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DEGENERATED BOGDANOV-TAKENS BIFURCATIONS IN AN IMMUNO-TUMOR MODEL

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ABSTRACT. A mathematical immuno-tumor model proposed by A. Kavaliauskas [Nonlinear Anal. Model. Control **8**, 55 (2003)] and consisting of a Cauchy problem for a system of two first-order ordinary differential equations is studied. For some particular parameters values, this model has saddle-node, Hopf and Bogdanov-Takens (BT) singularities. In the case of the BT singularities, we herein derive the normal forms of the governing equations by using ideas and a method from S.-N. Chow, C. Li, and D. Wang [*Normal forms and bifurcation of planar vector fields* (1994)] and Yu. A. Kuznetsov [*Elements of applied bifurcation theory* (1994)], based on an appropriate splitting of associated Hilbert spaces. It is found that a limit case of parameters associated with medicine administration corresponds to degenerate BT bifurcations and, so, to a large variety of responses to the medical treatments for admissible parameters near the limit ones.

1. Introduction

The tumor growth is caused by a large number of biological effects. Prevention and medical treatment are based on understanding of tumor evolution. Tumors may be malignant or benign. The differences between them are their rate of growth, differentiation degree, invasion in normal tissue. Some tumors are neither malignant nor benign. They develop, infiltrate neighboring tissues like malignant tumors, have not capsules, some carry to metastasis which grow tens of years.

Tumor cells may be in "cancer dormancy" (i.e. tumor is "near-steady-state"). This state may be disturbed by stress factors, age, infections and, as a result, dormand tumor cells grow uncontrolled.

Malignant cells and microenvironment, which causes their survival and death, are in a dynamic interaction. The factors that enter into combination with immune reactivity predispose to malignance. Many tumor cells are immunogen and tumor growth is stopped by immune response. From immunological point of view between tumor growth and antitumor immune response priority has immune response. Frequently, the tumors are infiltrate by mononuclear cells: lymphocytes, monocytes, plasmocytes. Human tumor is characterized by tumor cells and macrofages (which suggest an antitumor immune response). The proliferation of all T lymphocytes types (Th, Ts, Tc) is stimulated by tumor antigen (macrofages).

Division of cells B, T, NK (natural killer) is stimulated by interleukin IL-1. In addition, IL-1 generates febrile response in inflammation reaction, but TFN-α causes tumor cells necrosis.

IL-2 is secreted by lymphocytes TCD_4 and NK. Tc has an important role for tumor cells disintegration and their growth under the influence of chemical, physical or biological factors. It is a specific interaction between Tc and malignant cell.

Consequently, immune reaction is characterized by two steps:

- activation of nonspecific effector cells (macrofages, NK, neutrofiles), production of local inflammation reaction. The tumor rate growth decreases and the presentation level of tumor antigen by malignant cells increases;
- immune protection against tumor is assured by Tc.

Effector cells of cellular mediate immunity are efficient for metastases prevention, but they are nonefficient for a microtumor.

Researchers of various areas (e.g. mathematics, medicine, physics, biology) have focused their effort on modelling response of cell population to chemical factors. The studies of Yu. Gusev, V. A. Kuznetsov, H. M. Byrne, M. A. J. Chaplain, F. Mollica, etc. have shown that the obtained mathematical results agree with the medical ones. In addition, some parameter values may tell us which is the result of a special treatment in dependence upon the immune system of the patient, how quickly tumor cells grow in time. It is just with the study of the influence of parameters on the various cell growth that we are dealing with in the following. More precisely, we derive those (bifurcation) values of the parameters at which the growth changes qualitatively. We do not discuss modelling aspects, which can be found in [1]. Rather we start with the model from [2] and perform a local dynamical bifurcation around point corresponding to special values of the four parameters. It is worth remarking that, alike in other studies of our group [3, 4], the parameter values corresponding to highest structurally instable immune-tumor system are limits of admissible values and not the admissible values themselves. Among these values we chose only those corresponding to BT bifurcation. This bifurcation proved to be degenerated, namely, of codimension at least equal to three. Consequently, a slight variation of parameters, characterizing medicines administrated, around those limit values gave rise to the response of the system of four types: structurally stable and bifurcations of codimension one, two, three. Moreover, the regions of structural stability and various codimensions are multiple, implying regions of different qualitative dynamical response of the all populations much more than three. This shows how complicate is the system in [2] to drug administration and how bifurcation treatment can be useful.

