1\|))$ and similar inequality holds for $|G_2(\phi_1, \phi_2)|$. This implies, that the function $(G_1, G_2)$ maps bounded sets of $C$ into bounded sets of $\mathbb{R}^2$ (so their closures are compact). Thus, if the solution to (3.1) can not be prolonged beyond the interval $[0, T)$, for some finite $T$, then $\lim_{t \to T} \|x(t)\| + \|y(t)\| = +\infty$ (see [42, Chapter 2, Theorem 2.7]).

In the following, we show that $x$ and $y$ are bounded on $[0, T)$ hence, the solution exists for all $t \geq 0$.

Let $\delta > 0$ be an arbitrary number such that $\int_0^\delta f_i(\tau) \, d\tau > 0$ for $i = 1, 2$. Using the step method we choose the time step equal to $\delta$ and we show that the solution to (3.1) can be prolonged on the interval $[0, \delta]$ and hence on the interval $[n\delta, (n + 1)\delta]$, for any $n \in \mathbb{N}$. Let letters $C_i$ denote constants that will be chosen later in a suitable way.

First, we provide an upper bound of the solution. Due to boundedness of $y(t)$ for $t \leq 0$, we may write

$$\int_0^\infty f_1(\tau) e^{\beta (t-\tau)} \, d\tau = \int_0^\delta f_1(\tau) e^{\beta (t-\tau)} \, d\tau + \int_\delta^\infty f_1(\tau) e^{\beta (t-\tau)} \, d\tau \geq \int_\delta^\infty f_1(\tau) e^{\beta (t-\tau)} \, d\tau \geq C_1,$$

for all $t \in [0, \delta]$. This estimation leads to a conclusion

$$\frac{d}{dt} x(t) \leq rh(C_1) \implies x(t) \leq C_2 \quad \text{for } t \in [0, \delta].$$

From the second equation of (3.1), arguing in a similar way, we have

$$\frac{d}{dt} y(t) \leq rh(C_1) + (b - \mu) e^{C_3} + \mu \implies y(t) \leq C_4, \quad \text{for } t \in [0, \delta].$$

Now we proceed with a lower bound of the solutions. Splitting integral on the interval $(0, +\infty)$ into two integrals and using the fact that $y(t)$ is bounded we obtain

$$\int_0^\infty f_1(\tau) e^{\beta (t-\tau)} \, d\tau = \int_0^\delta f_1(\tau) e^{\beta (t-\tau)} \, d\tau + \int_\delta^\infty f_1(\tau) e^{\beta (t-\tau)} \, d\tau \leq \int_\delta^\infty f_1(\tau) e^{\beta t} \, d\tau + C_5 \leq \int_0^\infty f_1(\tau) e^{\beta t} \, d\tau + C_5 \leq e^{C_3} + C_5 \leq C_6.$$
where \( y_M \) is an upper bound of \( y(t) \) on the interval \([\tau, \delta]\). This estimation together with a similar argument applied to the second integral in the second equation of (3.1) yields
\[
\int_0^\infty f_2(\tau)e^{\alpha y(\tau)}\,d\tau \leq C_7.
\]
Therefore, from the second equation of (3.1) we have
\[
\frac{d}{dt}y(t) \geq rh(C_8) - bC_7 \implies y(t) \geq C_8, \text{ for } t \in [0, \delta].
\]
The boundedness of \( y \) together with the form of first equation of (3.1) implies boundedness of \( x(t) \) on \([0, \delta]\). Hence, mathematical induction yields the boundedness of the solutions to (3.1) on each compact interval included in \([0, +\infty)\), which completes the proof. 

\[\blacksquare\]

### 3.2 Stability and Hopf bifurcation

In this section we study local stability of the steady state \((0,0)\) using standard linearisation technique. Linearisation for system (3.1) around the steady state \((0,0)\) has the following form
\[
\frac{d}{dt}x(t) = rh'(1) \int_0^\infty f_1(\tau)y(t-\tau)\,d\tau,
\]
\[
\frac{d}{dt}y(t) = \frac{2}{3}(b-\mu)x(t) + \int_0^\infty \left( rh'(1)f_1(\tau) - \alpha bf_2(\tau) \right)y(t-\tau)\,d\tau,
\]
and, due to the equality \( h'(1) = -1 \) (see Property (P3)), the corresponding characteristic function is given by
\[
W(\lambda) = \det \begin{bmatrix}
\lambda & r \int_0^\infty f_1(\tau)e^{-\lambda \tau}\,d\tau \\
-\frac{2}{3}(b-\mu) & \lambda + \int_0^\infty \left( rf_1(\tau) + \alpha bf_2(\tau) \right)e^{-\lambda \tau}\,d\tau
\end{bmatrix}.
\]
Thus,
\[
W(\lambda) = \lambda^2 + \lambda \int_0^\infty \left( rf_1(\tau) + \alpha bf_2(\tau) \right)e^{-\lambda \tau}\,d\tau + \frac{2r}{3}(b-\mu) \int_0^\infty f_1(\tau)e^{-\lambda \tau}\,d\tau.
\]
In general, as the kernels one considers the specific distributions which describe the experimental data or studied phenomena in the best way. In in the presented paper, we consider two particular types of the kernels. One type is given by
\[
f_i(\tau) = \frac{1}{e_i^2} \begin{cases} 
\epsilon_i - \sigma_i + \tau, & \tau \in [\sigma_i - \epsilon_i, \sigma_i), \\
\epsilon_i + \sigma_i - \tau, & \tau \in [\sigma_i, \sigma_i + \epsilon_i], \\
0 & \text{for } \sigma_i \geq \epsilon_i, i = 1, 2, \quad (3.2)
\end{cases}
\]
We call kernels defined by (3.2) piecewise linear kernels. Note, that for \( \epsilon_i \to 0 \) the functions \( f_i \) converge to Dirac delta at the points \( \sigma_i \) and therefore, system (2.1) becomes a system with discrete delays considered by [8][17][33][34]. Since we assume that all considered kernels are defined on interval \([0, \infty)\) condition \( \sigma_i \geq \epsilon_i \) must be fulfilled. Note, that for \( \sigma_i \geq \epsilon_i \) the average value of \( f_i \) is equal to \( \sigma_i \) and the standard deviation is equal to \( \epsilon_i/\sqrt{6} \). For \( \sigma_i < \epsilon_i \) one obtains so-called neutral equations, for details see [43].

In this paper, we also consider second type of kernels so-called the Erlang kernels separated or not from zero by \( \sigma_i \geq 0 \), i.e. we study system (2.1) with functions given by
\[
f_1(\tau) = g_{m_1}(\tau - \sigma_1), \quad f_2(\tau) = g_{m_2}(\tau - \sigma_2), \quad (3.3)
\]
where $g_{mi}(\tau)$, $i = 1, 2$, are called non-shifted Erlang distributions and are defined by

$$g_{mi}(s) = \frac{a_i}{(mi - 1)!} (as)^{mi-1} e^{-as}, \quad (3.4)$$

with $a_i > 0$, $s \geq 0$. The mean value of a non-shifted Erlang distribution $g_{mi}$ is given by $\frac{m_i}{a_i}$, while the variance is equal to $\frac{m_i}{a_i^2}$. Hence, the average delay is equal to this mean and the deviation $\sqrt{\frac{m_i}{a_i^3}}$ measures the degree of concentration of the delays about the average delay. Clearly, the non-shifted Erlang distribution is a special case of the Gamma distribution, where the shape parameter $m_i$ is an integer. It is also easy to see that the non-shifted Erlang distribution is the generalisation of the exponential distribution since for parameter $m_i = 1$ one gets the exponential distribution. On the other hand, for non-shifted Erlang distributions when $m_i \to +\infty$ the kernels $g_{mi}$ converge to a Dirac distributions and hence the system with discrete delays (1.1) is recovered as a limit of Erlang distributions for system (2.1). For shifted Erlang distribution the mean value is $\sigma_i + \frac{m_i}{a_i}$, while variances stay the same as for the non-shifted case.

