COMPARISON OF THE MODELS FOR CARCINOGENESIS MUTATIONS — ONE - STAGE CASE

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ABSTRACT

The present paper is focused on the analysis of three very simple models of carcinogenesis mutations that are based on reaction - diffusion systems and Lotka - Volterra food chains. We focus on the Turing instability and show that this type of instability is not possible for these models. We also propose some modifications of the considered equations. Results are illustrated by computer simulations.

BASIC MODELS

Tumour growth dynamics is one of the most intensively studied processes within last years. It is connected with the number of lethal outcomes of tumour diseases and the amount of money spent on the treatment. One of the possible methods that can improve cancer therapy is mathematical modelling (compare [1]). The aim of this paper is to study simple models of carcinogenesis mutations. The basic models come from [2] and describe a process of carcinogenesis mutations with n different steps of mutations (from normal to malignant cells). It is known that for different types of cancers it is possible to divide the process into different number of stages (e.g. in [3] it is claimed that typically this number varies between 3 and 7).

Let $Y_i(t,x)$ be a density of mutant cells at the i - th stage, $i = 0,\ldots,n$, from normal cells, for $i = 0$, through the intermediate stages (e.g. Benign cells or pre - malignant cells), for $i = 1,\ldots,n-1$, to the final stage — malignant cells, for $i = n$. Following [2] we assume that cells at every stage are governed by the logistic equation and the interactions have the following structure — the number of encounters of cells at $(i-1) - th$ and $i - th$ stages (i.e. biochemical reactions between these cells) is the term that creates new cells at the stage i and destroy cells at the stage $i-1$ (for details see [2]). Therefore, we consider equations of the form:

$$\frac{\partial Y_i}{\partial t} = D_i \Delta Y_i + a_i Y_i \left(1 - \frac{Y_i}{K_i}\right) + \eta_i Y_i Y_{i-1} - \mu_{i+1} Y_i Y_{i+1}, \tag{1}$$

for $i = 0, \ldots, n-1$, with $\eta_0 = 0$ and the Neumann (zero - flux) boundary conditions on $[-\pi, \pi]$ (compare the Lotka - Volterra food chain, see e. g. [4]). We study one dimensional spatial diffusion for simplicity, but the presented results can be proved also for higher dimensions.

For $i = n$, we have different equations depending on the environmental conditions.

- The latest stage of mutation in a favourable environment. In this case it is assumed that the malignant cells behaviour is similar to the previous stages. The only difference is that they cannot create the next stages and hence,

$$\frac{\partial Y_n}{\partial t} = D_n \Delta Y_n + a_n Y_n \left(1 - \frac{Y_n}{K_n}\right) + \eta_n Y_n Y_{n-1}.$$

- The latest stage of mutation in a competitive environment. Here we assume that there are not enough environmental resources for malignant cells. Therefore, pre - malignant and malignant cells must compete that leads to the equation

$$\frac{\partial Y_n}{\partial t} = D_n \Delta Y_n + a_n Y_n \left(1 - \frac{Y_n}{K_n}\right) - \eta_n Y_n Y_{n-1}.$$

- The latest stage of mutation in a unfavourable environment. In this case the only source of malignant cells are pre - malignant cells. The environment is unfavourable for malignant cells and without pre - malignant cells they are destroyed. Therefore,

$$\frac{\partial Y_n}{\partial t} = D_n \Delta Y_n - b Y_n + \eta_n Y_n Y_{n-1}.$$

At the and we assume that the environment for malignant cells is unbounded. Therefore, $K_n \to +\infty$ and after re-scaling we obtain:

$$\frac{\partial y_i}{\partial t} = d_i \Delta y_i + a_i y_i (1 - y_i) + \eta_i y_i y_{i-1} - \mu_{i+1} y_i y_{i+1},\ i = 0, \ldots, n-1,$$

from Eq. (1) with

1. $$\frac{\partial y_n}{\partial t} = \Delta y_n + y_n + \eta_n y_n y_{n-1},$$

2. $$\frac{\partial y_n}{\partial t} = \Delta y_n + y_n - \eta_n y_n y_{n-1},$$

3.
$$\frac{\partial y_n}{\partial t} = \Delta y_n - y_n + \eta_n y_n y_{n-1},$$

respectively.

In [2] the analysis of one and two-stage models is focused on the existence of travelling wave solutions. Now, we would like to study one-stage case on the background of Turing (diffusion-driven) instability.

