STABILITY ANALYSIS AND COMPARISON OF THE MODELS FOR CARCINOGENESIS MUTATIONS IN THE CASE OF TWO STAGES OF MUTATIONS.

Urszula Foryś

Inst. Appl. Math. Mech., UW, Banacha 2, Warsaw, Poland

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 consider the case with two stages of mutations and study the systems of three reaction - diffusion equations with zero-flux boundary conditions. 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.

Keywords. Carcinogenesis mutation, Bening, pre-malignant and malignant stages of mutations, reaction - diffusion equation, Lotka - Volterra food chain, equilibrium state, stability, global stability, Turing instability.

1 Basic model.

Tumour growth dynamics is one of the most intensively studied processes within last years. It is connected with the large number of lethal outcomes of tumour diseases and the amount of money spent on the treatment. One of the possible methods that can help to improve cancer therapy is mathematical modelling (compare [1]). The aim of this paper is to study simple models of carcinogenesis mutations of DNA. 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, normally between 4 and 7 stages [3] (e. g. for malignant melanoma there are 4 stages of mutations). 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 $i = n$. In reality, tumour cells are located in some bounded region of $\mathbf{R}^3$, namely in patient's body. Therefore, the space coordinate $x \in \mathbb{U}$, where $U \subset \mathbf{R}^3$ is bounded. On the other hand, analysis of reaction-diffusion equations in three-dimensional space leads to complicated calculations. It occurs that the obtained results are similar to the case of one-dimensional diffusion. Thus, we consider $x \in [0, \pi]$, for simplification.

Following [2] we assume that the growth of cells at every stage are governed by the logistic equation (compare [4, 5]). For each type of cells we can have different net growth rates a_i and carrying capacities K_i. The net growth rates means the difference between proliferation and apoptosis of cells. Cells at the $i - th$ stage produce some signals (mostly chemical) that stimulate reproduction of cells at the next stage and inhibit it on the previous stage. Finally, 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 i-th stage with the rate η_i and destroy cells at the $(i-1)$-th stage with the rate μ_i (for more details see [2]). Therefore, we consider the system of 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 $\eta_0 = 0$ (compare the Lotka-Volterra food chains, see e. g. [6, 7, 8]).

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

- the latest stage of mutation in a favourable environment:

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

  which means that malignant cells proliferate and its growth is supported by malignant and pre-malignant cells encounters;

- the latest stage of mutation in a competitive environment:

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

  which means that malignant cells proliferate but they must compete with pre-malignant cells;

- the latest stage of mutation in a unfavourable environment:

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

which means that malignant cells are not able to proliferate, the only source of these cells are malignant - pre-malignant cells encounters.

In general case, ΔY_i denotes the Laplace operator, in one-dimensional case it is simply equal to $\frac{\partial^2 Y(t,x)}{\partial x^2}$, and D_i denote diffusion coefficients for cells at the $i-th$ stage. We study Eqs. (1) with the Neumann boundary conditions on $[0,\pi]$, i.e., $\frac{\partial Y(t,x)}{\partial x}\Big|_{x=0} = \frac{\partial Y(t,x)}{\partial x}\Big|_{x=\pi} = 0$ and with positive initial conditions $Y_i(0,x) > 0$ for $x \in [0,\pi]$.

Finally, we assume that for malignant state the environment is unbounded. This assumption reflects the fact that to obtain the latest stage of mutation the environment should change dramatically. Therefore, $K_n \to +\infty$ and after re-scaling (for details see [2]) we obtain:

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

from Eqs. (1) with

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

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

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

2 The models with two stages of mutations.

The simplest case of the models presented in the previous Section is the case with only two types of cells — normal and mutant (malignant) ones (compare e. g. [9]), but it is not very interesting from the biological point of view.

In this paper we focus on the case with two stages of mutations. Therefore, we consider three types of cells — normal cells (with the concentration y_0), pre-malignant cells (y_1) and malignant ones (y_2). After re-scaling we analyse the following three reaction - diffusion models:

$$\begin{cases} \dot{y}_0 &= y_0 \left(a_0(1 - y_0) - \mu_1 y_1 \right) + d_0 \Delta y_0 \\ \dot{y}_1 &= y_1 \left(a_1(1 - y_1) - \mu_2 y_2 + \eta_1 y_0 \right) + d_1 \Delta y_1 \\ \dot{y}_2 &= y_2 \left(1 + \eta_2 y_1 \right) + \Delta y_2 \end{cases}, \tag{2}$$

3

$$\begin{cases} \dot{y}_0 &= y_0\left(a_0(1-y_0)-\mu_1 y_1\right)+d_0\Delta y_0 \\ \dot{y}_1 &= y_1\left(a_1(1-y_1)-\mu_2 y_2+\eta_1 y_0\right)+d_1\Delta y_1 \\ \dot{y}_2 &= y_2\left(1-\eta_2 y_1\right)+\Delta y_2 \end{cases} \tag{3}$$

$$\begin{cases} \dot{y}_0 &= y_0\left(a_0(1-y_0)-\mu_1 y_1\right)+d_0\Delta y_0 \\ \dot{y}_1 &= y_1\left(a_1(1-y_1)-\mu_2 y_2+\eta_1 y_0\right)+d_1\Delta y_1 \\ \dot{y}_2 &= y_2\left(-1+\eta_2 y_1\right)+\Delta y_2 \end{cases} \tag{4}$$

with positive coefficients.