### 3.2.1 Erlang kernels

The Erlang kernels separated from zero by $\sigma_i$ read

$$f_i(\tau) = \frac{a_i^{m_i}(\tau - \sigma_i)^{m_i-1}}{(m_i - 1)!} e^{-a_i(\tau-\sigma_i)}, \quad \text{for } \tau \geq \sigma_i$$

and 0 otherwise, for $i = 1, 2$. Note, that in this paper we consider only the case $a_i = a > 0$. Then for kernels given by (3.3)–(3.4) we have

$$\int_0^\infty f_i(\tau) e^{-\lambda \tau} d\tau = \frac{a_i^{m_i}}{(a + \lambda)^{m_i}} e^{-\lambda \sigma_i}.$$

Hence, the characteristic function has the following form

$$W(\lambda) = \lambda^2 + \lambda \left( r \frac{a_i^{m_1}}{(a + \lambda)^{m_1}} e^{-\lambda \sigma_1} + a_2 b \frac{a_i^{m_2}}{(a + \lambda)^{m_2}} e^{-\lambda \sigma_2} \right) + \frac{2r}{3} \frac{(b - \mu)}{(a + \lambda)^{m_1}} e^{-\lambda \sigma_1}. \quad (3.5)$$

Define

$$\beta = r + a b \quad \text{and} \quad \gamma = \frac{2r(b - \mu)}{3}. \quad (3.6)$$

**Theorem 3.3** Let $b > \mu$. The trivial steady state of system (3.1) with non-shifted Erlang kernel distributions given by (3.3)–(3.4) ($\sigma_i = 0$, $i = 1, 2$) with $a_i = a$ is locally asymptotically stable if

(i) $a \beta > \gamma$ for $m_1 = m_2 = 1$;

(ii) $2a(a + r) > \left( a(a + ab) + \gamma \right) + \frac{4a^2\gamma}{(a(a+ab) + \gamma)}$ for $m_1 = 1$ and $m_2 = 2$;

(iii) $a \geq \frac{1}{2} \beta + \frac{2x}{\beta} - ab$ for $m_1 = 2$ and $m_2 = 1$;

(iv) $a \geq \frac{1}{2} \beta + \frac{2x}{\beta}$ for $m_1 = m_2 = 2$;

(v) $a \geq \frac{3}{4} \beta$ and $8\beta a^3 - 3(8\gamma + 3\beta^2) a^2 + 3\gamma \beta a - \gamma^2 > 0$ for $m_1 = m_2 = 3$. 
and stability condition has the following form

\[ W(\lambda) = \lambda^2 + \lambda \left( r \frac{a^{m_1}}{(a + \lambda)^{m_1}} + ab \frac{a^{m_2}}{(a + \lambda)^{m_2}} \right) + \frac{2r}{3} (b - \mu) \frac{a^{m_1}}{(a + \lambda)^{m_1}}. \]

As it can be seen, the advantage of using the Erlang distributions (not separated from zero) is that instead of studying existence of the zeros of the characteristic function one can study existence of roots of a polynomial, thus the stability analysis is easier.

First, consider \( m_1 = m_2 = m \). We investigate the behaviour of the roots of polynomial

\[ \lambda^2 (a + \lambda)^m + a^m (\lambda \beta + \gamma), \]

where \( \beta \) and \( \gamma \) are given by (3.6).

For \( m = 1 \) (i.e. for the exponential distribution not separated from zero) we have a polynomial of degree three. For the third-order polynomial, Routh-Hurwitz stability criterion implies that the necessary and sufficient conditions for the stability of trivial steady state of system (3.1) are that the coefficient of \( \lambda^2 \) and the free term are positive, and that the coefficient of \( \lambda^2 \) multiplied by the coefficient of \( \lambda \) is greater than the free term. The first two conditions are fulfilled immediately as \( a, \beta, \gamma > 0 \), while the last one holds because of the assumption \( ab > \gamma \).

For \( m = 2 \), (3.7) reads

\[ \lambda^4 + 2a \lambda^3 + a^2 \lambda^2 + \beta a^2 \lambda + \gamma a^2 \]

and from Routh-Hurwitz Criterion the necessary and sufficient condition is

\[ \beta(2a - \beta) > 4\gamma \iff a > \frac{1}{2} \beta + \frac{2\gamma}{\beta}. \]

For \( m_1 = 1 \) and \( m_2 = 2 \), (3.7) reads

\[ \lambda^4 + 2a \lambda^3 + a(\alpha + r) \lambda^2 + \left( a^2 \beta + \gamma a \right) \lambda + \gamma a^2, \]

and the condition is

\[ 2a(\alpha + r) > \left( a(\alpha + ab) + \gamma \right) + \frac{4\gamma a^2}{(a(a + ab) + \gamma)}. \]

For \( m_1 = 2 \) and \( m_2 = 1 \), (3.7) reads

\[ \lambda^4 + 2a \lambda^3 + a(\alpha + ab) \lambda^2 + a^2 \beta \lambda + \gamma a^2, \]

and stability condition has the following form

\[ a > \frac{1}{2} \beta + \frac{2\gamma}{\beta} - ab. \]

The case \( m_i = 3, i = 1, 2 \), is the most complicated since a direct calculation shows that is such a case, (3.7) is the polynomial of degree 5

\[ \lambda^5 + 3a \lambda^4 + 3a^2 \lambda^3 + a^3 \lambda^2 + a^3 \beta \lambda + a^3 \gamma. \]

Applying the Routh-Hurwitz Criterion and using the fact that \( a_i = a, \gamma, \beta > 0 \), after some tedious calculations, we obtain postulated conditions.

**Proposition 3.4** For \( b > \mu, \sigma_i = 0, a_i = a, i = 1, 2, m_1 = 1, m_2 = 2 \) and

\[ r < ab \quad \text{or} \quad r > \frac{ab}{2} + \frac{2\gamma}{ab}, \]

there exists \( \tilde{a} > 0 \) such that for \( a > \tilde{a} \) the trivial steady state of system (3.1) with non-shifted Erlang kernel distributions given by (3.3)–(3.4) is locally asymptotically stable and it is unstable for \( a \in (0, \tilde{a}) \).
Thus, polynomial (3.9) has one simple real positive root denoted by $\bar{a}$. This indicates that since the number of sign changes between consecutive non-zero coefficients is equal to 1 polynomial (3.9) has one simple real positive root denoted by $\bar{a}$. We denote it by $\bar{a}$. Thus, a simple case the trivial steady state system (3.1) is locally asymptotically for $a > \bar{a}$ and unstable for $0 < a < \bar{a}$.

**Proposition 3.5** If the trivial steady state of system (3.1) with shifted Erlang kernel distributions given by (3.3)–(3.4) and $a_i = a$, $m_i = m$, $i = 1, 2$

(i) is unstable for $\sigma_i = 0$, $i = 1, 2$ then it is unstable for any $\sigma > 0$,

(ii) is locally asymptotically stable for $\sigma_i = 0$, $i = 1, 2$, then there exists $\sigma_0$ such that it is locally stable for all $\sigma \in [0, \sigma_0)$ and unstable for $\sigma > \sigma_0$. At $\sigma = \sigma_0$ the Hopf bifurcation occurs.

**Proof:** If $m_1 = m_2 = m$, then (3.5) has the following form

$$W(\lambda) = \frac{1}{(a + \lambda)^m} \left( \lambda^2 (a + \lambda)^m + a^m (\lambda \beta + \gamma) e^{-\lambda \sigma} \right).$$

Consider

$$D(\lambda) = \lambda^2 (a + \lambda)^m + a^m (\lambda \beta + \gamma) e^{-\lambda \sigma},$$

and for $\lambda = i \omega$ define the auxiliary function

$$F(\omega) = || - \omega^2 (a + i \omega)^m ||^2 - a^{2m} \left( \gamma^2 + \omega^2 \beta^2 \right).$$

Thus,

$$F(\omega) = \omega^4 \left( a^2 + \omega^2 \right)^m - a^{2m} \left( \omega^2 \beta^2 + \gamma^2 \right), \quad (3.9)$$

and for $u = \omega^2$ we have

$$F(u) = u^2 \left( a^2 + u \right)^m - a^{2m} (u \beta^2 + \gamma^2). \quad (3.10)$$

We are interested in the existence of the real positive roots of (3.9). The Descartes’ rule of signs indicates that since the number of sign changes between consecutive non-zero coefficients is equal to 1 polynomial (3.9) has one simple real positive root denoted by $u_0$. Clearly, the fact that coefficient of $u^{2m}$ is positive and $F(0) < 0$, implies $F'(u_0) \geq 0$.

Moreover,

$$F'(u) = 2u \left( a^2 + u \right)^m + mu^2 \left( a^2 + u \right)^{m-1} - a^{2m} \beta^2$$

and thus, $F''(u) > 0$. Hence, $F'(u_0) > 0$.

Now, we investigate the case $m_1 \neq m_2$ for shifted Erlang distribution. Let $\sigma_i = \sigma$, $i = 1, 2$, $m_1 \neq m_2$ and $m_M = \max(m_1, m_2)$. Then characteristic function (3.5) has the following form

$$W(\lambda) = \frac{1}{(a + \lambda)^{m_M}} \left( \lambda^2 (a + \lambda)^{m_M} + \left( \lambda (r a^m (a + \lambda)^{m_m-m_1} + a b \alpha a^m (a + \lambda)^{m_m-m_2}) + \gamma a^m (a + \lambda)^{m_m-m_1} \right) e^{-\lambda \sigma} \right).$$

Set

$$D(\lambda) = \lambda^2 (a + \lambda)^{m_M} + \left( \lambda (r a^m (a + \lambda)^{m_m-m_1} + a b \alpha a^m (a + \lambda)^{m_m-m_2}) + \gamma a^m (a + \lambda)^{m_m-m_1} \right) e^{-\lambda \sigma}. \quad (3.11)$$
We calculate the auxiliary function \( F \) in the following manner
\[
F(\omega) = \omega^4(a^2 + \omega^2)^{m_2} - \|i\omega(ra^{m_1}(a + i\omega)^{m_1} + ab\beta^m(a + i\omega)^{m_1-m_2}) + \gamma a^{m_1}(a + i\omega)^{m_2-m_1}\|^2. 
\]  
(3.12)

Eq. (3.11) is not symmetric with respect to \( m_i \) parameters. Therefore, cases \( m_1 > m_2 \) and \( m_2 > m_1 \) need to be considered separately.