Briefly, our study concerns the case when an equilibrium is of a degenerated BT type, hence a bifurcation at least codimension three occurs. As a consequence, a quite complex behavior of the quoted response takes place for parameters near the values corresponding to the equilibrium. In Section 2 we write the model, while in Section 3 we derive the normal form of the vector field at a BT singularity, elimitating the second- and third-order nonresonant terms, showing the degeneracy of the bifurcation.

2. Mathematical model

The model from [2] represents a generalization of a two-parameters model from [1]. In this model we take into account the lymphocytes-tumor cells interaction and the influence of medical treatment to immune system, characterized by four parameters.

The hypotheses and transformation from [2] are mathematically described by the ordinary differential equations (ODE)

$$\begin{cases} \dot{x} = -l_1 x + (ay+b)\dfrac{x}{1+x}, \\ \dot{y} = -ex + l_2 y - (ay+b)c\dfrac{x}{1+x}, \end{cases} \tag{2.1}$$

where $x,\ y$ are the state functions and represent the *growth of free lymphocytes number on tumor surface* and *total number of tumor cells* respectively, $l_1,\ a,\ b,\ e,\ l_2,\ c \in \mathbb{R}_+$ are the parameters.

In [2] it is shown that the equilibrium $(0,\ 0)$ is a Hopf singularity.

We study a particular system deduced from (**2.1**), namely the system of ODEs (SODE)

$$\begin{cases} \dot{x} = -x - x^2 + xy, \\ \dot{y} = -(e+b)x + ly - ex^2 + (l+c)xy - b, \end{cases} \qquad e,\ b,\ l,\ c \in \mathbb{R}, \tag{2.2}$$

which has three equilibria $\mathbf{m_1} = (0,\ b/l),\ \mathbf{m_2} = (-1, 0)$ and $\mathbf{m_3} = \left(\dfrac{b-l}{l+c-e}, \dfrac{b+c-e}{l+c-e}\right)$ if $e,\ b,\ l,\ c \neq 0,\ l+c \neq e$.

3. Singularities of Bogdanov-Takens type

In the following limit cases of at least two vanishing parameters: $l = b = 0$; $l = c = 0,\ b = 0,\ e \neq 0$; $b = c = 0,\ l = 0,\ e \neq 0$ and $l = b = c = 0,\ e \neq 0,\ y_0 = 1$; $e = l = b = 0,\ c \neq 0,\ y_0 = 1$ and $e = b = 0,\ l = 0,\ c \neq 0$ the nonhyperbolic singularity $(x_0,\ y_0)$ has a double zero eigenvalue. In the following we deduce the particular normal forms of the governing equations only at these singularities. According to the vanishing or nonvanishing of the coefficients of these forms, various situation occur: $(x_0,\ y_0)$ is a degenerated or nondegenerated BT bifurcation.

$\mathbf{l = b = 0},\ \mathbf{e},\ \mathbf{c} \in \mathbb{R}_+,\ \mathbf{y_0 = 1}$. Let us consider the change of coordinates $u_1 = x,\ u_2 = y - 1$ and the change of parameters $e_1 = e - e_0,\ c_1 = c - c_0$. The equilibrium $(0,\ y_0)$ is carried at the origin of coordinates $\mathbf{u_0} = (u_{01},\ u_{02}) = (0,\ 0) = \mathbf{0}$. Thus, the SODE (**2.2**) becomes

$$\begin{cases} \dot{u}_1 = -u_1^2 + u_1 u_2, \\ \dot{u}_2 = -(e_1 + e_0 - c_1 - c_0)u_1 - (e_1 + e_0)u_1^2 + (c_1 + c_0)u_1 u_2. \end{cases} \tag{3.1}$$

The system linearized around $\mathbf{0} = (u_{01},\ u_{02}) = (0,\ 0)$ has the matrix $A(\mathbf{0},\ \boldsymbol{\lambda}) = \begin{pmatrix} 0 & 0 \\ -(e_1 - c_1 + e_0 - c_0) & 0 \end{pmatrix}$, depending on the parameter $\boldsymbol{\lambda} = (e_1,\ c_1)$. For $\boldsymbol{\lambda} = \mathbf{0}$, i.e. at the double-zero singularity, (**3.1**) has the form

$$\begin{cases} \dot{u}_1 = -u_1^2 + u_1 u_2, \\ \dot{u}_2 = -(e_0 - c_0)u_1 - e_0 u_1^2 + c_0 u_1 u_2. \end{cases} \tag{3.2}$$

Correspondingly, A becomes $A(\mathbf{0},\ \mathbf{0}) = \begin{pmatrix} 0 & 0 \\ -d_0 & 0 \end{pmatrix} \neq \mathbf{0}_2$, where $d_0 = (c_0 - e_0)^{-1}$, such that $detA = 0,\ trA = 0$ and $p_\pm = 0$. It follows that this equilibrium is a double zero singularity.

