TIME DELAYS IN ONE-STAGE MODELS FOR CARCINOGENESIS MUTATIONS

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ABSTRACT

In the paper we consider three very simple models of carcinogenesis mutations in the case of one stage for mutant cells. The difference between the models lies in the type of environmental conditions. We analyse the influence of time delay on the dynamics of the systems. It occurs that this influence is significant only for the model in unfavourable environmental conditions when the positive critical point exists. In this case the Hopf bifurcation is observed. Results are illustrated by computer simulations.

INTRODUCTION

In [1] three types of simple models of carcinogenesis mutations were proposed. The authors consider n different steps of mutations that lead to malignant cells. In [3] we analysed the simplest systems with one stage of mutations. It is known that for different types of cancers it is possible to divide the process into several stages (e.g. in [2] the number of mutations is described as varying between 3 and 7, for p53 typically it is equal to 4). These models describes only interactions between cells on different stages of mutations. The only influence of the environment appears in the last equation. Processes occurring at the last stage depend on the environmental conditions in patient's body. The first but the worst for patients are favourable conditions. In these conditions mutant cells proliferate without restriction and are produced due to biochemical signals coming from both normal (in one stage case) and mutant cells. In the second model it is assumed that the conditions are not so good such that normal and malignant cells compete of environmental resources as glucose or oxygen. In the last case the environmental conditions are unfavourable — mutant cells do not proliferate and the only source of these cells are the biochemical signals mentioned above. In this paper we would like to improve the models introducing time delay to the term that describes the biochemical signals. It is one of the possible ways of introducing delay, but it seems to be the most common in biomathematical literature (compare e.g. [5]). We also would like to give another interpretation of the presented systems.

We start from the description of the models (see also [6]). Let $y_0(t)$, $y_1(t)$ denote the (scaled) concentration of normal and mutant cells, respectively. As in [3] we consider the mean values of concentrations without the spatial effects (compare [1, 4]). In the favourable conditions we obtain

$$\left\{ \begin{array}{rcl} \dot{y}_0(t) & = & y_0(t)\,(a(1-y_0(t)) - \mu y_1(t)) \\ \dot{y}_1(t) & = & y_1(t)\,(1+\eta y_0(t-\tau)) \end{array} \right. , \tag{1}$$

where:

– a is the proliferation coefficient for normal cells and the concentration of these cells is scaled such that the carrying capacity is equal to 1;

– μ measures the number of normal - mutant cells encounters that leads to normal cells destruction;

– the concentration of mutant cells is scaled such that the proliferation coefficient is equal to 1;

– η measures the production of mutant cells due to biochemical signals and τ is the delay of this process.

In the author's opinion most of malignant tumours are described by Eqs. (1) and without treatment it is not possible to cure the disease. The models in competitive and unfavourable conditions can be interpreted as some kind of treatment. For competitive conditions we get:

$$\left\{ \begin{array}{rcl} \dot{y}_0(t) & = & y_0(t)\,(a(1-y_0(t)) - \mu y_1(t)) \\ \dot{y}_1(t) & = & y_1(t)\,(1-\eta y_0(t-\tau)) \end{array} \right. , \tag{2}$$

that can be interpreted as blocking growth factors and sending inhibiting signals. In the case of unfavourable conditions the model reads as:

$$\left\{ \begin{array}{rcl} \dot{y}_0(t) & = & y_0(t)\,(a(1-y_0(t)) - \mu y_1(t)) \\ \dot{y}_1(t) & = & y_1(t)\,(-1+\eta y_0(t-\tau)) \end{array} \right. , \tag{3}$$

so now the treatment is just killing mutant cells. Such a treatment is an idealisation, of course.

ANALYSIS OF THE MODELS

The case without delay. In [3] the properties of solutions in the case without delay ($\tau = 0$) were pointed out. For Eqs. (1) the right - hand side of the second equation is always positive for positive initial conditions that leads to unrestricted tumour growth, independently on the magnitude of the parameters. For two other models Eqs. (2) and (3) there are three critical points: $A = (0, 0)$, $B = (1, 0)$ and $C = \left(\frac{1}{\eta}, \frac{a}{\mu}\left(1 - \frac{1}{\eta}\right)\right)$ (C exists for $\eta > 1$). The point A is unstable in both models.