First, assume \( m_M = m_1 \), then
\[
W(\lambda) = \frac{1}{(a + \lambda)^{m_1}} D(\lambda),
\]
where
\[
D(\lambda) = \lambda^2(a + \lambda)^{m_1} + \left(\lambda(ra^{m_1} + ab\beta^m(a + \lambda)^{m_1-m_2}) + \gamma a^{m_1}\right) e^{-\lambda r}.
\]
In such a case the auxiliary function has the following form
\[
F(\omega) = \omega^4(a^2 + \omega^2)^{m_1} - \|i\omega(ra^{m_1} + ab\beta^m(a + i\omega)^{m_1-m_2}) + \gamma a^{m_1}\|^2.
\]

Consider the case \( m_1 = 2 \) and \( m_2 = 1 \). Then for \( u = \omega^2 \) we have
\[
F(u) = u^4 + 2a^2u^3 + u^2a^2(a^2 - \alpha^2b^2) - ua^3\left(2\alpha\beta^2 - 2\alpha\beta^2\right) - \gamma^2a^4.
\]  
(3.13)

**Proposition 3.6** For the trivial steady state of system (3.1) with shifted Erlang kernel distributions given by (3.3)–(3.4) with \( \sigma_i = \sigma_i, a_i = a_i, i = 1, 2 \) and \( m_1 = 2, m_2 = 1 \) the following statements are true.

(i) If the steady state is locally asymptotically stable for \( \sigma = 0 \), and the function \( F \) given by (3.13) has no positive multiple roots, then it is locally asymptotically stable for some \( \sigma \in [0, \sigma_0] \) and it is unstable for \( \sigma > \sigma \), with \( \sigma_0 \leq \sigma \). At \( \sigma = \sigma_0 \) the Hopf bifurcation occurs.

(ii) If
\[
a \geq ab \min \left\{1, \frac{2\gamma}{\beta^2} \right\},
\]  
(3.14)
or
\[
a < ab \min \left\{1, \frac{2\gamma}{\beta^2} \right\} \quad \text{and} \quad \left(a^2 + 2a\beta^2\right)^3 < 27(2\alpha\beta + a(\alpha^2\beta^2 - \beta^2))^2,
\]  
(3.15)
then at most one stability switch of the steady state is possible. Moreover, if the steady state is locally asymptotically stable for \( \sigma = 0 \), then it is stable for some \( \sigma \in [0, \sigma_0] \) and it is unstable for \( \sigma > \sigma_0 \). For \( \sigma = \sigma_0 \) the Hopf bifurcation is observed.

**Proof:** First, note that for the auxiliary function given by (3.13) inequality \( F(0) < 0 \), holds. Thus, \( F \) has at least one real positive zero. Hence, if \( F \) has only simple positive zero, by Theorem 1 from [44] the steady state of system (3.1) is unstable for sufficiently large \( \sigma \), which completes the proof of part (i).

Now, we prove statement (ii). Assume that (3.14) holds. Then, if \( a \geq ab \), then the coefficient of \( u^2 \) is non-negative and independently on the sign of the coefficient of \( u \) the Descartes’ rule of signs indicates that there is exactly one simple positive real zero of \( F(u) \). Thus, at most one stability switch of the steady state can occur. On the other hand, if condition \( a \geq 2\alpha\beta^2b^2 \) holds, then the coefficient of \( u \) in \( F(u) \) is non-positive. Hence, independently of the sign of coefficient of \( u^2 \) the single change of the sign is observed. Thus, \( F(u) \) has exactly one simple real positive zero.

Now assume that (3.15) holds. To shorten notation denote
\[
\alpha_1 = 2\alpha\beta^2 - a\beta^2, \alpha_2 = \alpha^2b^2 - a^2.
\]  
(3.16)
The first inequality of (3.15) is equivalent to \( \alpha_1 > 0 \) and \( \alpha_2 > 0 \). Denote \( F_1(\zeta) = F(a\zeta)/a^4 \), with \( \zeta = u/a \). Clearly, \( F(u) = 0 \) is equivalent to \( F_1(\zeta) = 0 \). The function \( F_1 \) reads

\[
F_1(\zeta) = \zeta^4 + 2a\zeta^3 - a_2\zeta^2 + \zeta\alpha_1 - \gamma^2.
\]

We show that under the assumption (3.15) the function \( F_1 \) is a strictly monotonic function of \( \zeta \), which implies that \( F \) is a strictly monotonic function of \( u \). This, together with the fact \( F(0) < 0 \) implies that \( F \) has exactly one simple positive zero so the assertion of the point (ii) is true.

In order to show monotonicity of \( F_1 \), we prove that its first derivative is positive. We have

\[
F_1'(\zeta) = 4\zeta^3 + 6a\zeta^2 - 2a_2\zeta + \alpha_1.
\]

The assumption \( \alpha_1 > 0 \) implies \( F_1'(0) > 0 \). We now derive a condition that guarantees positivity of \( F_1' \) for all \( \zeta > 0 \). To this end, we calculate the minimum of \( F_1'(\zeta) \) in the interval \( [0, +\infty) \). Calculating the second derivative of \( F_1 \) we find that the minimum of \( F_1' \) is reached at the point

\[
\tilde{\zeta} = \frac{1}{2}(-a + \sqrt{a^2 + \frac{2}{3}a_2}).
\]

Using the fact that \( F_1''(\tilde{\zeta}) = 0 \) we have

\[
F_1'(\tilde{\zeta}) = \alpha_1 - 2\zeta^3 - a_2\tilde{\zeta}.
\]

Thus, \( F_1 \) is strictly increasing for all \( \zeta > 0 \) if and only if

\[
(2\zeta^2 + a_2)\tilde{\zeta} < \alpha_1. \tag{3.17}
\]

A few algebraic manipulations indicate that (3.17) is equivalent to

\[
\left(a^2 + \frac{2}{3}a_2\right)^{3/2} - a(a^2 + a_2) < \alpha_1.
\]

Using the definition of \( a_2 \) the above inequality reads

\[
\frac{1}{3}\sqrt[3]{3}(a^2 + 2a^2b^2)^{3/2} < \alpha_1 + a^2b^2.
\]

Due to the assumption \( \alpha_1 > 0 \) both sides of the above inequality are positive, so squaring that inequality we obtain

\[
(a^2 + 2a^2b^2)^3 < 27(a_1 + a^2b^2)^2.
\]

Now using the definition of \( a_1 \) we get

\[
(a^2 + 2a^2b^2)^3 < 27(2ab\gamma + a(a^2b^2 - \beta^2))^2,
\]

which is fulfilled due to the second inequality of (3.15). This completes the proof.

Note, that there exist sets of parameters of system (3.1) with shifted Erlang kernel distributions given by (3.3)–(3.4) with \( \sigma_i = \sigma, a_i = a, i = 1, 2 \) and \( m_1 = 2, m_2 = 1 \) such that the steady state is locally asymptotically stable for \( \sigma = 0 \) and conditions (3.15) hold. As a proper example we formulate the remark above.

**Remark 3.7** If

\[
ab < \beta, \quad \text{and} \quad 1 < \frac{2\gamma}{\beta^2}, \tag{3.18}
\]

then for all \( a > \frac{1}{2}\beta + \frac{2\gamma}{\beta} - ab \) the steady state of system (3.1) with shifted Erlang kernel distributions given by (3.3)–(3.4) with \( \sigma_i = \sigma, a_i = a, i = 1, 2 \) and \( m_1 = 2, m_2 = 1 \) loses its stability at \( \sigma = \tilde{\sigma} \) and the Hopf bifurcation occurs at this point.
\textbf{Proof}: First, note that under the assumptions of the remark if \( a \geq ab \min \left\{ 1, \frac{2\gamma}{\beta^2} \right\} \), then condition (3.14) holds and Proposition 3.6 implies the assertion of the remark. If \( a > \frac{1}{2} \beta + \frac{2\gamma}{\beta} - ab \) and conditions (3.15) hold then Proposition 3.6 also implies the assertion of the remark. In this case we show that for some set of parameters these conditions can be fulfilled simultaneously.

Consider \( a < ab \min \left\{ 1, \frac{2\gamma}{\beta^2} \right\} \). The second inequality of (3.18) implies that \( \min \left\{ 1, \frac{2\gamma}{\beta^2} \right\} = 1 \). Hence, stability condition of steady state for \( \sigma = 0 \) and the first condition (3.15) reads

\[
\frac{1}{2} \beta + \frac{2\gamma}{\beta} - ab < a < ab.
\]

First, we show for some parameters inequalities (3.19) give a non empty set of \( a \). This is true if

\[
\frac{1}{2} \beta + \frac{2\gamma}{\beta} < 2ab < 2\beta
\]

hold, where the second inequality in (3.20) is just the first one in (3.18). Inequalities (3.20) do not contradict each other if and only if

\[
\frac{1}{2} \beta + \frac{2\gamma}{\beta} < 2\beta.
\]

Thus, if \( \frac{2\gamma}{\beta^2} < 3/2 \), then there is a non-empty set of \( ab \) such that inequalities (3.20) hold and for such \( ab \) (3.19) determines a non-empty set of \( a \).

