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Time Delays in Solid Avascular Tumour Growth

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ABSTRACT

In the paper the model of early stage of tumour growth is described. Two main cellular processes are considered — proliferation and apoptosis. We focused on the effect of time delays in both processes. Mathematical analysis and computer simulations are presented.

INTRODUCTION

Many models which study different stages and effects of tumour growth were proposed and studied within last years, e.g. [1] – [7]. The model we study is based on the idea of avascular multicellular spheroids (MCS) modelling, see [3] – [7]. In this paper we focus on the case of uniformly proliferating tumour, i.e., MCS without a hypoxic region and necrotic core inside. We consider the diffusion of nutrient and two basic processes. One of them is a cell proliferation and second one is underlying apoptosis. The aim of this paper is to introduce time delays into both processes. For the case with equal delays some analysis was done in [7]. We consider the more general case, i.e., with two different delays, which is more interesting but also more difficult from the analytical point of view.

At the beginning, we formulate the basic model without delays. We assume that the growth of MCS is symmetric and the space co-ordinate is the radius r. We study the changes of two variables

- $\sigma(r,t)$ — the diffusiable chemical (a vital nutrient) concentration at radius r and time t,
- $R(t)$ — the outer MCS (tumour) radius at time t.

The changes of nutrient (e.g. oxygen or/and glucose) are described by reaction - diffusion equation. It is assumed that the nutrient is simply consumed by tumour cells with the consumption rate s. Because the tumour doubling time - scale (weeks) is much longer than the nutrient diffusion time - scale (minutes or hours) we make the quasi - steady approximation in the nutrient equation. Therefore, we assume that the derivative of σ with respect to time is equal to 0 and obtain the following equation

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial \sigma}{\partial r}) = a, \tag{1}$$

where the left - hand side of Eq. (1) represents Laplasian in spherical co-ordinates.

The changes of MCS volume are governed by the principle of mass balance, i.e.,

$$\frac{1}{4\pi}\frac{d}{dt}(\frac{4}{3}\pi R^3(t)) = S(t) - Q(t), \tag{2}$$

where

$$S(t) = \int_0^{R(t)} s\sigma(r,t)r^2 dr, \quad Q(t) = \int_0^{R(t)} scr^2 dr \tag{3}$$

are the total rate of cell proliferation and the total rate of cell death, respectively. In Eq. (3) s and sc are positive constants and denote the rates of cell proliferation and cell death within the tumour. For simplicity, we assume that $s = 1$ (if not we can re-scale the coefficients σ_e, a and c). We close the model be prescribing the following boundary and initial conditions

$$\sigma(R(t),t) = \sigma_e, \quad \frac{\partial \sigma}{\partial r}(0,t) = 0, \quad R(0) = R_0, \tag{4}$$

where σ_e is the constant nutrient concentration external to the tumour. It is reasonable to assume that $\sigma_e > c$. Calculating σ from Eq. (1) under the conditions defined in Eqs. (4) we obtain

$$\sigma(r,t) = \sigma_e - \frac{a}{6}(R^2(t) - r^2). \tag{5}$$

STATEMENT OF THE MODEL WITH DELAYS

In this section we study the model with delays in proliferation and underlying apoptosis. Both of these processes incorporate time delays. In the first case, the delay represents the time taken for the cells to undergo mitosis. In the second one, the delay represents the time taken for the cells to modify the rate of cell loss due to apoptosis. We assume that these delays are constant (τ_1, $\tau_2 > 0$). Hence, instead of Eq. (3) we consider

$$S(t) = \int_0^{R(t-\tau_1)} \sigma(r, t-\tau_1) r^2 dr, \quad Q(t) = \int_0^{R(t-\tau_2)} cr^2 dr. \tag{6}$$

Using Eqs. (6) and (2) we obtain

$$\frac{d}{dt}R^3(t) = \sigma_e R^3(t-\tau_1) - \frac{a}{15}R^5(t-\tau_1) - cR^3(t-\tau_2).$$

Let denote $x(t) = R^3(t)$. Hence,

$$\frac{d}{dt}x(t) = \sigma_e x(t-\tau_1) - \frac{a}{15}x^{\frac{5}{3}}(t-\tau_1) - cx(t-\tau_2). \tag{7}$$

Using the steep method (see, e.g., [8]) it is easy to see that for every nonnegative initial function $x^0(t) : [-\widetilde{\tau}, 0] \to \mathbb{R}^+$, $\widetilde{\tau} = \max(\tau_1, \tau_2)$ the unique solution to Eq. (7) exists, because on every time interval of the form $[n\bar{\tau}, (n+1)\bar{\tau}]$, $n \in \mathbb{N}$, $\bar{\tau} = \min(\tau_1, \tau_2)$ the solution is defined by the formula

$$x(t) = x(n\bar{\tau}) + \int_{n\bar{\tau}}^{t} (\sigma_e x(s-\tau_1) - \frac{a}{15}x^{\frac{5}{3}}(s-\tau_1) - cx(s-\tau_2))ds,$$

where $x(s-\tau_1)$ and $x(s-\tau_2)$ are known. It is also easy to see that for nonnegative initial condition x^0 the solution may be negative (for details see [7]).