Bringing of matrix $A(\mathbf{0},\ \mathbf{0})$ to canonical form implies the transformation of the canonical base $(\mathbf{e_1},\ \mathbf{e_2})$ of $\mathbb{R}^2$ to the base $\{\mathbf{v}_+,\ \mathbf{v}_-\}$, where $\mathbf{v}_+$ is the eigenvector of A and $\mathbf{v}_-$ is its associated (generalized) eigenvector. Namely, we have $\mathbf{v}_+ = (0,\ 1),\ \mathbf{v}_- = (d_0,\ 0)$ and $A\mathbf{v}_+ = 0,\ A\mathbf{v}_- = \mathbf{v}_+,\ \langle \mathbf{v}_+,\ \mathbf{v}_- \rangle = 0$. By the change of coordinates $u_1 = d_0\, n_2,\ u_2 = n_1$, the system (**3.2**) becomes

$$\begin{cases} \dot{n}_1 = n_2 + c_0 d_0 n_1 n_2 - e_0 d_0^2 n_2^2, \\ \dot{n}_2 = n_1 n_2 - d_0 n_2^2. \end{cases} \tag{3.3}$$

In (**3.3**), the vector homogeneous polynomial of order two is
$\mathbf{X} = \begin{pmatrix} c_0 d_0 n_1 n_2 - e_0 d_0^2 n_2^2 \\ n_1 n_2 - d_0 n_2^2 \end{pmatrix}$ and the matrix of the first order terms reads $A = \begin{pmatrix} n_2 & 0 \\ 0 & 0 \end{pmatrix}$.
It is this A that is considered further.

Elimination of the second-order terms from (3.3)

Denote $\mathbf{q} = (q_1,\ q_2)^T,\ \mathbf{n} = (n_1,\ n_2)^T$.

Proposition 3.1. *The SODE (3.3) is topologically equivalent to the SODE*

$$\begin{cases} \dot{q}_1 = q_2 + \dfrac{1}{2}\, q_1^2 + \dfrac{d_0}{2}\, q_1^3 + \dfrac{(c_0^2 - 3c_0 - e_0)d_0^2}{2}\, q_1^2 q_2 + (2e_0 - e_0 c_0) d_0^3 q_1 q_2^2 + O(|\mathbf{q}|^4), \\ \dot{q}_2 = \dfrac{(c_0 - 2)d_0}{2}\, q_1^2 q_2 + (1 - e_0) d_0^2 q_1 q_2^2 + O(|\mathbf{q}|^4). \end{cases} \tag{3.4}$$

Proof. For the determination of transformation $\mathbf{n} = \mathbf{q} + \mathbf{h}(\mathbf{q})$ which carries (**3.3**) in (**3.4**) we apply the method described in [5].

Let $\mathcal{H}_2^2$ the Hilbert space of vector homogeneous polynomials of degree two. Let $\mathcal{B} = \{\mathbf{u_1},\ \mathbf{u_2},\ \mathbf{u_3},\ \mathbf{u_4},\ \mathbf{u_5},\ \mathbf{u_6}\}$, where $\mathbf{u_1} = n_1^2\mathbf{e_2},\ \mathbf{u_2} = n_1 n_2 \mathbf{e_2},\ \mathbf{u_3} = n_2^2 \mathbf{e_2},\ \mathbf{u_4} = n_1^2 \mathbf{e_1},\ \mathbf{u_5} = n_1 n_2 \mathbf{e_1},\ \mathbf{u_6} = n_2^2 \mathbf{e_1},\ \mathbf{e_1} = (1,\ 0)$ and $\mathbf{e_2} = (0,\ 1)$, be a base for $\mathcal{H}_2^2$. Obviously $\dim\mathcal{H}_2^2 = 6$. Denote by L_A^2 the Lie parenthesis of the operator defined by A. In this case $L_A^2(\mathbf{u_1}) = 2\mathbf{u_2} - \mathbf{u_4},\ L_A^2(\mathbf{u_2}) = \mathbf{u_3} - \mathbf{u_5},\ L_A^2(\mathbf{u_3}) = \mathbf{u_6},\ L_A^2(\mathbf{u_4}) = 2\mathbf{u_5},\ L_A^2(\mathbf{u_5}) = \mathbf{u_6},\ L_A^2(\mathbf{u_6}) = 0$.