Now, we show that if (3.18) and the first inequality of (3.15) hold then the second inequality of (3.15) also holds.

Note that the assumption \( ab < \beta \) means that the right hand side of the second inequality of (3.15) is a decreasing function of \( a \) (of course we need to use here the first inequality of (3.15) that guarantees the positivity of the expression under the second power), while the left hand-side is an increasing function of \( a \). As our assumptions imply that \( a < ab \), it is enough to check if inequality (3.15) holds for \( a = ab \).

Rearranging terms we obtain

\[
27a^{6}b^{6} < 27\left( \alpha^{3}b^{3} + ab(2\gamma - \beta^2) \right)^{2}.
\]

The above inequality obviously holds as \( 2\gamma > \beta^2 \), which completes the proof. \( \square \)

Now, consider \( m_{M} = m_{2} \), then auxiliary function (3.12) reads

\[
F(\omega) = \omega^{4} (a^{2} + \omega^{2})^{m_{2}} - \left\| \iota\omega(ra^{m_{1}}(a + i\omega)^{m_{2} - m_{1}} + ab\alpha^{m_{2}}) + \gamma a^{m_{1}}(a + i\omega)^{m_{2} - m_{1}} \right\|^{2}.
\]

\textbf{Proposition 3.8} There exists exactly one \( \sigma_{0} > 0 \) such that if the trivial steady state of system (3.1) with shifted Erlang kernel distributions given by (3.3)-(3.4), with \( m_{1} = 1, m_{2} = 2 \) and \( a_{i} = a, \sigma_{i} = \sigma = 0, i = 1, 2, \) is locally asymptotically stable, then for \( \sigma \in [0, \sigma_{0}) \) it is locally asymptotically stable and it is unstable for \( \sigma > \sigma_{0} \). At \( \sigma = \sigma_{0} \) the Hopf bifurcation occurs.

\textbf{Proof}: For \( m_{1} = 1 \) and \( m_{2} = 2 \) instead of (3.22) one gets

\[
F(\omega) = \omega^{4} + 2a^{2}\omega^{6} + a^{4}\omega^{4} - a^{2} \left( \gamma a - r\omega^{2} \right)^{2} - a^{2} \omega^{2} (ab + \gamma)^{2}.
\]

Putting \( u = \omega^{2} \) we get

\[
F(u) = u^{3} + 2a^{2}u^{3} + a^{4}(a^{2} - r^{2})u^{2} - a^{2} \left( a^{2}b^{2} + 2a\alpha b\gamma + \gamma^{2} \right) u - a^{4}\gamma^{2}.
\]

We show that the coefficient of \( u \) in (3.23) is negative and hence the Descartes’ rule of signs implies that a single stability switch for the trivial steady state of (3.1) occurs. This is equivalent to the inequality

\[
G(a) = a^{2}b^{2} + 2a\alpha b\gamma + \gamma^{2} > 0,
\]
for \( a \geq 0 \). For \( b > \mu \) (that is the condition required for the existence of the trivial steady state of (3.1)) a discriminant of \( G \) is the following
\[
4\gamma^2 \left( a^2b^2 - \beta^2 \right) = 4\gamma^2 \left( a^2b^2 - (r + \alpha b)^2 \right) = -4\gamma^2 (r + 2\alpha b) < 0.
\]
Thus, \( G(u) > 0 \), so \( F \) has exactly one simple positive root \( u_0 \). Moreover, \( F(0) < 0 \) hence \( F'(u_0) > 0 \) and the proof is completed.

For general case of system (3.1) with shifted Erlang kernel distributions given by (3.3)–(3.4) characteristic function \( D(\lambda) \) is given by (3.11) and the auxiliary function \( F \) is given by (3.12). It is easy to see that the highest power of \( \omega \) is \( 4 + 2m_M \) and the coefficient of it is 1. Moreover, we have \( F(0) < 0 \). Thus, there exists \( \omega_0 > 0 \) such that \( F(\omega_0) = 0 \) and roots cross the imaginary axis from the left to the right half-plane. Thus, using Theorem 1 from [44], we can deduce following

**Remark 3.9** If all roots of \( F(\omega) \) given by (3.12) are simple, and the trivial steady state of system (3.1) with shifted Erlang kernel distributions given by (3.3)–(3.4), with \( a_i = a \) and \( \sigma_i = \sigma_i \), \( i = 1,2, \) is locally asymptotically stable for \( \sigma = 0 \), then it loses its stability due to the Hopf bifurcation for some \( \sigma_0 > 0 \) and is unstable for \( \sigma > \sigma_\infty \) with some \( \sigma_\infty \geq \sigma_0 \).

It seems that the case of multiple roots of \( F(\omega) \) is non-generic, however we will not prove it here.

### 3.2.2 Piecewise linear kernels

For the function defined by (3.2) we have
\[
\int_0^\infty f_i(\tau) e^{-\lambda \tau} d\tau = \frac{e^{-\lambda \epsilon_i}}{\lambda^2 \epsilon_i^2} \left( e^{\lambda \epsilon_i} + e^{-\lambda \epsilon_i} - 2 \right) = \frac{2 e^{-\lambda \epsilon_i}}{\lambda^2 \epsilon_i^2} \left( \cosh(\lambda \epsilon_i) - 1 \right)
\]
and thus the characteristic function for trivial steady state of system (3.1) reads
\[
W(\lambda) = \lambda^2 + \lambda \int_0^\infty \left( r f_1(\tau) + ab f_2(\tau) \right) e^{-\lambda \tau} d\tau + \gamma \int_0^\infty f_1(\tau) e^{-\lambda \tau} d\tau,
\]
which is equivalent to
\[
W(\lambda) = \lambda^2 + (\lambda \tau + \gamma) \frac{2 e^{-\lambda \epsilon_1}}{\lambda^2 \epsilon_1^2} \left( \cosh(\lambda \epsilon_1) - 1 \right) + \lambda a b \frac{2 e^{-\lambda \epsilon_2}}{\lambda^2 \epsilon_2^2} \left( \cosh(\lambda \epsilon_2) - 1 \right).
\] (3.24)

Finding zeros of function (3.24) is not a trivial task. In the case when the characteristic function has form \( W(\lambda) = P(\lambda) + Q(\lambda) e^{-\lambda \tau} \), where \( P \) and \( Q \) are polynomials, one could use the Mikhailov Criterion [45], to estimate the number of zeros of characteristic function lying in the right half of complex plane. However, in the considered case we do not have strict polynomials. Therefore, we use a generalised Mikhailov Criterion (for details see A). Clearly, since \( \cosh(\epsilon) = \sum_{n=0}^{\infty} \frac{\epsilon^{2n}}{(2n)!} \), for \( \epsilon \in \mathbb{C} \) is an analytical function, hence \( \frac{\cosh(\epsilon)^{-1}}{\epsilon} \) is also analytical. Consequently, the function \( W \) defined by (3.24) is also analytical. Moreover, obviously condition (A.1) holds. Thus, we can apply the generalized Mikhailov Criterion.

Considering \( \sigma_i = \sigma \geq \epsilon_i = \epsilon > 0, i = 1,2, \) we have
\[
W(\lambda) = \lambda^2 + (\lambda \beta + \gamma) g(\lambda \epsilon) e^{-\lambda \tau},
\] (3.25)
where
\[
g(x) = \frac{2(\cosh x - 1)}{x^2}, \quad g_1(x) = \frac{2 - 2 \cos x}{x^2}.
\] (3.26)
Thus,\[
\text{Re}(W(i\omega)) = -\omega^2 + g_1(\omega \epsilon)\left(\gamma \cos(\omega \sigma) + \beta \omega \sin(\omega \sigma)\right), \tag{3.27}
\]
\[
\text{Im}(W(i\omega)) = g_1(\omega \epsilon)\left(\beta \omega \cos(\omega \sigma) - \gamma \sin(\omega \sigma)\right). \tag{3.28}
\]

Here we formulate sufficient condition for stability of the trivial steady state of system (3.1) for the piecewise linear distributions defined by (3.2) with \(\sigma_i = \sigma \geq \epsilon_i = \epsilon > 0\). This condition is clearly not necessary, what we will show numerically in the next section.

**Proposition 3.10** Let \(b > \mu, \beta \) and \(\gamma \) be defined by (3.6). Then for
\[
\sigma < \frac{\pi}{\beta + \sqrt{\beta^2 + 4\gamma + \frac{\gamma}{\beta} \pi}} \tag{3.29}
\]
the trivial steady state of system (3.1) with piecewise linear distributions defined by (3.2) and \(\sigma_i = \sigma \geq \epsilon_i = \epsilon > 0\) is locally asymptotically stable.