We start our analysis from the case without diffusion, i.e. we analyse the following systems of ODE:

$$\begin{cases} \dot{y}_0 &= y_0\left(a_0(1-y_0)-\mu_1 y_1\right) \\ \dot{y}_1 &= y_1\left(a_1(1-y_1)-\mu_2 y_2+\eta_1 y_0\right) \\ \dot{y}_2 &= y_2\left(1+\eta_2 y_1\right) \end{cases} \tag{5}$$

$$\begin{cases} \dot{y}_0 &= y_0\left(a_0(1-y_0)-\mu_1 y_1\right) \\ \dot{y}_1 &= y_1\left(a_1(1-y_1)-\mu_2 y_2+\eta_1 y_0\right) \\ \dot{y}_2 &= y_2\left(1-\eta_2 y_1\right) \end{cases} \tag{6}$$

$$\begin{cases} \dot{y}_0 &= y_0\left(a_0(1-y_0)-\mu_1 y_1\right) \\ \dot{y}_1 &= y_1\left(a_1(1-y_1)-\mu_2 y_2+\eta_1 y_0\right) \\ \dot{y}_2 &= y_2\left(-1+\eta_2 y_1\right) \end{cases} \tag{7}$$

Studying the properties of Eqs. (5), (6) and (7) it is easy to see that for positive initial condition $y_0(0)$, $y_1(0)$, $y_2(0) > 0$ every model has positive solution. Therefore, for Eqs. (5) we obtain the approximation of the growth of malignant cells

$$\dot{y}_2 \geq y_2.$$

This implies that the density of these cells increases at least exponentially, $y_2(t) \geq y_0(0)e^t$ for Eqs. (5). Estimating the right-hand sides of the first and second equations (that are the same for these three models) we obtain:

$$\dot{y}_0 \leq (a_0(1-y_0))$$

and

$$\dot{y}_1 \leq y_1\left(a_1(1-y_1)+\eta_1 y_0\right).$$

Hence, we get a logistic approximation for the first co-ordinate of the solution that means $y_0(t) \leq \max\{y_0(0),1\}$, where the value 1 is equal to the carrying capacity for normal cells in every model (due to the proper re-scaling). Let $\hat{y}_0 = \max\{y_0(0),1\}$. Then the approximation for the second equation takes the form:

$$\dot{y}_1 \leq y_1\left(a_1(1-y_1)+\eta_1\hat{y}_0\right),$$

that is also logistic with the carrying capacity equal to $1 + \frac{\eta_1 \hat{y}_0}{a_1}$. Therefore, $y_1(t) \leq \hat{y}_1 = \{\max y_1(0), 1 + \frac{\eta_1 \hat{y}_0}{a_1}\}$.

Knowing the approximations above, we see that for the third co-ordinate the approximation $\dot{y}_2 \leq \alpha y_2$ holds, where $\alpha = 1 + \eta_2 \hat{y}_1$ for Eqs. (5), $\alpha = 1$ for Eqs. (6) and $\alpha = \eta_2 \hat{y}_1 - 1$ for Eqs. (7), respectively. Therefore, the density of malignant cells increases at most linear for every Eqs. (5), (6) and (7). This implies that any solution to the models with non-negative initial data exist for every $t > 0$ and y_2 tends exponentially to $+\infty$ for Eqs. (5).

Now, we want to study the behaviour of such a solution for which the third co-ordinate y_2 tends to $+\infty$ as $t \to +\infty$. Assume that $y_2 \to +\infty$ for Eqs. (2), or (3), or (4). Then the following approximation for the second co-ordinate can be obtained:

$$\dot{y}_1 \leq y_1 (A - \mu_2 y_2) \leq -y_1,$$

for sufficiently large t and $A = a_1 + \eta_1 \hat{y}_0$ (namely, for t such that $y_2(t) > \frac{1+A}{\mu_2}$. This implies that $y_1 \to 0$ as $t \to \infty$. Therefore, we can estimate the first equation by two logistic equations with carrying capacity equal to 1 and $1 - \frac{\mu_1 \epsilon}{a_0}$ for any $\epsilon > 0$, i.e.

$$y_0 (a_0 - \mu_1 \epsilon - a_0 y_0) \leq \dot{y}_0 \leq a_0 y_0 (1 - y_0).$$

Letting $\epsilon \to 0$ we obtain $y_0 \to 1$.

Therefore, any solution with $y_2 \to +\infty$ has the property $(y_0, y_1) \to (1, 0)$. This result is interesting only from mathematical point of view. From the biological point of view, if the density of malignant cells increases to $+\infty$, this means unrestricted tumour growth and without the treatment a patient has no chance to survive. Hence, the asymptotic properties of densities of other cells are not important in such a case.

On the other hand, if $y_1 \to 0$ in the solution to Eqs. (7), then $\dot{y}_2 \leq -\alpha y_2$ for some $\alpha > 0$ and sufficiently large t. Therefore, $y_2 \to 0$ and it contradict the assumption $y_2 \to +\infty$. Hence, y_2 cannot tend to $+\infty$ for Eqs. (7), while for Eqs.(5) and (6) it is possible.

Corollary 1 *If $y_2 \to \infty$ as $t \to \infty$ for Eqs. (2) or (3), then $y_1 \to 0$ as $t \to \infty$.*

If $y_1 \to 0$ for any of Eqs. (2), (3) or (4), then $y_0 \to 1$. Moreover for Eqs. (4), $y_2 \to 0$ in this case.

General theory of reaction-diffusion equations guaranties that the solution to the models with nonzero diffusion, i.e. Eqs. (2), (3) and (4) and nonnegative continuous initial functions with values from the neighbourhood of equilibrium point also exists for every $t > 0$ (the right-hand side of the models is locally Lipschitz continuous, see e. g. [10]) and we can study asymptotic properties of

it. We are mainly interested in the case of healthy organism (described by the equilibrium point $(1, 0, 0)$) disturbed at the point $t = 0$ such that the concentrations of pre-malignant and malignant cells are (small) positive. In more general case, assuming that the level of malignant cells is bounded for every $t > 0$ in the models without diffusion, we can use the invariant sets theory (see e. g. [11, 12]) to obtain the global existence of solutions. Uniqueness follows from the comparison theorem, [11].