Possible behaviour of solutions to Eqs. (2) in the phase space are shown in Fig. 1. If there is no C (i.e. $\eta \le 1$), then we observe unrestricted tumour growth for

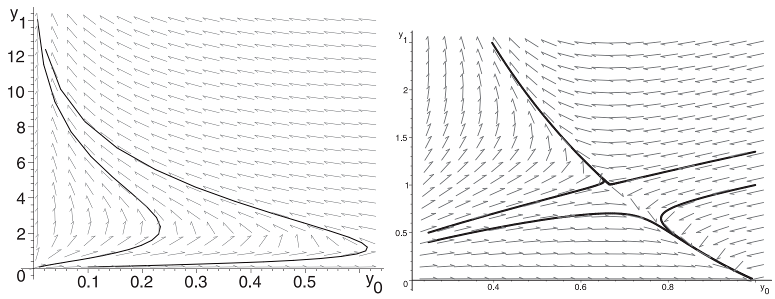

Fig. 1. Two type of the phase space for Eqs. (2).

every positive initial data (compare the left - hand graph in Fig. 1). If C exists (i.e. $\eta > 1$), then it is a saddle. Its stable manifold divides the phase space into two regions — one of them is the basin of attraction of the point B (which is locally stable in this case), in the second one we have unrestricted tumour growth (see the right - hand graph in Fig. 1).

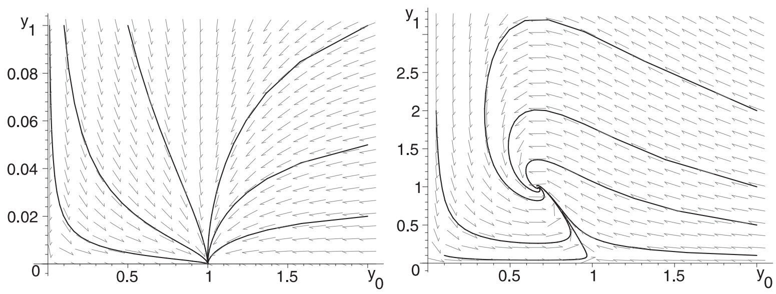

Fig. 2. Two type of the phase space for Eqs. (3).

In the case of Eqs. (3) the behaviour of solutions is completely different. If C exists, then it is globally stable as a solution to Eqs. (3). If there is no C, then B is globally stable. Hence, solutions are always bounded and there exists globally asymptotically stable critical point (either C or B). Two types of the phase portraits for Eqs. (3) are shown in Fig. 2.

The case with positive delay. It is easy to see that solutions to every model with positive initial functions are positive and exist for every $t \geq 0$ (compare e.g. [7]). To study local stability of critical points we use the framework of linearization, Mikhailov criterion and the Hopf bifurcation (see [7, 8]). It is easy to see that every critical point that is unstable for $\tau = 0$ is also unstable for every positive delay. Hence, A is unstable for every models, as in the case without delay. Moreover, the magnitude of delay has no influence on the qualitative behaviour of solutions to Eqs. (1). It is connected with the form of the right - hand side of this system.

Consider Eqs. (2). It is easy to see that studying stability of the point B we obtain the linearized system exactly the same as for $\tau = 0$. Hence, local stability of B does not depend on τ. As we noticed above, C is unstable independently on the delay.