THE MODELS FOR ONE-STAGE CASE

In this paper we consider the simplest case when there are only two stages — normal and mutant (malignant) cells (compare e.g. [5]). In [2] it is called one-stage models because we consider only one stage of mutations. Therefore, we study the following models

$$\left\{ \begin{array}{lcl} \dot{y}_0 & = & y_0\left(a_0(1-y_0) - \mu_1 y_1\right) + d_0 \Delta y_0 \\ \dot{y}_1 & = & y_1\left(1 + \eta_1 y_0\right) + \Delta y_1 \end{array} \right. , \tag{2}$$

$$\left\{ \begin{array}{lcl} \dot{y}_0 & = & y_0\left(a_0(1-y_0) - \mu_1 y_1\right) + d_0 \Delta y_0 \\ \dot{y}_1 & = & y_1\left(1 - \eta_1 y_0\right) + \Delta y_1 \end{array} \right. , \tag{3}$$

$$\left\{ \begin{array}{lcl} \dot{y}_0 & = & y_0\left(a_0(1-y_0) - \mu_1 y_1\right) + d_0 \Delta y_0 \\ \dot{y}_1 & = & y_1\left(-1 + \eta_1 y_0\right) + \Delta y_1 \end{array} \right. , \tag{4}$$

with positive coefficients.

In the case without diffusion it is easy to see that for positive initial condition $y_0(0)$, $y_1(0) > 0$ every model has positive solution and any solution to the models exist for every $t > 0$. Studying Eq. (2) we conclude that y_1 tends exponentially to $+\infty$ as $t \to +\infty$.

General theory of reaction-diffusion equations guaranties that the solution to the models with nonzero diffusion also exists for every $t > 0$ (see e.g. [6, 7]) and we can study asymptotic properties of it. In next Sections we focus on the possibility of diffusion-driven (Turing) instability for Eqs. (3) and (4). It is obvious that this type of instability is not possible for Eq. (2) (all stationary solutions to this model are unstable due to $\lim_{t\to+\infty} y_1(t) = +\infty$).

We begin our analysis with the case without diffusion (ODE systems). Then we have:

1. Eqs. (3) are the model of competition without carrying capacity for the second species. In this model we have three stationary states: $A = (0,0)$, $B = (1,0)$ and $C = \left(\frac{1}{\eta_1}, \frac{a_0}{\mu_1}\left(1 - \frac{1}{\eta_1}\right)\right)$. The state C exists for $\eta_1 > 1$. We see that A and C are unstable, B is stable for $\eta_1 > 1$ (when C exists) and unstable for $\eta < 1$ (then there is no C). Therefore, we observe the following behaviour of solutions to Eqs. (3).

   — If there is no C, then the density of mutant cells increases to $+\infty$ (as for Eqs. (2)).

   — If C exists, then it is a saddle. Its stable manifold (a curve) is a separatrix for the system — under this curve the density of mutant cells increases to $+\infty$, below it the solution tends to B.

2. Eqs. (4) are the Lotka - Volterra prey - predator model with carrying capacity for preys. The stationary states are obviously the same as to Eqs. (3) because these two models differ only in the sign of the right-hand side of the second equation. Now, A is also unstable, B is stable for $\eta_1 < 1$ (when there is no C) and unstable for $\eta > 1$ (when C exists). Finally, C is always stable when it exists. For Eqs. (4) we obtain the following result.

   — If there is no C, then B is globally stable.

   — If C exists, then it is globally stable.

Now we show that in the models with diffusion stability properties do not change.

Consider at the beginning states A and B. The characteristic values for them are the terms on the diagonal of its Jacobi matrix. The difference between the cases without and with diffusion is that for non - zero diffusion we add to these terms: $-d_0k^2$ to the first term and $-k^2$ to the second term, k is an integer. Hence, if the characteristic value is negative, then it does not change the sign for any k. This shows that if A and B are unstable for the case without diffusion, then the characteristic value with $k = 0$ is positive and these states are also unstable for the case with nonzero diffusion. On the other hand, when B is stable, its characteristic values are negative and they stay negative after adding $-d_0k^2$ or $-k^2$. This implies that the Turing instability is not possible for these two states.

For Eqs. (3) without diffusion the Jacobi matrix of C has the form:

$$MJ_1 = \begin{pmatrix} -a_0\bar{y}_0 & -\mu_1\bar{y}_0 \\ -\eta_1\bar{y}_1 & 0 \end{pmatrix},$$

where $\bar{y}_0$ and $\bar{y}_1$ are the co - ordinates of C. We have $\mathrm{tr}(MJ_1) = -a_0\bar{y}_0 < 0$ and $\det MJ_1 = -\mu_1\eta_1\bar{y}_0\bar{y}_1 < 0$ that implies instability of the state C as the solution to Eqs. (3) in both (non - diffusive and diffusive) cases.