In the next Sections we focus on the possibility of Turing instability (see [13, 14]) for Eqs. (3) and (4). It is obvious that this type of instability cannot occur for Eqs. (2) because all stationary solutions to this model are unstable.

3   Some general remarks on the Turing instability for systems with two and three equations.

In order to analyse our models with three equations we need some knowledge about the possibility of diffusion driven (Turing) instability in some special cases. Consider the following system of equations

$$\dot{y}_i = f_i(y) + D_i \Delta y_i, \tag{8}$$

where $y = (y_0, \dots, y_n)$, $D_i > 0$ are diffusion coefficients, $f = (f_0, \dots, f_n)$ is of class $\mathbf{C}^1$, with zero-flux boundary conditions on $[0, \pi]$. Let $\bar{y}$ be the critical point for the system, i.e. $f(\bar{y}) = 0$, and the assumptions of the theorem of linearization (see e.g. [11]) are satisfied. We are interested in Turing (diffusion driven) instability. This means the destabilisation of $\bar{y}$ caused by diffusion. In such a case a spatially non-homogenous solution can appear. This non-homogenous solution is called a Turing pattern. Precisely, if $\bar{y}$ is a critical point and the assumtions of linearization theorem are satisfied, then the characteristic values of Jacobi matrix determine stability. For the point $\bar{y}$ we need stability in the case without diffusion, i.e. for $D_i = 0$. Hence, the characteristic equation

$$\det\left(df(\bar{y}) - \lambda I\right) = 0 \tag{9}$$

(where I is the identity matrix, $df(\bar{y})$ is the Jacobi matrix at $\bar{y}$ for the system without diffusion) has the solutions $\lambda_0, \dots, \lambda_n$ with negative real parts. Considering the linearized system for the case with diffusion ($D_i > 0$) we obtain

$$\begin{cases} \dot{y}_0 &= \frac{\partial f_0}{\partial y_0}(\bar{y})y_0 + \dots + \frac{\partial f_0}{\partial y_n}(\bar{y})y_n + D_0 \Delta y_0 \\ \vdots &= \\ \dot{y}_n &= \frac{\partial f_n}{\partial y_0}(\bar{y})y_0 + \dots + \frac{\partial f_n}{\partial y_n}(\bar{y})y_n + D_n \Delta y_n \end{cases}$$

Using the theorem of linearization (see e.g. [11]) we are looking for the solutions to the system above of the form $y_i(t, x) = y_i^0 e^{\lambda_k t} \cos(kx)$, where k is called a wave number (we omit the part with $\sin(kx)$ due to zero-flux boundary conditions). Therefore, instead of Eq. (9) we have

$$\det\left(df(\bar{y}) - (\lambda_k + k^2 D_k)I\right) = 0.$$

If the equation above has thesolutions with negative real parts for every wave number k, then the critical point $\bar{y}$ is stable also in the case with non-zro diffusion.

In the paper we need some information considering the case of two or three equations.

The Jacobi matrix MJ for ODE changes to $MJ - k^2 \begin{pmatrix} d & 0 \\ 0 & 1 \end{pmatrix}$ for two equations or $MJ - k^2 \begin{pmatrix} d_0 & 0 & 0 \\ 0 & d_1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$ for three equations (see e. g. [14]), where k is a natural number (assuming that we scaled variables such that the last diffusion coefficient is equal to 1).

1. Let the Jacobi matrix for two-dimensional system be of the form $MJ_1 = \begin{pmatrix} - & - \\ + & 0 \end{pmatrix}$ or $MJ_1 = \begin{pmatrix} - & - \\ + & - \end{pmatrix}$, i.e. $MJ_1 = \begin{pmatrix} -a & -b \\ c & -d \end{pmatrix}$, where a, b, $c > 0$ and $d \geq 0$ are arbitrary constants. The characteristic polynomial for this matrix is equal to $W(\lambda) = \lambda^2 + \lambda(a + d) + ad + cd$ with $a + d > 0$ and $ad + cd > 0$. It is obvious that zeros of this polynomial are either real and negative or complex with negative real parts. This implies stability of the stationary solution to ODE with the Jacobi matrix MJ_1.

   Studying the corresponding reaction-diffusion system we obtain the matrix

   $$\begin{pmatrix} -a - D_0 k^2 & -b \\ c & -d - D_1 k^2 \end{pmatrix}$$

   of exactly the same form as MJ_1 that excludes the possibility of diffusion driven instability, because for every wave number k the characteristic values have the same properties as before. Hence, there is no characteristic value with positive real part.

2. Let the Jacobi matrix of three-dimensional system has the following form

   $$MJ_2 = \begin{pmatrix} - & - & 0 \\ + & - & - \\ 0 & + & 0/- \end{pmatrix}, \text{ i.e. } MJ_2 = \begin{pmatrix} -a & -b & 0 \\ c & -d & -e \\ 0 & f & -g \end{pmatrix},$$

7

where a, b, c, d, e, $f > 0$ and $g \geq 0$ are arbitrary constants. The characteristic equation for MJ_2 has the following form: $\lambda^3 + \alpha\lambda^2 + \beta\lambda + \gamma = 0$ with $\alpha = a + d + g > 0$, $\beta = ad + bc + ef + ag + dg > 0$, $\gamma = aef + adg + bcg > 0$. The Routh-Hurwitz criterion (see e. g. [15]) implies that $\gamma < \alpha\beta$ guaranties stability. In our case the inequality $\gamma < \alpha\beta$ is easily fulfilled. Therefore, we obtain stability. Turning to the system with diffusion we obtain the matrix

$$\begin{pmatrix} -a - D_0 k^2 & -b & 0 \\ c & -d - D_1 k^2 & -e \\ 0 & f & -g - D_2 k^2 \end{pmatrix}.$$

Hence, the analysis is exactly the same as in Case (1) — the forms of matrix and characteristic equation do not change. Hence, the diffusion driven instability is impossible.