Now we focus on Eqs. (3). Similarly as for Eqs. (2), stability of B does not depend on the magnitude of delay. The most interesting behaviour is observed for

Eqs. (3) when C exists. The characteristic matrix for C and Eqs. (3) has the form:

$$\begin{pmatrix} -\frac{a}{\eta} - \lambda & -\frac{\mu}{\eta} \\ \frac{a}{\mu}(\eta - 1)e^{-\lambda\tau} & -\lambda \end{pmatrix}.$$

Therefore, we obtain the characteristic equation:

$$\lambda^2 + \frac{a}{\eta}\lambda + \frac{a}{\eta}(\eta - 1)e^{-\lambda\tau} = 0. \tag{4}$$

The switch of stability is possible only when there exists purely imaginary root of Eq. (4). Let $\lambda = i\omega$. Then

$$\begin{cases} \frac{a}{\eta}\omega & = & \frac{a}{\eta}(\eta - 1)\sin(\omega\tau) \\ \omega^2 & = & \frac{a}{\eta}(\eta - 1)\cos(\omega\tau) \end{cases}$$

and after squaring and adding up both equations one gets $\omega^4 + \frac{a^2}{\eta^2}\omega^2 = \frac{a^2}{\eta^2}(\eta - 1)^2$. Hence, there exists exactly one positive ω_0 such that $\pm i\omega_0$ are characteristic values. The sequence of delays

$$\tau_k = \tau_0 + 2k\pi, \quad k \in \mathbb{N}, \quad \tau_0 = \frac{1}{\omega_0}\mathrm{arctg}\left(\frac{a}{\eta\omega_0}\right)$$

are the possible points of stability switches. To close this analysis one needs to check the transversality condition, i.e. if $\lambda = \lambda(\tau) = \Re(\lambda) + i\Im(\lambda)$, then $\frac{d}{d\tau}\Re(\lambda)|_{\tau_k} \neq 0$ yields the Hopf bifurcation. In our case:

$$\frac{d}{d\tau}\Re(\lambda)|_{\tau_k} = \frac{a^2\omega_0^2 + 2\eta^2\omega_0^4}{4\omega_0^2\eta^2 + 2a\eta\omega_0^2\tau_k + a^2 + a^2(\eta - 1)^2\tau_k^2}$$

which is positive for every $k \in \mathbb{N}$. This means that the point C is locally stable for $\tau < \tau_0$, looses stability at $\tau = \tau_0$ and the Hopf bifurcation occurs at this point. Other stability switches are not possible due to the positivity of the derivative above.

SIMULATION AND DISCUSSION

Now we illustrate the results obtained in the previous Section by computer simulations. We are mainly interested in the case of healthy patient (that is described by the critical point B) for which some mutant cells occur. Hence, the initial functions used in simulations are $y_0(t) = 1$ and $y_1(t) = 0.1$ for $t \in [-\tau, 0]$. We use the following parameter values: $a = \mu = 1$ and $\eta = 2$ in the case when the point C exists or $\eta = 0.5$ otherwise.

As we know, the dynamics of Eqs. (1) does not significantly depend on the magnitude of delay. In Fig. 3 the behaviour of solutions for $\tau = 0.5$ and $\tau = 5$ are presented.

It occurs that for Eqs. (2) the result is similar. In Fig. 4 we see the behaviour of solutions to this model. The upper graph corresponds to the case with no C — we observe very fast stabilization on the healthy state and the dynamics do not change with increasing delay ($\tau = 0.5$ for this graph). The graphs below correspond to the

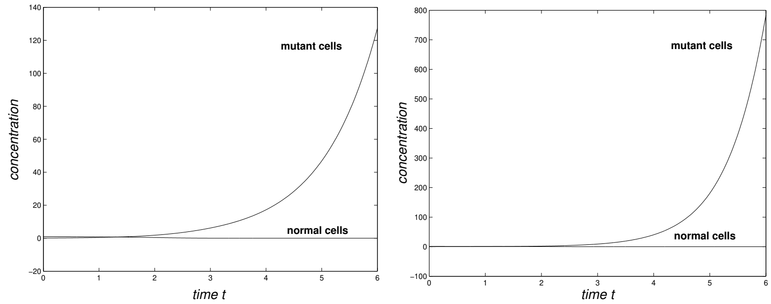

Fig. 3. Solutions to Eqs. (1) for different delays.