Let $Im\ L_A^2$ be the range of L_A^2. We have the splitting

$$Im\ L_A^2 \oplus Ker\ L_A^2 = \mathcal{H}_2^2.$$

A base for $Im\ L_A^2$ is $\mathcal{B}_1 = \{L_A^2(\mathbf{u_1}),\ L_A^2(\mathbf{u_2}),\ L_A^2(\mathbf{u_3}),\ L_A^2(\mathbf{u_4})\}$, followed by the above algebra, reads $\mathcal{B}_1 = \{2\mathbf{u_2} - \mathbf{u_4},\ \mathbf{u_3} - \mathbf{u_5},\ \mathbf{u_6},\ 2\mathbf{u_2}\}$. Choose $\mathcal{B}_2 = \{\mathbf{u_1},\ \mathbf{u_4}\}$ as the base of $Ker\ L_A^2$. Thus, the vectors from the $\mathcal{B}$ base can be expressed in terms of the vectors from $\mathcal{B}_1$ and $\mathcal{B}_2$ in the following way $\mathbf{u_1} = 0 + \mathbf{u_1},\ \mathbf{u_2} = (2\mathbf{u_2} - \mathbf{u_4})/2 + \mathbf{u_4}/2,\ \mathbf{u_3} = [(\mathbf{u_3} - \mathbf{u_5}) + 2\mathbf{u_5}/2] + 0,\ \mathbf{u_4} = 0 + \mathbf{u_4},\ \mathbf{u_5} = 2\mathbf{u_5}/2 + 0,\ \mathbf{u_6} = \mathbf{u_6} + 0$.

Let $\boldsymbol{\xi_1} = (\xi_1,\ \xi_2)^T = \alpha_1\mathbf{u_1} + \alpha_2\mathbf{u_2} + \alpha_3\mathbf{u_3} + \alpha_4\mathbf{u_4} + \alpha_5\mathbf{u_5} + \alpha_6\mathbf{u_6}$ be an arbitrary element of $\mathcal{H}_2^2$. Then it can be written, equivalently, in the form $\boldsymbol{\xi_1} = L_A^2(\frac{\alpha_2}{2}\mathbf{u_1} + \alpha_3\mathbf{u_2} + \frac{\alpha_3+\alpha_5}{2}\mathbf{u_4} + \alpha_6\mathbf{u_5}) + [\alpha_1\mathbf{u_1} + (\alpha_4 + \alpha_2/2)\mathbf{u_4}] = L_A^2(\mathcal{H}_2^2) + [\alpha_1\mathbf{u_1} + (\alpha_4 + \alpha_2/2)\mathbf{u_4}]$, as a sum of a nonresonant vector from $Im\ L_A^2$ and resonant term from $Ker\ L_A^2$. Let us now determine a transformation, defined by a polynomial vector $\mathbf{h}$, such that the nonresonant terms be eliminated. Thus, the SODE (**3.3**) reads $\dot{\mathbf{n}} = A\mathbf{n} + \boldsymbol{\xi_1}$, where $\boldsymbol{\xi_1} = \begin{pmatrix} c_0d_0n_1n_2 - e_0d_0^2n_2^2 \\ n_1n_2 - d_0n_2^2 \end{pmatrix}$. This particular $\boldsymbol{\xi_1}$ has $\alpha_1 = \alpha_4 = 0,\ \alpha_2 = 1,\ \alpha_3 = -d_0,\ \alpha_5 = c_0d_0,\ \alpha_6 = -e_0d_0^2$. Then, by the normal form method [5], $\mathbf{h}$ is determined from the relation $L_A^2\mathbf{h}(\mathbf{n}) = \mathbf{X}(\mathbf{n})$, namely, this relation yields $\mathbf{h}(\mathbf{n}) = \begin{pmatrix} (c_0 - 1)d_0n_1^2/2 - e_0d_0^2n_1n_2 \\ n_1^2/2 - d_0n_1n_2 \end{pmatrix}$.
Then the transformation $\mathbf{n} = \mathbf{q} + \mathbf{h}(\mathbf{q})$, written as

$$\begin{cases} n_1 = q_1 + (c_0 - 1)d_0q_1^2/2 - e_0d_0^2q_1q_2, \\ n_2 = q_2 + q_1^2/2 - d_0q_1q_2, \end{cases} \tag{3.5}$$

and substituted in (**3.3**), leads to (**3.4**). □

Elimination of third-order nonresonant terms from (3.4)