3. Let the Jacobi matrix MJ_3 in three-dimensional case have the form such that $\det(MJ_3 - \lambda I)$ is equal to the product of the terms on the main diagonal. It is obvious that the diffusion-driven instability is also impossible in this case.

4 Equilibrium states for the models.

For both Eqs. (3) and (4) we have the same equilibrium states (the first and second equations are the same, the third equation differs in sign). Let $(\bar{y}_0, \bar{y}_1, \bar{y}_2)$ denote the equilibrium state. The third equation implies that $\bar{y}_2 = 0$ or $\bar{y}_1 = \frac{1}{\eta_2}$. In the case $\bar{y}_2 = 0$ we obtain up to 4 equilibrium states: $A = (0,0,0)$, $B = (0,1,0)$ and $C = (1,0,0)$ exist independently on the parameters, $D = \left(\frac{a_1(a_0 - \mu_1)}{a_0 a_1 + \mu_1 \eta_1}, \frac{a_0(a_1 + \eta_1)}{a_0 a_1 + \mu_1 \eta_1}, 0 \right)$ exists for $a_0 > \mu_1$. If $\bar{y}_1 = \frac{1}{\eta_2}$, then we obtain another two equilibrium states: $E = \left(0, \frac{1}{\eta_2}, \frac{a_1(\eta_2 - 1)}{\mu_2 \eta_2} \right)$ and $F = \left(\frac{a_0\eta_2 - \mu_1}{a_0\eta_2}, \frac{1}{\eta_2}, \frac{a_0 a_1 \eta_2 - a_0 a_1 + a_0 \eta_1 \eta_2 - \mu_1 \eta_1}{a_0 \mu_2 \eta_2} \right)$. It is easy to check that:

- D exists if $a_0 > \mu_1$. If $a_0 = \mu_1$, then $D = B$. Hence, D bifurcates form B.

- E exists if $\eta_2 > 1$. If $\eta_2 = 1$, then $E = B$. Hence, E also bifurcates form B.

- F exists if $a_0\eta_2 > \mu_1$ and $a_0\eta_2(a_1 + \eta_1) > a_0 a_1 + \eta_1\mu_1$. Therefore, F exists if $\eta_2 > \max\{\frac{\mu_1}{a_0}, \frac{a_0 a_1 + \eta_1\mu_1}{a_0(a_1 + \eta_1)}\}$.

Now we study the co-existence of the equilibrium states D, E and F.

1. Let $\mu_1 < a_0$. Then D exists and the inequalities

$$\frac{\mu_1}{a_0} < \frac{a_0 a_1 + \eta_1 \mu_1}{a_0(a_1 + \eta_1)} < 1$$

are satisfied. Therefore,

— if $\eta_2 < \frac{a_0 a_1 + \eta_1 \mu_1}{a_0(a_1+\eta_1)}$, then there are no E and F;

— if $\eta_2 = \frac{a_0 a_1 + \eta_1 \mu_1}{a_0(a_1+\eta_1)}$, then there is no E and F bifurcates form D;

— if $\eta_2 \in \left(\frac{a_0 a_1 + \eta_1 \mu_1}{a_0(a_1+\eta_1)}, 1 \right)$, then there is no E but F exists;

— if $\eta_2 = 1$, then F exists and E bifurcates from B;

— if $\eta_2 > 1$, then there are all six equilibrium states.

2. Let $\mu_1 = a_0$. Then $D = B$ and D bifurcates from B. In this case $F = \left(\frac{\eta_2 - 1}{\eta_2}, \frac{1}{\eta_2}, \frac{(a_1+\eta_1)(\eta_2-1)}{\eta_2 \mu_2} \right)$. Hence,

— if $\eta_2 < 1$, then there are no E and F;

— if $\eta_2 = 1$, then $E = F = B$. This means that E and F bifurcates form B;

— if $\eta_2 > 1$, then E and F exist.

3. Let $\mu_1 > a_0$. Then D does not exist. In this case the opposite inequalities

$$1 < \frac{a_0 a_1 + \eta_1 \mu_1}{a_0(a_1 + \eta_1)} < \frac{\mu_1}{a_0}$$

are fulfilled. Hence,

— if $\eta_2 < 1$, then E and F do not exist;

— if $\eta_2 = 1$, then E bifurcates from B but F does not exist;

— if $\eta_2 \in \left(1, \frac{\mu_1}{a_0} \right)$, then there is E and F does not exist;

— if $\eta_2 = \frac{\mu_1}{a_0}$, then F bifurcates from E;

— if $\eta_2 > \frac{\mu_1}{a_0}$, then we have both E and F.

Summing up, we observe that the parameters of pre-malignant state are not very important for the number of equilibrium states.

5 Stability in the model for unfavourable conditions.

The Jacobi matrix for the system of ODE in unfavourable conditions has the form:

$$\begin{pmatrix} a_0(1-2y_0) - \mu_1 y_1 & -\mu_1 y_0 & 0 \\ \eta_1 y_1 & a_1(1-2y_1) - \mu_2 y_2 + \eta_1 y_0 & -\mu_2 y_1 \\ 0 & \eta_2 y_2 & \eta_2 y_1 - 1 \end{pmatrix}. \qquad (10)$$

We see that if the co-ordinate $\bar{y}_0 \neq 0$ for the equilibrium state, then

$$a_0(1-2\bar{y}_0) - \mu_1 \bar{y}_1 = -a_0 \bar{y}_0.$$

Similarly, if $\bar{y}_1 \neq 0$, then

$$a_1(1-2\bar{y}_1) - \mu_2 \bar{y}_2 + \eta_1 \bar{y}_0 = -a_1 \bar{y}_1.$$

Taking into account the formula (10) and the above equalities we obtain the following:

- A is unstable independently on the parameters (characteristic values are equal to a_0, a_1 and -1).