**Proof**: We use the generalized Mikhailov Criterion (for details see [A]) to show that the change of the argument of \(W(i\omega)\) as \(\omega\) varies from 0 to \(\infty\) is equal to \(\pi\). In fact, we show that the behaviour of the hodograph is more restrictive, namely that for some \(\tilde{\omega} > 0\) we have \(\text{Re}(W(i\omega)) < 0\) for \(\omega > \tilde{\omega}\), while \(\text{Im}(W(i\omega)) > 0\) for \(\omega \in [0, \tilde{\omega}]\). To this end first, note that if \(g_1(\omega \epsilon) = 0\) and \(\omega > 0\), then \(\text{Re}(W(i\omega)) < 0\). Thus, without loss of generality we assume that \(g_1(\omega \epsilon) > 0\).

First, let us estimate the real part of \(W(i\omega)\) given by (3.27). Since \(b > \mu\) and \(g_1(\epsilon \omega) \leq 1\) we have
\[
\text{Re}(W(i\omega)) \leq -\omega^2 + \gamma + \omega \beta =: g_R(\omega).
\]

Now, let us consider the imaginary part of \(W(i\omega)\). In fact, since we are interested in the sign of it and
\[
g_1(\epsilon \omega) \geq 0 \text{ it is enough to consider the sign of}
\]
\[
\omega \beta \cos(\omega \sigma) - \gamma \sin(\omega \sigma) = g_1(\omega \sigma),
\]

where
\[
g_1(x) = \frac{\beta}{\sigma} x \cos x - \gamma \sin x.
\]

Note, that (3.29) implies \(\beta > \gamma \sigma\), and thus \(g_1(x) > 0\) for \(x\) close to 0. On the other hand, \(g_1(\pi/2) = -\gamma < 0\). It is also easy to check, that \(g_1(x)\) has a unique zero in \((0, \pi/2)\) for \(\beta > \gamma \sigma\). Below, we give some estimation for this zero.

Since \(\tan x < \frac{\pi}{2} \frac{x}{\pi/2 - x}\), for \(x \in (0, \pi/2)\) we have
\[
\frac{\beta}{\gamma \sigma} x \geq \frac{\pi}{2} \frac{x}{\pi/2 - x} > \tan x. \tag{3.30}
\]

A simple algebraic yields that the first inequality of (3.30) is fulfilled for all
\[
0 < x \leq \frac{\pi}{2} \left(1 - \sigma \cdot \frac{\gamma}{\beta}\right) < \frac{\pi}{2}.
\]

Thus, as long as \(\omega \sigma \leq \frac{\pi}{2} \left(1 - \sigma \cdot \frac{\gamma}{\beta}\right)\) we have \(\text{Im}(W(i\omega)) > 0\).

However, \(g_R\) is a quadratic polynomial with \(g_R(0) > 0\). Moreover, the coefficient of \(\omega^2\) is negative and the positive root of \(g_R\) is equal to \(\frac{1}{2} \left(\beta + \sqrt{\beta^2 + 4\gamma}\right)\). Easy algebraic manipulation shows that condition (3.29) is equivalent to
\[
\frac{\sigma}{2} \left(\beta + \sqrt{\beta^2 + 4\gamma}\right) < \frac{\pi}{2} \left(1 - \sigma \cdot \frac{\gamma}{\beta}\right)
\]
and thus \(g_R(\omega) < 0\) for all \(\sigma \omega > \frac{\pi}{2} \left(1 - \sigma \cdot \frac{\gamma}{\beta}\right)\), which completes the proof. \qed
Proposition 3.11 Let \( b > \mu, \beta \) and \( \gamma \) be defined by (3.6). Then for
\[
\frac{\beta}{\gamma} < \sigma < \frac{2\pi}{\beta + \sqrt{\beta^2 + 4\gamma}}
\] (3.31)
the trivial steady state of system (3.1) with piecewise linear distributions defined by (3.2) with \( \sigma_i = \sigma \geq \varepsilon, \varepsilon_i = \varepsilon > 0 \) is unstable.

Proof: The idea of the proof is similar to the proof of Proposition 3.10. However, this time we want to show that for \( \sigma \omega \in (0, \pi) \) the imaginary part \( \text{Im}(W(i\omega)) < 0 \), while for \( \sigma \omega > \pi \) the real part \( \text{Re}(W(i\omega)) < 0 \). This indicates that the hodograph goes below the \((0, \pi)\) point on the complex plane when \( \omega \) tends to \(+\infty\) and hence the change of the argument of \( W(i\omega) \) differs from \( \pi \). Hence, from the generalized Mikhailov Criterion it is clear that the trivial steady state of system (3.1) is unstable.

Note, that for \( \omega \sigma \in (\pi/2, \pi) \) we have \( \text{Re}(W(i\omega)) < 0 \) due to the fact that on this interval cosine is negative and sine is positive. Consider now \( \omega \sigma \in (0, \pi/2) \). Thus, cosine is positive and inequality \( \beta \omega \cos(\omega \sigma) - \gamma \sin(\omega \sigma) < 0 \) is equivalent to
\[
\frac{\beta}{\sigma \gamma} \omega \sigma < \tan(\omega \sigma).
\] (3.32)
The right hand side of (3.32) is strictly increasing convex function on \((0, \pi/2)\) and have first derivative at 0 equal to 1. Thus, first inequality of (3.31) implies (3.32).

Now, it is enough to show that \( g_\sigma(\pi/\sigma) < 0 \). A straightforth calculation yields
\[
-\left(\frac{\pi^2}{\sigma}\right)^2 + \beta \frac{\pi^2}{\sigma} + \gamma < 0.
\]
Solving quadratic equation we get
\[
\sigma < \frac{2\pi}{\beta + \sqrt{\beta^2 + 4\gamma}},
\]
which is the second inequality of (3.31).

Remark 3.12 Note, that (3.29) implies \( \sigma < \beta/\gamma \) and consequently, conditions (3.31) and (3.29) are mutually exclusive.

Proposition 3.13 If the trivial steady state of system (3.1) with piecewise linear distributions defined by (3.2) and \( \sigma_i = \sigma \geq \varepsilon, \varepsilon_i = \varepsilon > 0 \) is locally asymptotically stable for \( \sigma = \varepsilon \) and the function
\[
F(\omega) = \omega^4 - \varepsilon^2 \left(\omega^2 \beta^2 + \gamma^2\right)g_1^2(\varepsilon)\omega,
\]
where \( g_1 \) is defined by (3.26) has no multiple positive zeros, then the steady state is locally asymptotically stable for some \( \sigma \in [\varepsilon, \sigma_0) \) and it is unstable for \( \sigma > \tilde{\sigma} \), with \( \sigma_0 \leq \tilde{\sigma} \). At \( \sigma = \sigma_0 \) the Hopf bifurcation occurs.

Proof: For \( \sigma_i = \sigma \) and \( \varepsilon_i = \varepsilon, i = 1, 2 \), the characteristic function is given by (3.25). It can be easily seen that if \( W(i\omega) = 0 \), then
\[
\| - i\omega \| = \varepsilon^2 \| i\omega \beta + \gamma \| = \| g(i\omega \varepsilon) \|,
\]
and thus
\[
\omega^4 = \varepsilon^2 \left(\omega^2 \beta^2 + \gamma^2\right)g_1^2(\varepsilon \omega),
\]
where \( g_1 \) is defined by (3.26). The function \( F \) has the following properties
\[
F(0) = -\varepsilon^2 \gamma^2 < 0, \quad \text{and} \quad \lim_{\omega \to +\infty} F(\omega) = +\infty.
\]
Hence, we conclude that there exists \( \omega_0 > 0 \) such that \( F(\omega_0) = 0 \) and \( F'(\omega_0) \geq 0 \). It is assumed that all zeros of \( F(\omega) \) are simple, thus \( F'(\omega_0) > 0 \) and by Theorem 1 from [44], the thesis of Theorem is proved.
Remark 3.14 Note, that the case where the function $F$ has multiple positive zeros is not generic.

Proof: Consider the case of multiple positive zero(s) of $F$. First, note the following facts:

(a) $F$ is an analytic function so it has isolated zeros;

(b) For $\omega > \max\{\epsilon \sqrt{\beta^2 + \gamma^2}, 1\}$ inequality $F(\omega) > 0$ holds.

(c) If $g_1(\epsilon \omega) = 0$, then $F(\omega) = (2k\pi/\epsilon)^d > 0$ for some $k \in \mathbb{N}, k \geq 1$.

Facts (a) and (b) imply, that $F$ has a finite number of zeros. Suppose that for the arbitrary values of $\beta_0$ and $\gamma_0$ the function $F$ has the multiple zero at $\omega_{m,j}$, for some $j = 1, 2, ..., j_M$, where $j_M \geq 1$ is a natural number. Now, consider the interval $I = [0, \max\{\epsilon \sqrt{\beta^2 + \gamma^2}, 1\} + 1]$. Clearly, $\partial F/\partial \gamma < 0$ holds for all $\omega \neq 2k\pi/\epsilon$. Moreover, $F'$ is also an analytical function so it has a finite number of zeros in the interval $I$. Thus, we may choose $0 < \epsilon, < 1$ so small that for all $\gamma \in (\gamma_0 - \epsilon, \gamma + \epsilon) \setminus \{\gamma_0\}$ the function $F$ has no multiple root in the interval $I$. This completes the proof.