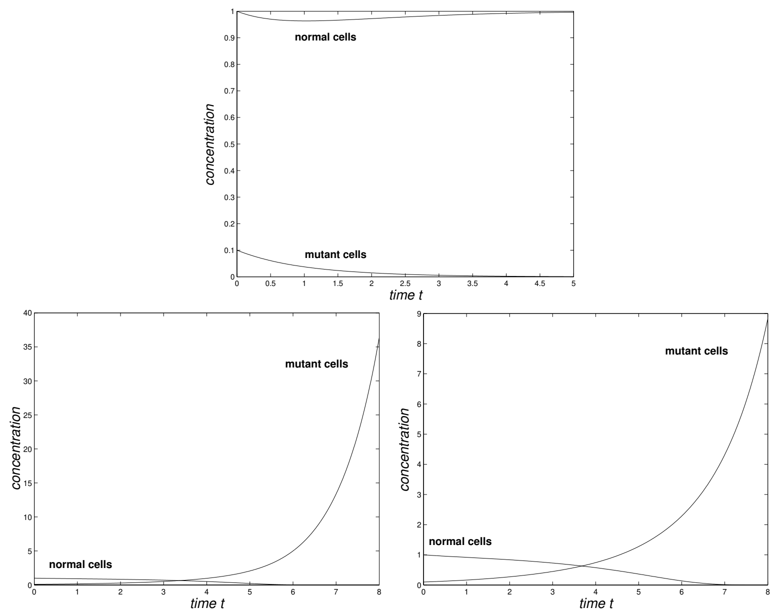

Fig. 4. Solutions to Eqs. (2) for different delays.

case when C exists — for greater delay the growth of mutant cells is not so fast ($\tau = 0.5$ for the left-hand side and $\tau = 3.5$ for the right one).

In Fig. 5 the solutions to Eqs. (3) are shown. All graphs describe the dynamics in the case when C exists. For small delays ($\tau = 0.5$ — the left-hand graph) the behaviour is similar to the case without delay (compare [3]). With increasing delay ($\tau = 2.5$ — the centre graph) the undumping oscillations appear and the period of these oscillations increases with the magnitude of delay ($\tau = 3.5$ — the right-hand graph). In the case without the point C the behaviour of solutions is exactly the same as the upper graph in Fig. 4.

It is known (compare e.g. [9, 10]) that malignant tumour growth involves oscillatory dynamics. Although in the models analysed in this paper we do not consider many process connected with malignancy, like angiogenesis modelled e.g. in [9], we hope that it can help in better understanding of mutations and the role of delay in the last stage of it. It seems that the models with positive delay can better described the observed behaviour. Although we considered only the simplest case of one-stage mutations, the preliminary analysis presented in [4] for more dimensional systems suggest that undumping oscillations are not possible in the case without

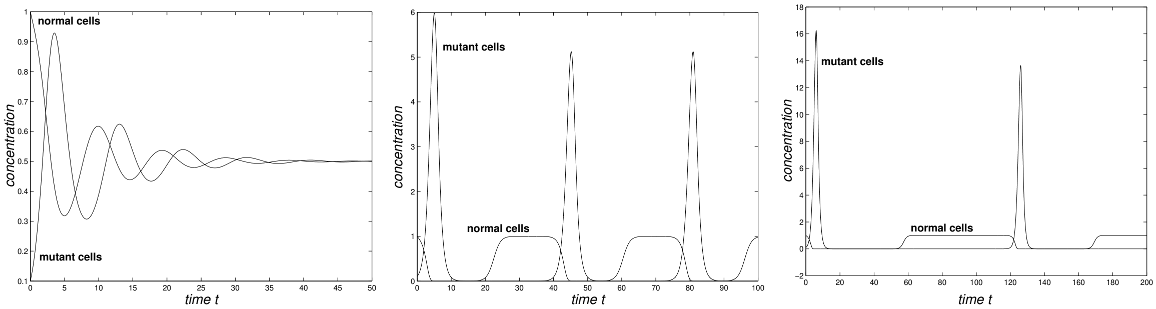

Fig. 5. Solutions to Eqs. (3) for different delays.

delay. Following [9] we conclude that this might underline the significance of time delays in tumour growth dynamics.

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