- For B, the Jacobi matrix has the form MJ_3. Characteristic polynomial is equal to $W(\lambda) = (a_0 - \mu_1 - \lambda)(-a_1 - \lambda)(\eta_2 - 1 - \lambda)$. Hence, we have stability for $a_0 < \mu_1$ and $\eta_2 < 1$ that implies the absence of E, D and F.

- For C, the Jacobi matrix also has the form MJ_3. Characteristic polynomial is equal to $W(\lambda) = (-a_0 - \lambda)(a_1 + \eta_1 - \lambda)(-1 - \lambda)$. Hence, C is always unstable.

- For E, the characteristic equation is of the form:

$$\left(\frac{a_0 \eta_2 - \mu_1}{\eta_2} - \lambda \right) \left(\lambda^2 + \frac{a_1}{\eta_2} \lambda + \frac{a_1(\eta_2 - 1)}{\eta_2} \right) = 0.$$

Hence, if $\frac{a_0 \eta_2 - \mu_1}{\eta_2} > 0$, then E is unstable. If E exists, then $\eta_2 > 1$ and this implies that there is no influence of the quadratic term on the stability (characteristic values are either real negative or complex with negative real part $-\frac{a_1}{2\eta_2}$). Therefore, E is stable when F does not exist.

In the case with diffusion, we can divide the stability analysis into two components. The first one is connected with the first characteristic value. It changes from $\lambda_0 = \frac{a_0 \eta_2 - \mu_1}{\eta_2}$ into $\lambda_0 - d_0 k^2$, where d_0 is the diffusion

10

coefficient for y_0. Then there is no influence of the diffusion in y_0 direction on the stability of E. In the plane (y_1, y_2) we have the matrix of the form MJ_1. Therefore, E cannot be destabilised by diffusion.

- For D we obtain the similar formula as in the previous case:

$$\left(\frac{a_0\eta_2(a_1 + \eta_1)}{a_0a_1 + \mu_1\eta_1} - 1 - \lambda\right)\left(\lambda^2 + \alpha\lambda + \beta\right) = 0,$$

where $\alpha = \frac{a_0a_1(a_0 - \mu_1 + a_1 + \eta_1)}{a_0a_1 + \eta_1\mu_1} > 0$ and $\beta = \frac{a_0a_1(a_0 - \mu_1)(a_1 + \eta_1)}{a_0a_1 + \mu_1\eta_1} > 0$ when D exists. The quadratic term have no influence on the stability, once again. This means that D is stable when E and F does not exist.

In the case with diffusion we use exactly the same arguments as for E to show that D cannot be destabilised by diffusion.

- For F the Jacobi matrix has the following form:

$$\begin{pmatrix} -\frac{a_0\eta_2 - \mu_1}{\eta_2} & -\frac{\mu_1(a_0\eta_2 - \mu_1)}{a_0\eta_2} & 0 \\ \frac{\eta_1}{\eta_2} & -\frac{a_1}{\eta_2} & -\frac{\mu_2}{\eta_2} \\ 0 & \frac{a_0a_1(\eta_2 - 1) + \eta_1(a_0\eta_2 - \mu_1)}{a_0\mu_2} & 0 \end{pmatrix}.$$

We see that this matrix is of the form MJ_2 when F exists. This implies stability. Moreover, this also shows that diffusion - driven instability cannot occur. In the case without diffusion we can show something more — if the equilibrium state is locally stable, then it is globally stable (we show this property of Eqs. (4) in Appendix).

Corollary 2 *There is no possibility of diffusion - driven instability for Eqs. (4). For every parameter values there exists one stable equilibrium state:*

- *if there is F, then it is stable;*

- *if there is no F but E exists, then E is stable;*

- *if there is no E and F but D exists, then D is stable;*

- *if there is no E, D and F, then B is stable.*

6   Stability in the model for competitive conditions.

The Jacobi matrix for our system of ODE in competitive conditions has the form:

$$
\begin{pmatrix}
a_0(1-2y_0)-\mu_1 y_1 & -\mu_1 y_0 & 0 \\
\eta_1 y_1 & a_1(1-2y_1)-\mu_2 y_2 + \eta_1 y_0 & -\mu_2 y_1 \\
0 & \eta_2 y_2 & 1-\eta_2 y_1
\end{pmatrix}. \tag{11}
$$

Therefore, for the states with $\bar{y}_1 = \frac{1}{\eta_2}$, i.e. for E and F, stability conditions do not change in comparison with Eqs. (4). The states A and C are also unstable, because its instability does not depend on the last characteristic value (that changes the sign comparing to the case of unfavourable conditions). For B the third characteristic value changes the sign and it is crucial for stability of this state. Now, B is stable if $\eta_2 > 1$ and $a_0 < \mu_1$. In this case there is no D, but E exists and if $\eta_2 > \frac{\mu_1}{a_0}$, then F also exists. Hence, for $\eta_2 > \frac{\mu_1}{a_0} > 1$ we have two stable equilibrium states B and F, and for $\eta \in \left(1, \frac{\mu_1}{a_0}\right)$ we have also two stable states B and E. For the state D the last characteristic value is also the most important. It changes the sign and therefore, D is stable for $\eta_2 > \frac{a_0 a_1 + \mu_1 \eta_1}{a_0(a_1 + \eta_1)}$ and unstable for the opposite inequality. Then D is stable when F exists but E may exists or not. If D is stable we also have two stable equilibrium states D and F.

Summing up:

- if $a_0 > \mu_1$ and $\eta_2 > \frac{a_0 a_1 - \mu_1 \eta_1}{a_0(a_1 + \eta_1)}$ then D and F are stable

- if $a_0 < \mu_1$ and $\eta_2 > \frac{\mu_1}{a_0}$, then B and F are stable

- if $a_0 < \mu_1$ and $\eta_2 \in \left(1, \frac{\mu_1}{a_0}\right)$, then B and E are stable.