Assume that the positive solution to Eq. (7) exists for every $t > 0$. Then we can study its asymptotic behaviour.

There are two stationary solutions to Eq. (7) – the trivial one and the positive nontrivial $\bar{x} = \left(\frac{15(\sigma_e - c)}{a}\right)^{\frac{3}{2}}$.

Lemma 1. *The trivial stationary solution to Eq. (7) is unstable independently on the values of both delays.*

Proof. Linearizing Eq. (7) around the trivial solution we obtain

$$\frac{d}{dt}x(t) = \sigma_e x(t-\tau_1) - cx(t-\tau_2).$$

The characteristic quasi - polynomial has the form $D(\lambda) = \lambda - \sigma_e e^{-\lambda\tau_1} + ce^{-\lambda\tau_2}$. The assumption $\sigma_e > c$ implies that the zero solution is unstable for every $\tau_1 \geq 0$ and $\tau_2 \geq 0$ (for details see [8]). □

For the nontrivial solution $\bar{x}$ we have the linearized equation of the form

$$\frac{d}{dt}x(t) = -(\frac{2}{3}\sigma_e - \frac{5}{3}c)x(t-\tau_1) - cx(t-\tau_2) \tag{8}$$

and the characteristic equation of the form

$$z = -(\frac{2}{3}\sigma_e - \frac{5}{3}c)e^{-z\tau_1} - ce^{-z\tau_2}. \tag{9}$$

Theorem 1. *If Eq. (9) has no purely imaginary roots and* $\frac{|2\sigma_e - 5c|}{3}\tau_1 + c\tau_2 \leq 1$, *then the nontrivial solution* $\bar{x}$ *is stable.*

Proof. If $2\sigma_e = 5c$, then for $c\tau_2 \leq 1$ it easy to see that $\bar{x}$ is stable. Let $2\sigma_e \neq 5c$ and

$$A_1 = \frac{2}{3}\sigma_e - \frac{5}{3}c, \quad A_2 = c, \quad \lambda = \frac{z}{|A_1|}, \quad A = \frac{A_2}{|A_1|}, \quad \tau_1 = \frac{r_1}{|A_1|}, \quad \tau_2 = \frac{r_2}{|A_1|}. \tag{10}$$

If $2\sigma_e - 5c > 0$, we obtain the normalised characteristic equation

$$\lambda = -e^{-\lambda r_1} - Ae^{-\lambda r_2}, \tag{11}$$

in the other case we obtain

$$\lambda = e^{-\lambda r_1} - Ae^{-\lambda r_2}. \tag{12}$$

Assume $2\sigma_e - 5c > 0$ and denote $D(\lambda) = \lambda + e^{-\lambda r_1} + Ae^{-\lambda r_2}$. Then for $\lambda = i\omega$, $\omega \geq 0$ we have

$$\Re(D(i\omega)) = \cos(\omega r_1) + A\cos(\omega r_2), \;\; \Im(D(i\omega)) = \omega - \sin(\omega r_1) - A\sin(\omega r_2). \tag{13}$$

To study stability we use the Mikhailov Criterion (see e.g. [9], [10] for details) that belongs to the class of criterions based on the principle of argument (compare the Nyquist Criterion, e.g. [9]). To obtain stability it is enough that the change of the argument of $D(i\omega)$ with ω increasing from 0 to $+\infty$ is equal to $\frac{\pi}{2}$. We see that $\Re(D(0)) = 1+A$ and $\Im(D(0)) = 0$. Moreover, $\sin(D(i\omega)) \to 1$ and $\cos(D(i\omega)) \to 0$ as $\omega \to +\infty$. Hence, if $\Im(D(i\omega)) \geq 0$ for every $\omega > 0$, then all the roots $D(\lambda)$ have strictly negative real parts. It easy to see that

$$\Im(D(i\omega)) \geq \omega(1 - r_1 - Ar_2), \tag{14}$$

and $\Im(D(i\omega)) > 0$ if $r_1 + Ar_2 \leq 1$.