4 Stability results for parameters estimated by Hahnfeldt et al.

In the previous section, we analytically investigated the stability of the trivial steady state of the family of the angiogenesis models with distributed delays (3.1) and distributions characterized by the probability densities $f_j$ given by (3.2) and (3.3)–(3.4). System (3.1) is a rescaled version of (2.1), where the trivial steady state of (3.1) corresponds to the positive steady state of (2.1).

In this section we illustrate our outcome for particular model parameters considered earlier in the literature, that is the parameters estimated by Hahnfeldt et al. in the case of model without the treatment (see [46]). Namely, we consider the following set of parameters:

$$
\mu = 0, \quad a_H = 8.73 \times 10^{-3}, \quad b = 5.85, \quad r = 0.192, \tag{4.1}
$$

and we take the function $h(\theta) = -\ln \theta$. We present stability results for distributed models for two different values of parameter $\alpha$. For model (3.1) with $\alpha = 1$ we would refer to as Hahnfeldt et al. model, while to model (3.1) with $\alpha = 0$ as d’Onofrio-Gandolfi model. However, in this paper we also consider positive values of $\mu$ that can be interpreted as a constant anti-angiogenic treatment.

4.1 Erlang kernels

First, focus on model (3.1) with non-shifted Erlang distributions given by (3.3)–(3.4) with $\sigma_i = 0$, $i = 1, 2$. In the case $m_i = m$ and $a_i = a$, $i = 1, 2$, the expression $m/a$ describes the average delay. On the other hand, in the more general case $m_1 \neq m_2$ the similar interpretation leads to the conclusion that the average delays are $m_1/a$ and $m_2/a$. One could also consider the arbitrary values $a_1$ and $a_2$, but in such case analytical expressions become very complicated and we decided not to study this case here.

In Fig. 1 the dependence of average critical delay value $\tau_{cr,0}$ with $m_i = m$ and $a_i = a$ ($i = 1, 2$) on the constant treatment coefficient $\mu$ are presented. Clearly, in case of non-shifted Erlang distributions the average delay is defined by $\tau_{cr,0} = m/a\epsilon_{cr,0}$ and the left-hand side panels and right-hand side panels present results for distributed Hahnfeldt et al. model ($\alpha = 1$) and distributed d’Onofrio-Gandolfi model ($\alpha = 0$), respectively. The curves were calculated from the stability conditions given in Theorem 3.3. The stability regions of the trivial steady state of (3.1) with non-shifted Erlang distributions are below curves, while above them there are the instability regions. It is worth to emphasise that the qualitative difference between cases $m = 1, 2$ (first two rows in Fig. 1) and 3 (the third row in Fig. 1). For the case $m = 2$ (Fig. 1 the middle row) the average critical values of delays...
Figure 1: Dependence of the average critical delay value in the case of non-shifted Erlang distributions given by (3.3)–(3.4) with $m_1 = m_2 = m$ and $a_1 = a_2 = a$ on the constant treatment coefficient $\mu$ for system (3.1). The average critical delay is defined by $\tau_{cr,0} = m/\alpha_{cr,0}$, where $\alpha_{cr,0}$ is the critical value of parameter $\alpha$ for which stability change occurs (see Theorem 3.3). In the left-hand side panels results for distributed Hahnletdt et al. model ($\alpha = 1$) are shown while in the right-hand side panels results for distributed d’Onofrion-Gandolfi model ($\alpha = 0$). All other parameters, except $\mu$, as defined by (4.1).

for $\mu \to b = 5.85$ are equal to $\tau_{cr,0} = 4/\beta$ that is 0.662 and 20.833 for the distributed Hahnletdt et al. and the distributed d’Onofrion-Gandolfi models, respectively. For the case $m = 1$ (Fig. 1, the top row) $\tau_{cr,0}$ tends to $+\infty$ as $\mu \to b$ while for $m = 3$ (Fig. 1, the bottom row) $\tau_{cr,0}$ approaches to 0. Nevertheless, for the distributed d’Onofrion-Gandolfi model the average critical value of delays are almost the same for the case $m = 1$ and $m = 2$ for $\mu \in [0, b)$, compare first two rows in Fig. 1. Moreover, in the all considered cases the average critical delay values in the case of non-shifted Erlang distributions are the increasing functions of $\mu$. This means that the increase of treatment increases the stability region.
Additionally, we plot the particular choices of parameters \( m_1 \) and \( m_2 \) of the distributed d’Onofrion-Gandolfi model for the strength of constant treatment \( \mu \). The regions above the plotted curves correspond to the stability regions for the particular choices of parameters \( m_i, i = 1, 2 \). For \( m_1 = 2, m_2 = 1 \) and \( \alpha = 1 \) the trivial steady state is always stable. All other parameters, except \( \mu \), as defined by (4.1).

In Fig. 2 we plot the critical value of parameter \( a \), that is \( a_{\text{cr},0} \), for the trivial steady state of system (3.1) with non-shifted Erlang kernel distributions given by (3.3)–(3.4) (i.e. \( \sigma_i = 0, i = 1, 2 \)) calculated based on Theorem 3.3. Here, the regions above the plotted curves correspond to the stability regions for the particular choices of parameters \( m_i, i = 1, 2 \), while those below correspond to the instability regions. It should be clarified that for the case \( \alpha = 1, m_1 = 2 \) and \( m_2 = 1 \) the steady state is stable for all values of \( a \). We see that all plotted functions are decreasing as functions of the strength of constant treatment \( \mu \). However, already for non-shifted Erlang kernel distributions we observe the large differences between both models regarding the model dynamics. For the distributed Hahnfeldt et al. model we have the largest stability region for \( m_1 = 2 \) and \( m_2 = 1 \), while in the case of the distributed d’Onofrion-Gandolfi model for \( m_1 = 1 \) and \( m_2 = 2 \). Moreover, for the case \( m_1 = 2 \) and \( m_2 = 1 \) the steady state is stable independently of the parameter \( a \) for the distributed d’Onofrion-Gandolfi model for the considered model with shifted Erlang distributions we have the largest stability region for \( m_1 = 2 \) and \( m_2 = 1 \), while in the case of the distributed d’Onofrion-Gandolfi model for \( m_1 = 1 \) and \( m_2 = 2 \). Moreover, for the case \( m_1 = 2 \) and \( m_2 = 1 \) the steady state is stable independently of the parameter \( a \) for the distributed Hahnfeldt et al. model, while for the same case of \( m_i \) for the distributed d’Onofrion-Gandolfi model the steady state might change its stability with the change of \( a \). Additionally, for \( \alpha = 0 \) the sizes of the stability regions for \( m_1 = 2 \) and \( m_1 = 2, m_2 = 1 \) are the same and it is not the case for \( \alpha = 1 \).

The stability of the steady state for non-shifted Erlang distributions can be determined by Routh-Hurwitz Criterion, although it may require tedious calculations, in particular for larger values of parameters \( m_1 \) and/or \( m_2 \). On the other hand, the analytical results we obtained for shifted Erlang distributions are rather limited. The results presented in Proposition 3.5 are only the existence results and give no information of the magnitude of the critical value of \( \sigma \) for which stability is lost. Although, it is possible to derive expression for the critical value of \( \sigma \), it would involve arccos of some algebraic function of \( \omega_0 \), which can not be, in general, determined analytically and the final result would not be informative. In consequence, we decided to calculated numerically the critical average values of delay \( \tau_{\text{cr},\alpha} \) for the considered model with shifted Erlang distributions for parameters given by (4.1). Clearly, if one wish to calculate the critical average delay for model with shifted Erlang distributions it appears that it depends on sigma directly and is given by \( \tau_{\text{cr},\alpha} = m/\alpha + \sigma_{\text{cr}} \), where \( \sigma_{\text{cr}} \) is a critical value of \( \sigma \) defined in Proposition 3.5. In Fig. 3 we present the stability results for the trivial steady state of system (3.1) with shifted Erlang kernel distributions given by (3.3)–(3.4). In particular, in Fig. 3 (left column) we plot the dependence of \( \tau_{\text{cr},\alpha} \) on the treatment strength \( \mu \) for the particular choices of parameters \( m_i \) and the particular choices of parameter \( a_i = a \) for model with \( \alpha = 1 \). Similarly as in Fig. 1 the regions below the plotted curves correspond to the stability regions. Additionally, we plot \( \tau_{\text{cr},0}(\mu) \) curves to indicate thresholds for which destabilizations occur in the case of \( \sigma = 0 \). If the curve for considered \( a \) is above the \( \tau_{\text{cr},0} \) curve, then the steady state is unstable for