For Eqs. (4) without diffusion the Jacobi matrix of C has the form:

$$MJ_2 = \begin{pmatrix} -a_0\bar{y}_0 & -\mu_1\bar{y}_0 \\ \eta_1\bar{y}_1 & 0 \end{pmatrix},$$

and $\mathrm{tr}(MJ_1) = -a_0\bar{y}_0 < 0$, $\det MJ_1 = \mu_1\eta_1\bar{y}_0\bar{y}_1 > 0$ that implies stability of the state C as the solution to Eqs. (4) in the case without diffusion. Adding the terms connected with diffusion, the matrix MJ_2 changes to

$$MJ_2^D = \begin{pmatrix} -a_0\bar{y}_0 - d_0k^2 & -\mu_1\bar{y}_0 \\ \eta_1\bar{y}_1 & -k^2 \end{pmatrix}.$$

We obtain $\mathrm{tr}(MJ_2^D) = -a_0\bar{y}_0 - d_0k^2 < 0$ and $\det MJ_2^D = a_0\bar{y}_0k^2 + d_0k^4 + \mu_1\eta_1\bar{y}_0\bar{y}_1 > 0$ that also implies stability.

SIMULATION AND DISCUSSION

In this section we compare results of mathematical analysis with computer simulations. We use healthy initial conditions — the state B — perturbed by cosine function with the small amplitude. We also use the following parameters: $a_0 = 1$, $d_0 = 0.1$, $\mu_1 = 0.5$ and $\eta_1 = 0.3$ for Fig. 1 or $\eta_1 = 1.5$ for Fig. 2.

In Fig. 1 we see unrestricted tumour growth for Eqs. (2) and (3) or tumour extinction for Eqs. (4). In Fig. 2 the behaviour of solution to Eqs. (2) does not change, obviously. The solution to Eqs. (3) tends to the healthy state and the solution to Eqs. (4) tends to the positive steady state $C = \left(\frac{2}{3}, \frac{2}{3}\right)$.

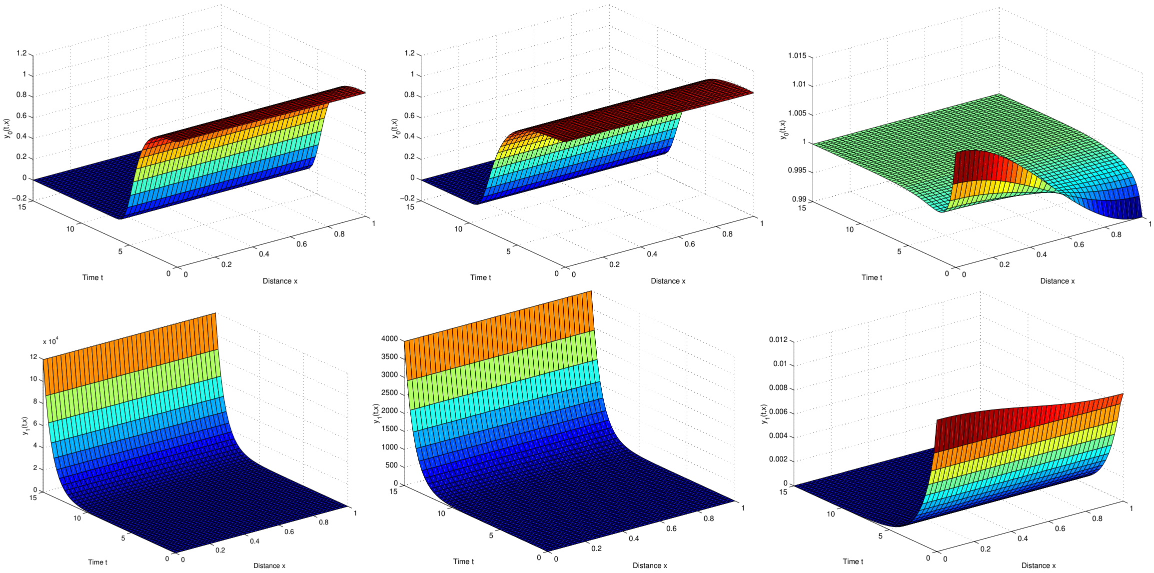

Fig. 1. Solutions to Eqs. (2), (3) and (4), from the left to the right-hand side, respectively. The case without positive stationary state C.