For $2\sigma_e - 5c < 0$ we denote $D(\lambda) = \lambda - e^{-\lambda r_1} + Ae^{-\lambda r_2}$. Then $\Re(D(i\omega)) = -\cos(\omega r_1) + A\cos(\omega r_2)$ and $\Im(D(i\omega)) = \omega + \sin(\omega r_1) - A\sin(\omega r_2)$. We have $\sin(D(i\omega)) \to 1$ and $\cos(D(i\omega)) \to 0$ as $\omega \to +\infty$. Moreover, $\Im(D(i\omega)) \geq \omega - |\sin(\omega r_1)| - A\omega r_2 \geq \omega(1-r_1-Ar_2)$, as before. This completes the proof. $\square$

Theorem 2. *If $2\sigma_e \neq 5c$ and $\frac{3c}{|2\sigma_e - 5c|} < 1$ and $\tau_1 \leq \frac{3}{|2\sigma_e-5c|+3c}$, then the nontrivial solution $\bar{x}$ is stable.*

Proof. We consider two cases. The first one for $2\sigma_e - 5c > 0$ is proved in [11]. Assume now that $2\sigma_e - 5c < 0$ (i.e., $A_1 < 0$). It is easy to see that for $r_1 = 0$ all the roots of Eq. (12) have strictly negative real parts. The nontrivial solution $\bar{x}$ could be unstable if for some $r_1 \leq \frac{1}{1+A}$ Eq. (12) has a pair of purely imaginary roots $\pm i\omega$. These roots satisfy

$$\cos(\omega r_1) = A\cos(\omega r_2), \quad \omega + \sin(\omega r_1) = A\sin(\omega r_2). \tag{15}$$

Squaring both equations and adding up, we obtain

$$\sin(\omega r_1) = \frac{-\omega^2 - 1 + A^2}{2\omega}. \tag{16}$$

Inequality $|sin(\omega r_1)| \leq 1$ implies that $\omega \leq 1 + A$. Denoting the absolute value of the right-hand side of Eq. (16) by $g(\omega)$ we have

$$g(\omega) \geq \frac{\omega}{2}\big[1 + \frac{1-A^2}{(1+A)^2}\big] = \omega\frac{1}{1+A} \geq \omega r_1 > |\sin(\omega r_1)|. \tag{17}$$

This contradicts the definition of $g(\omega)$. Therefore, all the roots of Eq. (12) have negative real parts. $\square$

NUMERICAL SIMULATIONS AND CONCLUSIONS

At the beginning of this Section, we present some numerical simulations of the model defined by Eq. (7) with two different delays. We focus on the influence of delays on the behaviour of solutions. For all numerical simulation we fixed the following parameter values: $a = 30$, $c = 1$, $\sigma_e = 5.5$ and $\tau_1 = 0.5$. We only change the magnitude of τ_2.

Stability of solutions depends on the behaviour of so - called Mikhailov hodograph. Therefore, at the beginning we present some examples of it — see Figs. 1-3. Figs. 4-5 show simulation results for Eq. (7). If the hodograph does not circle around the point $(0, 0)$, then the solution is stable (compare Fig. 1 and 4). If it crosses this point, then the Hopf bifurcation is possible and the solution may oscillate (see Figs. 3 and 5). Otherwise the solution is unstable. It should be noticed that for models with two different delays stability switches can occur what is not possible in the case with one delay.