For other inequalities all equilibrium states are unstable.

It is easy to check that Turing instability is impossible also for Eqs. (3).

Corollary 3 *For Eqs. (3) we observe either bistability or instability.*

7   Simulations and discussion

In this section we compare results of mathematical analysis with computer simulations. We use healthy initial conditions — the state C — perturbed by cosine function with the small amplitude (such that the initial functions are non-negative).

Figs. 1, 2, 3 were prepared for the following parameter values:

$$a_0 = a_1 = 1, \ \mu_1 = \mu_2 = 0.5, \ \eta_1 = \eta_2 = 0.3, \ d_0 = d_1 = 0.1.$$

For these parameters the non-trivial state E for Eqs. (3) and (4) does not exist. In
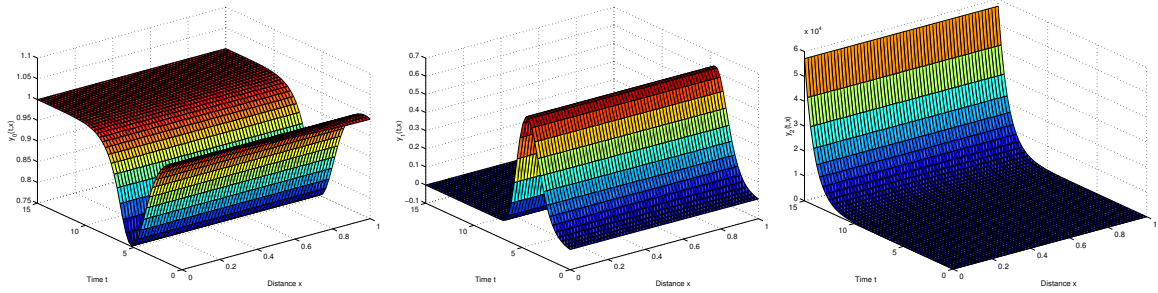

Figure 1: Solution to Eqs. (2).

Fig. 1 we see the solution to Eqs. (2) that are qualitatively the same independently on the parameters. Fig. 2 represents the case of competitive environment where the solution is similar to the solution in Fig. 1 (the only difference is that the number of malignant cells increases not so fast, here these cells must compete with premalignant ones) and Fig. 3 — the case of unfavourable one (the malignant cells tends to 0 and there arises some positive equlibrium between normal and premalignant cells).

For $a_0 = a_1 = 1, \mu_1 = \mu_2 = 0.5, \eta_1 = 0.3, \eta_2 = 1.5, d_0 = d_1 = 0.1$ the non-trivial equilibrium state exists. In Fig. 4 we see the solution to Eqs. (3) and in Fig. 5 — the solution to Eqs. (4) in such a case. Now, the solution to Eqs. (3) behaves similarly to the solution in Fig. 3 — malignant cells tends to 0 (but not
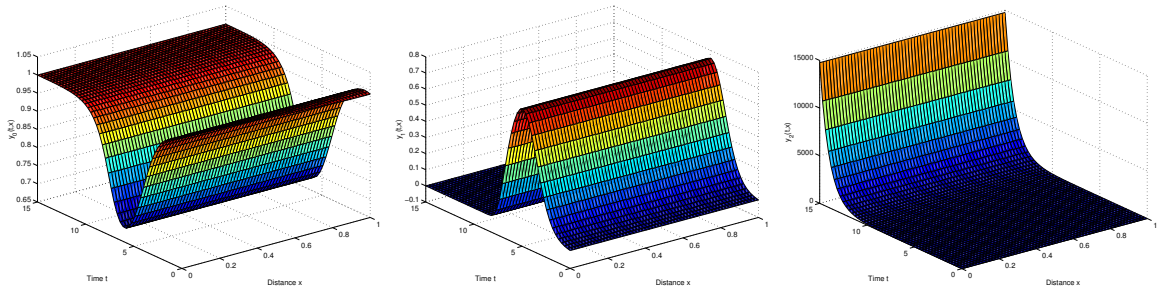

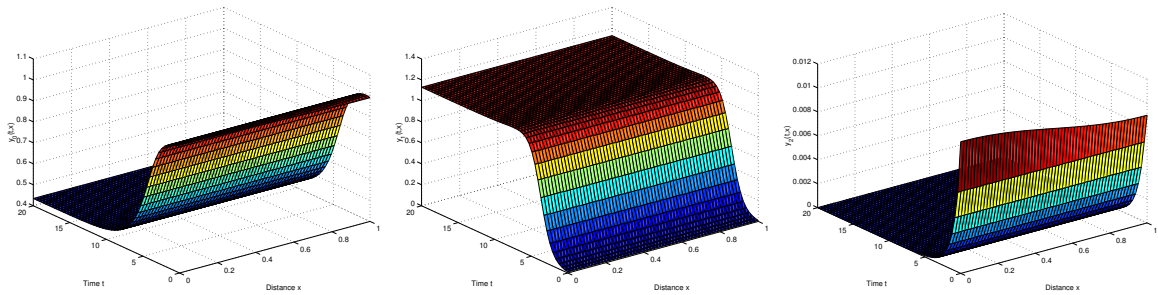Figure 2: Solution to Eqs. (3) in the case with no non-trivial equilibrium state.