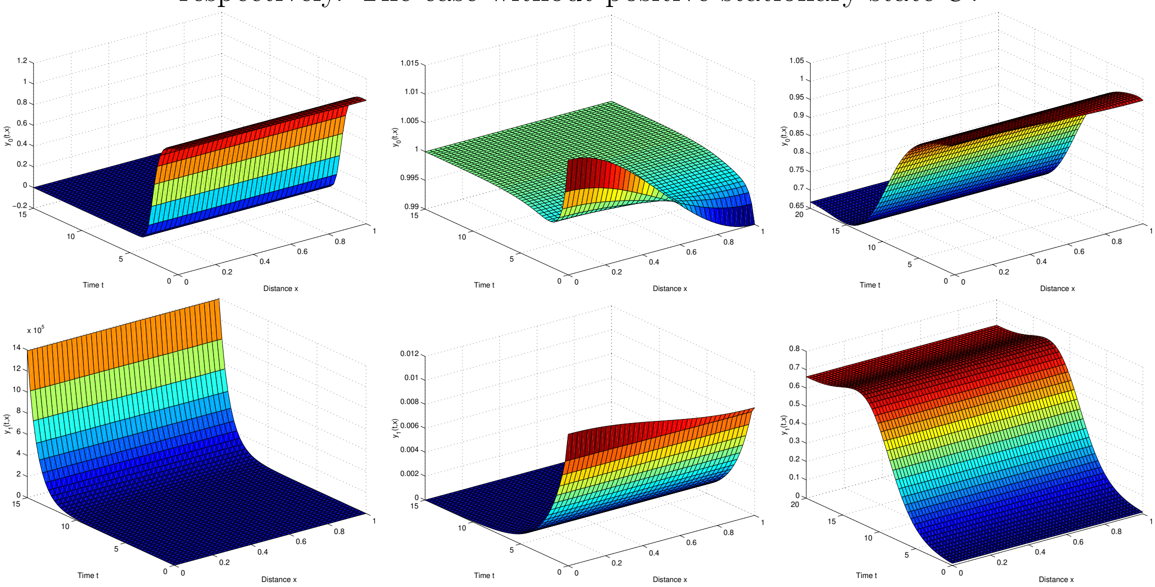

Fig. 2. Solutions to Eqs. (2), (3) and (4), from the left to the right-hand side, respectively. The case when the positive stationary state C exists.

In the author's opinion in most of malignant cancers Eqs. (2) is valid and therefore, without treatment the patient has no chance to survive. Applying some treatment it is possible to change the environmental (in patient's body) conditions such that there arises a chance to cure the disease (as in Eqs. (3) or (4)). If the dynamics of cancer is naturally governed by Eqs. (3) or (4), then it is much better for the patient. It is even possible that the disease can disappear without the treatment.

The above Figures show that the behaviour of solutions is similar to the case without diffusion. Therefore, it is not necessary to study the model where the cells can diffuse. From mathematical point of view this phenomenon may be connected with the linear diffusion. If we consider non - linear diffusion (e.g. the diffusion coefficient that depends on the density of cells), then we can obtain more interesting results. Another process which can be taken into account is chemotaxis. It is not necessary that cells at every stage move under the process of diffusion. It may be also considered that they move in the direction of some chemoattractants (see e.g. [1]). There are also many other possible improvement that can be done (e.g. time delays in reaction terms should be considered, see also [1]) and the author believe that will be done in the future.

REFERENCES

[1] "Cancer modelling and simulation". Edited by Luigi Preziosi, Chapman & Hall/CRC, 2003.

[2] R. Ahangar, X. B. Lin: "Multistage evolutionary model for carcinogenesis mutations". Elec. J. Diff. Eqs., Conference 10, pp.33-53, 2003.

[3] S. Kruś: "Pathological anathomy" (in Polish). PZWL, Warsaw, 2001.

[4] J. So: "A note on the global stability and bifurcation phenomenon of a Lotka - Volterra food chain". J. Theor. Biol., 80, pp.185-187, 1979.

[5] S. Michelson, J. Leith: "Positive feedback and angiogenesis in tumor growth control". Bull. Math. Biol., 59 (2), pp.233-254, 1997.

[6] J. Smoller: "Shock waves and reaction - diffusion equations". Springer - Verlag, New York, 1994.

[7] N. F. Britton: "Reaction - diffusion equations and their application to biology". Academic Press, New York, 1986.