Figure 2: Dependence of the critical value of parameter \( a \) for the trivial steady state of system (3.1) with non-shifted Erlang kernel distributions given by (3.3)–(3.4) (i.e. \( \sigma_i = 0, i = 1, 2 \)). The regions above the plotted curves corresponds to the stability regions for the particular choices of parameters \( m_i, i = 1, 2 \). For \( m_1 = 2, m_2 = 1 \) and \( \alpha = 1 \) the trivial steady state is always stable. All other parameters, except \( \mu \), as defined by (4.1).
Figure 3: Dependence of the average critical delay $\tau_{cr,\sigma}$ for the trivial steady state of system (3.1) with shifted Erlang kernel distributions given by (3.3)-(3.4) for the particular choice of parameter $\alpha$ and comparison with the critical value of average delay $\tau_{cr,0}$ in the case $\sigma = 0$. For the case of distributed Hahnfeldt et al. model (i.e. $\alpha = 1$), presented in the left column, the regions above the plotted curves correspond to the instability regions for the particular choices of parameters $m_1 = m_2$ and of parameter $\alpha$. The stability region is the region below curves. For distributed d’Onofrio-Gandolfi model (i.e. $\alpha = 0$) presented in the right column, the difference between critical value of the average delay $\tau_{cr,0}$ in the case $\sigma = 0$ and the average critical delays $\tau_{cr,\sigma}$ for chosen values of $\alpha$ are so small that the plot would be non-informative. Thus, in the right column we presented the difference $\sigma_+ = \tau_{cr,0} - \tau_{cr,\sigma}$. All other parameters, except $\mu$, as defined by (4.1).
\( \sigma = 0 \) and remains unstable for all \( \sigma > 0 \). In both cases \( m_i = 1 \) and \( m_i = 2 \) the increase of the value of the parameter \( a \) (which is equivalent to decrease of the average critical delay), defining the shape of distribution kernel, implies the decrease of the stability regions of the steady state. Since the corresponding curves for \( \alpha = 0 \) are very close to each other instead of plotting them directly we decided to plot the differences \( \sigma_+ = \tau_{cr,0} - \tau_{cr,\sigma} \) between the critical values of the average delays \( \tau_{cr,0} \) in the case \( \sigma = 0 \) and the average critical delays \( \tau_{cr,\sigma} \) for the chosen values of \( a \). Clearly, whenever plotted curve reaches the \( \mu \) axis the trivial steady state becomes unstable for all \( \sigma \geq 0 \). From Fig. 5 (right column) we deduce that the stability areas again decrease with the increase of the parameter \( a \).

### 4.2 Piecewise linear distributions

Let us focus on the stability and instability regions of the trivial steady state of system (3.1) with piecewise linear distributions defined by (3.2). Since in this case we have smaller number of parameters defining the shape of kernel distributions we are able to plot the stability regions in \( \varepsilon - \sigma \) plane, see Fig. 4. Note that, for \( \varepsilon > \sigma \) system (3.1) becomes a neutral system, which is out of our consideration hence this region is greyed. Clearly, the estimations obtained in Propositions 3.10 and 3.11 are rough. However, solving numerically a system \( \text{Re} W(i\omega) = 0, \text{Im} W(i\omega) = 0 \), where real and imaginary part of characteristic function are given by (3.27) and (3.28), respectively, we are able to calculate the stability region and the curve for which the stability change occurs. This line was plotted in Fig. 4 as a thick solid blue line.

Additionally, we plot (in both panels) the vertical dashed lines that denote the conditions guaranteeing stability (see Proposition 3.10) or instability (see Proposition 3.11) of the trivial steady state. For the distributed Hahnfeldt et al. model (left panel in Fig. 4) the condition (3.29) from Proposition 3.10 is denoted by a vertical dash line. In such a case, the condition (3.31) can not be fulfilled since the expression on the right-hand side of (3.31) is always smaller than \( \beta/\gamma \). For the distributed d’Onofrio-Gandolfi model the dash vertical line on the left to the solid vertical line indicates the condition (3.29). Two dashed vertical lines on the right to the solid one indicate the region in which the condition (3.31) is fulfilled and are defined by Propositions 3.10 and 3.11 respectively. Those numerical results show that the conditions from Propositions 3.10 and 3.11 are only sufficient but not necessary. From the figure we also deduce that the stability region for the trivial steady state for the distributed d’Onofrio-Gandolfi model is smaller than the one for the distributed Hahnfeldt et al. model. Moreover, the computed by us the critical values of \( \sigma \) for \( \varepsilon \to 0 \) and both \( \alpha = 1 \) and \( \alpha = 0 \) agrees with those calculated by Piotrowska and Foryś in [33] for the models with discrete equal delays. That agrees with the intuition, since for \( \varepsilon \to 0 \) models given by (3.1) with piecewise linear distributions defined by (3.2) reduce to the models with double discrete delay.

For \( \mu > 0 \) and the distributed Hahnfeldt et al. model we observe a move of the stability switch curve to the right with hardly any change in the shape indicating that the stability region increases with increase of parameter \( \mu \), see left panel in Fig. 5. This shift is very small. Moreover, for \( \mu = b \) we obtain limiting values: 0.26 for \( \varepsilon \to 0 \) and 0.33 for \( \varepsilon \to \sigma \). On the other hand, for the distributed d’Onofrio-Gandolfi model the change is more visible. The lines start to lean to the right. For small \( \mu \), the change is quite small, compare with right panel in Fig. 4. For example, for \( \mu = 3 \) we obtain \( \sigma = 0.509 \) for \( \varepsilon \to 0 \) and \( \sigma = 0.59 \) for \( \varepsilon = \sigma \). As \( \mu \) approaches to \( b \) the changes becomes more rapid. For \( \mu = 5.7 \) we have \( \sigma = 5.326 \) for \( \varepsilon \to 0 \) and \( \sigma = 5.632 \) for \( \varepsilon = \sigma \), while for \( \mu = b \) we have \( \sigma = 8.181 \) and \( \sigma = 10.065 \) for the cases \( \varepsilon \to 0 \) and \( \varepsilon = \sigma \), respectively.

### 5 Discussion

Although the discrete delays often appear in the models describing various biological phenomena, e.g. [47–57] and references therein, it is obvious that in natural processes delay, if it exists, is usually somehow distributed around some average value due to differences between individuals and/or
Figure 4: Stability and instability of the trivial steady state of system (3.1) with piecewise linear distributions defined by (3.2) with \( \sigma_i = \sigma > 0, \epsilon_i = \epsilon > 0, i = 1, 2 \) for the parameters given by (4.1) with \( \alpha = 1 \) (left hand-side panel) and \( \alpha = 0 \) (right-hand side panel). The greyed part is the denotes the region where \( \epsilon > \sigma \) for which system (3.1) becomes a neutral system. The solid lines indicate the stability switch. In the left-hand side panel, the vertical dash line denotes the condition (3.29) from Proposition 3.10. In the right-hand side panel, the vertical dash line in the stability region denotes the scope of the condition (3.29) from Proposition 3.10, while two vertical dash lines in the instability region denote the scope of condition (3.31) from Proposition 3.11.

Figure 5: Stability and instability of the trivial steady state of system (3.1) with piecewise linear distributions defined by (3.2) with \( \sigma_i = \sigma > 0, \epsilon_i = \epsilon > 0, i = 1, 2 \) for the parameters given by (4.1) with \( \alpha = 1 \) (left hand-side panel) and \( \alpha = 0 \) (right-hand side panel) and different \( \mu \). The greyed part is the denotes the region where \( \epsilon > \sigma \) for which system (3.1) becomes a neutral system. The solid lines indicate the stability switch for (from left to right) \( \mu = 0, 3, b \) for \( \alpha = 1 \) and for \( \mu = 0, 3, 5.7, b \) for \( \alpha = 0 \).

Environmental noise. Thus, we believe that distributed delays are more realistic. However, in some cases, when the distribution has small variance and compact support discrete delays may be treated as a good approximation. Clearly, models with discrete and distributed delays might have different dynamics in some ranges of parameters. In presented paper we have compared the behaviour of the both type of systems in the context of the stability of the steady state for a particular family of models describing the angiogenesis process.

Presented analysis of distributed models includes: the uniqueness, positivity and global existence of solutions, the existence of the steady state and the possibility of the existence of stability switches. We have analytically derived conditions, involving the parameters defining the distribution kernels,
Table 1: The average critical delay value $\tau_{cr,0}$ in the case of non-shifted Erlang distributions given by (3.3)–(3.4) with $m_1 = m_2 = m$ and $a_1 = a_2 = a$ for arbitrary chosen parameters $\mu$ for system (3.1).