Figure 3: Solution to Eqs. (4) in the case with no non-trivial equilibrium state.
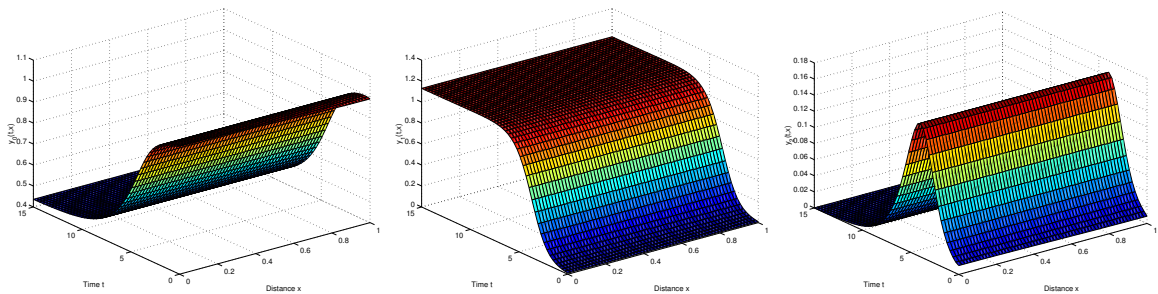

Figure 4: Solution to Eqs. (3) in the case when non-trivial equilibrium state exists.

monotonically, they achieve its maximum at some time and then decrease to 0), and malignant and pre-malignant cells tend to their positive equilibria. In Fig. 5 the solution tends to the non-trivial equilibrium F.

In the author's opinion in most of malignant cancers Eqs. (2) are 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.

Looking for Figures above one can also see 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
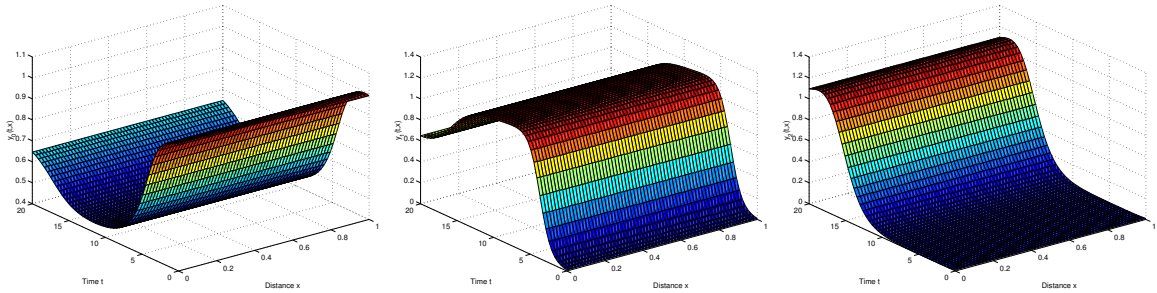
14

Figure 5: Solution to Eqs. (4) in the case when non-trivial equilibrium state exists.

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 chemoatractants (see e. g. [1]). There are also many other possible improvements that can be done (e. g. time delays in reaction terms should be considered) and the author believes that it will be done in the future.

8 Appendix

In this Section we study global stability of equilibrium states of the system defined by Eqs. (7) with positive positive initial data $y_0(0)$, $y_1(0)$, $y_2(0) > 0$.

At the beginning we prove the following Lemma.

Lemma 1 *If the inequality*

$$\eta_2 > \max\left\{\frac{\mu_1}{a_0}, \frac{a_0 a_1 + \mu_1 \eta_1}{a_0(a_1 + \eta_1)}\right\} \tag{12}$$

holds, then every solution to Eqs. (7) tends to the unique non-trivial equilibrium state $F = \left(\frac{a_0\eta_2 - \mu_1}{a_0\eta_2}, \frac{1}{\eta_2}, \frac{a_0 a_1(\eta_2 - 1) + \eta_1(a_0\eta_2 - \mu_1)}{a_0\mu_2\eta_2}\right)$.

Proof: If Ineq. (12) is satisfied, then F exists. It is the only equilibrium with all positive co-ordinates. Let $x_i = y_i - \bar{y}_i^F$, $i = 0, 1, 2$ and $\bar{y}_i^F$ are the corresponding co-ordinates of F. Then Eqs. (7) take the form

$$\begin{cases} \dot{x}_0 &= -(x_0 + \bar{y}_0^F)(a_0 x_0 + \mu_1 x_1) \\ \dot{x}_1 &= -(x_1 + \bar{y}_1^F)(a_1 x_1 + \mu_2 x_2 - \eta_1 x_0) \\ \dot{x}_2 &= \eta_2 x_1 (x_2 + \bar{y}_2^F) \end{cases} . \tag{13}$$

15

We know that $y_0(t)$, $y_1(t)$, $y_2(t) > 0$ for every $t \geq 0$ and therefore, $x_i > -\bar{y}_i^F$ for $i = 0, 1, 2$. Consider the standard (see e. g. [16]) Lapunov function

$$V_F(x_0, x_1, x_2) = \sum_{i=0}^{2} A_i \left(x_i - \bar{y}_i^F \ln \frac{x_i + \bar{y}_i^F}{\bar{y}_i^F} \right)$$

with $A_0 = \frac{\eta_1 \eta_2}{\mu_1}$, $A_1 = \eta_2$ and $A_2 = \mu_2$ in the domain $\Omega = \{(x_0, x_1, x_2) : x_i > -\bar{y}_i^F, \ i = 0, 1, 2\}$.

It is easy to see that $V_F(x_0, x_1, x_2) \geq 0$ in Ω and $V_F(x_0, x_1, x_2) = 0$ iff $x_0 = x_1 = x_2 = 0$. Calculating the derivative of V_F in the direction of a solution to Eqs. (13) one gets

$$\dot{V}_F(x_0, x_1, x_2) = A_0(-x_0)(a_0 x_0 + \mu_1 x_1) + A_1(-x_1)(a_1 x_1 + \mu_2 x_2 - \eta_1 x_0) + A_2 x_2 x_1 \eta_2$$

and finally,

$$\dot{V}_F(x_0, x_1, x_2) = -(A_0 a_0 x_0^2 + A_1 a_1 x_1^2).$$

We see that $\dot{V}_F \leq 0$ that implies global stability of F. To obtain global asymptotic stability we need something more. We have $\dot{V}_F(x_0, x_1, x_2) = 0$ for every $(x_0, x_1, x_2) = (0, 0, x_2)$. Let the point $(0, 0, x_2(\bar{t}))$ lies on the trajectory of Eqs. (13) for some $\bar{t} > 0$. Then calculating the second derivative we obtain $\ddot{V}_F(0, 0, x_2) = 0$. The next derivative $\dddot{V}_F(0, 0, x_2) = -\mu_2^2 \left(\bar{y}_1^F \right)^2 x_2^2(\bar{t}) < 0$. This shows that it is a point of inflection. Hence, V_F is strictly decreasing and therefore, F is globally stable. This completes the proof.