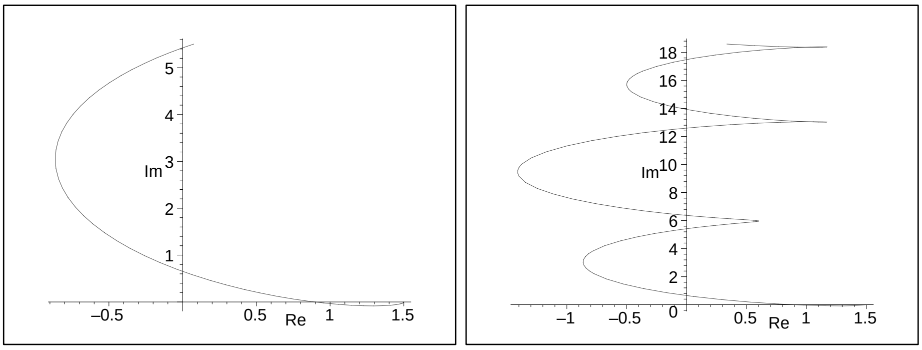

Figure 1. Mikhailov hodograph for $\tau_2 = 0.2$

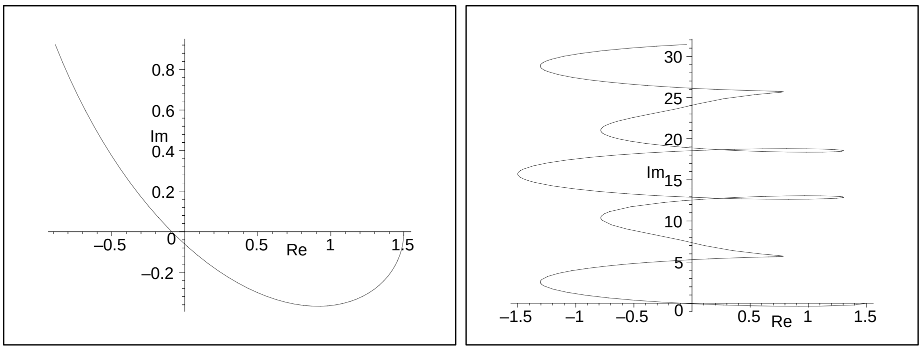

Figure 2. Mikhailov hodograph for $\tau_2 = 0.7$

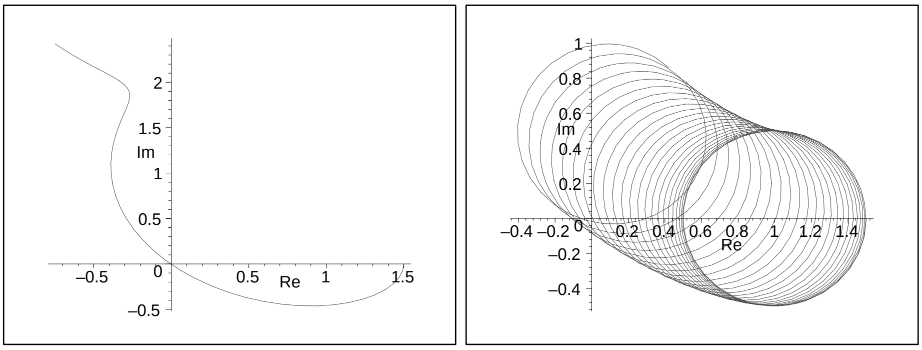

Figure 3. Mikhailov hodograph for $\tau_2 = 1.225$ (left) and $\tau_2 = 50$ (right)

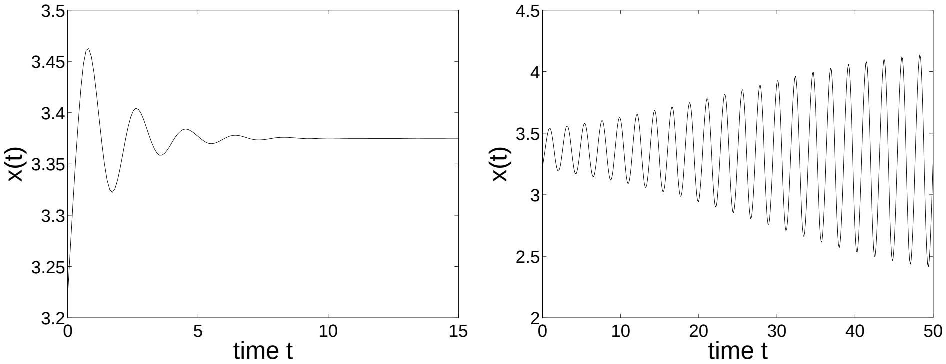

Figure 4. Solution evolution in time for $\tau_2 = 0.2$ (left) and $\tau_2 = 0.7$ (right)

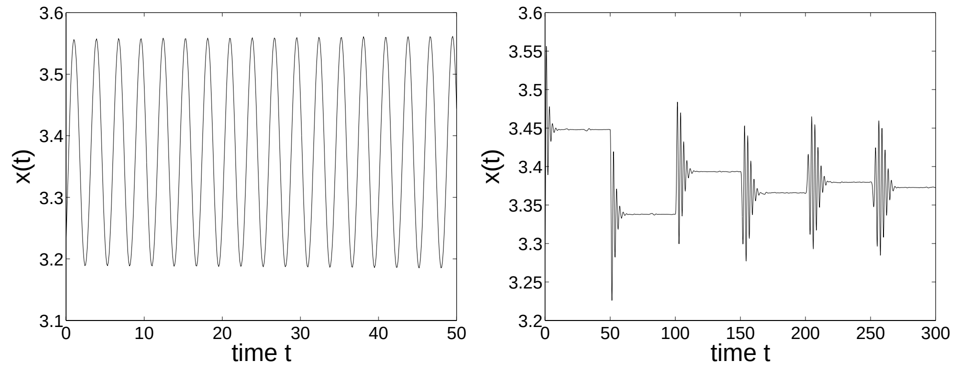

Figure 5. Solution evolution in time for $\tau_2 = 1.225$ (left) and $\tau_2 = 50$ (right)

Concluding our study we can say that the model with two delays admits much more complicated behaviour then the model without or with one discrete delay and it seems to be more realistic. From the medical point of view it shows that the outcome of the disease is closely related to the environment in patient's body. If this environment is described by the parameters from the region of regular behaviour, then it is much easier to propose a treatment. On the other hand, for the regions of irregular behaviour (quick stability switches) an appropriate treatment can be not possible.

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