The average critical delay is defined by $\tau_{cr,0} = m/\alpha_{cr,0}$, where $\alpha_{cr,0}$ is the critical value of parameter $a$ for which the stability change occurs (see Theorem 3.3).

| $\mu$ | Hahnfeldt et al. model ($\alpha = 1$) | d’Onofrio-Gandolfi model ($\alpha = 0$) |
|-------|--------------------------------------|----------------------------------------|
| $m_1 = m_2 = 1$ | 8.069 | 12.261 | 25.515 | 5.85 | 0 | 2 | 4 | 5.85 |
| | 20.833 | 0.252 | 0.645 | 0.253 | 0.382 | 0.780 | 20.833 |
| $m_1 = m_2 = 2$ | 0.611 | 0.628 | 0.645 | 0.662 | 0.253 | 0.382 | 0.780 | 20.833 |
| | 9.731 | 0.382 | 0.428 | 0.811 | 0.380 | 0.770 | 13.889 |
| $m_1 = m_2 = 3$ | 0.421 | 0.428 | 0.435 | 0.441 | 0.252 | 0.380 | 0.770 | 13.889 |

guaranteeing the stability or instability of the steady state. We have also shown that in some cases the single stability switch is observed and the Hopf bifurcation occurs.

For particular set of parameters, estimated by Hahnfeldt et al., we have investigated the stability regions for steady state. We compared the results for both the distributed Hahnfeldt et al. ($\alpha = 1$) and the distributed d’Onofrio-Gandolfi ($\alpha = 0$) models in the case of different kernel distributions. For both models we considered the Erlang shifted and non-shifted distributions as well as the piecewise linear distributions. We want to emphasise here that, in general case, it is hard to say for which model Hahnfeldt et al. or d’Onofrio-Gandolfi the stability region is larger since it strongly depends on the considered distribution kernels and theirs shapes. However, we observe a certain similarities.

First, for $\mu = 0$, i.e. the family models without treatment, we see that for the Hahnfeldt et al. model with non-shifted Erlang distribution kernel the greater $m_i = m$ are the smaller the stability region is, see Fig. 1 and Table 1. The same holds for the d’Onofrio–Gandolfi model with non-shifted Erlang distributions, see Table 1 and moreover, for all considered $m_i = m$, $i = 1, 2$ (and $\mu = 0$) for the distributed Hahnfeldt et al. model the stability region is larger than for d’Onofrio–Gandolfi one. Similarly, for the models with piecewise linear distributions the stability region for $\mu = 0$ for the Hahnfeldt et al. model is larger than the one for d’Onofrio-Gandolfi model, compare Fig. 4.

If we consider a positive parameter $\mu$, but smaller than $b$ to ensure the non-negativity of the steady state of model (2.1) (which corresponds to the trivial steady state of (3.1)), we observe a similar tendency for Erlang distributions in dependence on the parameters $m_1 = m_2$ (compare Table 1 for the non-shifted distribution case). However, the dependence on $\mu$ depends strongly on the chosen model. For the Hahnfeldt et al. model and $m_1 = m_2 \geq 2$, this dependence is almost linear and very weak, while for the d’Onofrio-Gandolfi model it is much stronger. In results, for $m_1 = m_2 \geq 2$ and any sufficiently large value of $\mu \in [0, b]$ the average critical delay for the Hahnfeldt et al. model becomes smaller than for the d’Onofrio-Gandolfi model. The case $m_1 = m_2 = 1$ is different. Dependence on $\mu$ is similar for both models and the average critical delay for the Hahnfeldt et al. model stays larger than for the d’Onofrio-Gandolfi model for any given value of $\mu$. Similarly, for different values of $m_i$, it seems that dependence on $\mu$ is stronger for the d’Onofrio-Gandolfi model, see Fig. 2. Nevertheless, for the d’Onofrio–Gandolfi model with non-shifted Erlang distributions there is not difference regarding the stability results between case $m_1 = m_2 = 2$ and $m_1 = 2, m_2 = 1$, which is not the case for Hahnfeldt et al. model, where for $m_1 = 2, m_2 = 1$ we have stability independently on the value of parameter $a = a_i, i = 1, 2$. For the shifted Erlang distributions we have investigated the changes of size of the stability region also in the context of the change of the value of parameter $a = a_i, i = 1, 2$. For both Hahnfeldt et al. and d’Onofrio-Gandolfi models we see that for all considered $m = m_i, i = 1, 2$, the increase of the parameter $a = a_i, i = 1, 2$, decrease the stability region, however in the case of d’Onofrio-Gandolfi model we have compared the differences of the $\tau_{cr,0}−\tau_{cr,\mu}$. A similar increase of stability region with a decrease of concentration of delay distribution was observed in [36] for one linear equation with distributed delay and Erlang kernel.

Nevertheless, we see that since for all considered cases of shifted and non-shifted Erlang distributed models $\tau_{cr,\mu}$ and $\tau_{cr,0}$, respectively, are increasing (sometimes slightly) functions of variable
\( \mu \) implying that the increase of the constant treatment strength enlarge the stability regions for the positive steady state of model (2.1). Our analysis also shows that the increase of positive parameter \( \mu \) enlarge the stability area for the steady state for both (Hahnfeldt et al. and d’Onofrio-Gandolfi) distributed models with piecewise linear distributions, but this time for distributed d’Onofrio-Gandolfi model this increase is more pronounced than for distributed Hahnfeldt et al. model, see Fig. 5. Moreover, for small values of parameter \( \mu \) the stability region for Hahnfeldt et al. model with piecewise linear distributions is larger than the one for d’Onofrio-Gandolfi model, while for the larger values of \( \mu \) the situation is opposite. Performed simulations show that the change occurs before \( \mu \approx 1.42 \).

The variances for the shifted and non-shifted Erlang distributions are given by \( \frac{m_i}{\sigma_i^2} \) and they give a measure of the degree of concentration of the delay around the mean. Actually, a better measure of the spread of the distribution around the mean for our purposes is the coefficient of variation, i.e. the ratio of the standard deviation to the mean, that is \( \sqrt{m_i}/(a_i\sigma_i + m_i) \). Clearly, for non-shifted distributions we have \( 1/\sqrt{m_i} \), which implies that larger parameter \( m_i \) is smaller the considered ratio is. Hence, increase of \( m_i \) decrease the percentage dispersion of the average delay. On the other hand, for the shifted Erlang distributions, the coefficient of variation is a decreasing function of \( \sigma_i \). This dependence is obvious since increasing \( \sigma_i \) with fixed \( m_i \) and \( a_i \) means that the average delay is increased while standard deviation remains constant. Coefficient of variation is also a decreasing function of parameter \( a_i \). On the other hand, if we fix \( a_i \) and \( \sigma_i \), and study the influence of \( m_i \), then the coefficient of variation increases if \( m_i < a_i\sigma_i \) and decreases otherwise.

For piecewise linear distributions (\( \sigma_i \geq \epsilon_i \)) we have the average value of \( f_i \) (defined by (3.2)) equal to \( \sigma_i \) and the standard deviation given by \( \epsilon_i/\sqrt{6} \). Hence, in such case the coefficient of variation equals to \( \epsilon_i/(\sigma_i\sqrt{6}) \). Thus, it is an increasing function of \( \epsilon_i \) (for fixed \( \sigma_i \)) and a decreasing function of \( \sigma_i \) (for fixed \( \epsilon_i \)). Hence, we conclude that the percentage dispersion of the average delay is the increasing function of \( \epsilon_i \) and decreasing function of \( \sigma_i \) and it is always smaller than 1. Clearly, all that should be taken into account whenever the probability distributions describing the characteristics of delays are estimated.

We believe that by proposed type of models one can in more realistic way describes the process of angiogenesis. Clearly, the model should be validated with the experimental data in the future and the proper distributions of delays should be derived based on the experimental measurements. Such models with distributed delays could be also studied in the context of efficiency of different types of tumour therapies.

## A Generalized Mikhailov Criterion

Here we formulate a generalized version of the Mikhailov Criterion (see eg. [45]). The classical formulation of the Mikhailov Criterion is for the characteristic functions that are sums of polynomials multiplied by an exponential function. However, the it can be generalized for wider class of functions. Below, we present a detailed formulation.

**Theorem A.1 (Generalised Mikhailov Criterion)** Let us assume that \( W : \mathbb{C} \to \mathbb{C} \) is an analytical function, has no zeros on imaginary axis and fulfils

\[
W(\lambda) = \lambda^n + o(\lambda^n), \quad W'(\lambda) = n\lambda^{n-1} + o(\lambda^{n-1}),
\]

for some natural number \( n \). Then the number of zeros of \( W \) in the right-hand complex half-plane is equal to \( n/2 - \Delta/\pi \) where

\[
\Delta = \Delta_{\omega=0(0,\pi)} \text{arg} W(i\omega).
\]

Note, that \( \Delta \) denotes the change of argument of the vector \( W(i\omega) \) in the positive direction of complex plane as \( \omega \) increases from 0 to \( +\infty \).
Proof: The proof is exactly the same as the proof of the Mikhailov Criterion in [45, Th. 1]. It is based on integration of the characteristic function on the following contour: part of imaginary axis, portion of the imaginary axis from $i\rho$ to $-i\rho$ and a semi-circle of radius $\rho$ with the middle in zero located in the right half of complex plane. The fact that $W$ is an analytic function implies that it has the isolated zeros and all integration can be done in the same way as in [45]. Moreover, the assumption (A.1) implies that all limits calculated in [45] remain the same.

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