$\square$

If F does not exist, then other equilibrium state is globally stable.

Lemma 2 If $\mu_1 > a_0$ and $1 < \eta_2 < \frac{\mu_1}{a_0}$, then the state $E = \left(0, \frac{1}{\eta_2}, \frac{a_1(\eta_2 - 1)}{\mu_2 \eta_2} \right)$ is globally stable.

Proof: Let $E = (0, \bar{y}_1^E, \bar{y}_2^E)$ and $x_0 = y_0$, $x_1 = y_1 - \bar{y}_1^E$, $x_2 = y_2 - \bar{y}_2^E$. Then Eqs. (7) take the form

$$\begin{cases} \dot{x}_0 &= x_0 \left(a_0(1 - x_0) - \mu_1(x_1 + \bar{y}_1^E) \right) \\ \dot{x}_1 &= -\left(x_1 + \bar{y}_1^E \right) \left(a_1 x_1 + \mu_2 x_2 - \eta_1 x_0 \right) \ . \\ \dot{x}_2 &= \eta_2 x_1 \left(x_2 + \bar{y}_2^E \right) \end{cases}$$

Consider the Lapunov function

$$V_E(x_0, x_1, x_2) = B_0 x_0 + \sum_{i=1}^{2} B_i \left(x_i - \bar{y}_i^E \ln \frac{x_i + \bar{y}_i^E}{\bar{y}_i^E} \right)$$

16

defined on $[0, \infty) \times (-\bar{y}_1^E, \infty) \times (-\bar{y}_2^E, \infty)$ and calculate the derivative $\dot{V}_E$ (assuming $x_0 > 0$). Then

$$\dot{V}_E = -B_0 \left(\mu_1 \bar{y}_1^E - a_0 \right) x_0 - B_0 a_0 x_0^2 - B_1 a_1 x_1^2$$

$$- B_0 \mu_1 x_0 x_1 + B_1 \eta_1 x_0 x_1 - B_1 \mu_2 x_1 x_2 + B_2 \eta_2 x_1 x_2.$$

Hence, for $B_1 \mu_2 = B_2 \eta_2$ and $B_1 \eta_1 = B_0 \mu_1$ one gets $\dot{V}_E < 0$ for every $x_0 > 0$ under the assumption $\mu_1 \bar{y}_1^E > a_0$. This implies that E is globally stable if it exists and the state F does not exist.

$\square$

Similarly we show global stability of the state $D = \left(\frac{a_1(a_0 - \mu_1)}{a_0 a_1 + \mu_1 \eta_1}, \frac{a_0(a_1 + \eta_1)}{a_0 a_1 + \mu_1 \eta_1}, 0 \right)$ for $a_0 > \mu_1$ under the assumption that F and E do not exist and global stability of $B = (0, 1, 0)$ for $a_0 < \mu_1$ and $\eta_2 < 1$ (when F, E and D do not exist). Appropriate Lapunov functions are $V_D(x_0, x_1, x_2) = \sum_{i=0}^{1} \alpha_i \left(x_i - \bar{y}_i^D \ln \frac{x_i + \bar{y}_i^D}{\bar{y}_i^D} \right) + \alpha_2 x_2$ and $V_B(x_0, x_1, x_2) = \beta_0 x_0 + \beta_1 \left(x_1 - \bar{y}_1^B \ln \frac{x_1 + \bar{y}_1^B}{\bar{y}_1^B} \right) + \beta_2 x_2$.

References

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

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

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

[4] Drasdo D., Höme S., Individual based approaches to birth and death in avascular tumours, *Math. Comp. Model.*, **37** (11) (2003), 1163-1175.

[5] Foryś U., Marciniak - Czochra A., Logistic equation in tumour growth modelling *J. Appl. Math. Comp. Sci.*, **13** (3) (2003) 317-325.

[6] So J. W. H., A note on the global stability and bifurcation phenomenon of a Lotka - Volterra food chain, *J. Theor. Biol.*, **80** (2) (1979), 185-187.

[7] Gard T., Hallam T., Persistence in food webs. I. Lotka - Volterra food chains, *Bull. Math. Biol.*, **41** (6) (1979), 877-891.

[8] Bhat N., Pande L., Three-step food chains in Gompertz and Lotka-Volterra models, *J. Theor. Biol.*, **91** (3) (1981), 429-435.

[9] S. Michelson, J. Leith: Positive feedback and angiogenesis in tumor growth Control, *Bull. Math. Biol.*, **59** (2) (1997), 233-254.

[10] Henry D., *Geometric theory of semilinear parabolic equations*, Springer-Verlag, Berlin, 1981.

[11] Smoller J., *Shock waves and reaction-diffusion equations*, Springer-Verlag, New York, 1994.

[12] Britton N. F., *Reaction-diffusion equations and their applications to biology*, Academic Press, New York, 1986.

[13] Turing A. M., The chemical basis of morphogenesis, *Phil. Trans. Roy. Soc. B*, **237** (1952), 37-72.

[14] Murray J. D., *Mathematical biology*, Springer-Verlag, Berlin, 1993.

[15] Gantmacher F. R., *Applications of the theory of matrices*, Interscience Publishers, Inc., New York, 1959.

[16] Hofbauer J., Sigmund K., *The theory of evolution and dynamical systems*, Cambridge University Press, Cambridge, 1998.