Proposition 3.2. *The SODE (3.4) is topologically equivalent to the SODE*

$$\begin{cases} \dot{r_1} = r_2 + \dfrac{1}{2}r_1^2 + \dfrac{(c_0+1)d_0}{6}r_1^3 + O(|\mathbf{r}|^4), \\ \dot{r_2} = O(|\mathbf{r}|^4). \end{cases} \tag{3.6}$$

Proof. In this case the Hilbert space $\mathcal{H}_2^3$ of homogeneous vector polynomials (of degree three and dimension two) has the dimension dim$\mathcal{H}_2^3 = 8$. The base of $\mathcal{H}_2^3$ is $\mathcal{B} = \{\mathbf{u}_i \in \mathcal{H}_2^3|\ \mathbf{u}_i = n_1^{4-i}n_2^{i-1}\mathbf{e_2},\ i = \overline{1,\ 4};\ \mathbf{u}_i = n_1^{8-i}n_2^{i-5}\mathbf{e_1},\ i = \overline{5,\ 8}$. Then $L_A^3(\mathbf{u_1}) = 3\mathbf{u_2} - \mathbf{u_5},\ L_A^3(\mathbf{u_2}) = 2\mathbf{u_3} - \mathbf{u_6},\ L_A^3(\mathbf{u_3}) = \mathbf{u_4} - \mathbf{u_7},\ L_A^3(\mathbf{u_4}) = -\mathbf{u_8},\ L_A^3(\mathbf{u_5}) = 3\mathbf{u_6},\ L_A^3(\mathbf{u_6}) = 2\mathbf{u_7},\ L_A^3(\mathbf{u_7}) = \mathbf{u_8},\ L_A^3(\mathbf{u_8}) = 0$. Thus, similarly,

$$Im\ L_A^3 \oplus Ker\ L_A^3 = \mathcal{H}_2^3.$$

A base of $Im\ L_A^3$ is $\mathcal{B}_1 = \{3\mathbf{u_2} - \mathbf{u_5},\ 2\mathbf{u_3} - \mathbf{u_6},\ \mathbf{u_4} - \mathbf{u_7},\ -\mathbf{u_8},\ 3\mathbf{u_6},\ 2\mathbf{u_7}\}$. Choose $\mathcal{B}_2 = \{\mathbf{u_1},\ \mathbf{u_5}\}$ as the base of $Ker\ L_A^3$. Thus, the decompositions along $\mathcal{B}_1$ and $\mathcal{B}_2$ of vectors from $\mathcal{B}$ are $\mathbf{u_1} = 0 + \mathbf{u_1},\ \mathbf{u_2} = [\frac{1}{3}(3\mathbf{u_2} - \mathbf{u_5})] + \frac{1}{3}\mathbf{u_5},\ \mathbf{u_3} = [\frac{1}{2}(2\mathbf{u_3} - \mathbf{u_6}) + \frac{1}{6}3\mathbf{u_6}],\ \mathbf{u_4} = [(\mathbf{u_4} - \mathbf{u_7}) + \frac{1}{2}2\mathbf{u_7}] + 0,\ \mathbf{u_5} = 0 + \mathbf{u_5},\ \mathbf{u_6} = \frac{1}{3}3\mathbf{u_6} + 0,\ \mathbf{u_7} = \frac{1}{2}2\mathbf{u_7} + 0,\ \mathbf{u_8} = -(-\mathbf{u_8}) + 0$. Correspondingly, for an arbitrary element $\boldsymbol{\xi_2}$ of $\mathcal{H}_2^3$, the succession of equalities $\boldsymbol{\xi_2} = \sum_{i=\overline{1,8}}\alpha_i\mathbf{u}_i = L_A^3\left(\frac{\alpha_2}{3}\ \mathbf{u_1} + \frac{\alpha_3}{2}\ \mathbf{u_2} + \alpha_4\mathbf{u_3} - \alpha_8\mathbf{u_4} + \frac{\alpha_3+2\alpha_6}{6}\ \mathbf{u_5} + \frac{\alpha_4+\alpha_7}{2}\ \mathbf{u_6}\right) + \left(\alpha_1\mathbf{u_1} + \frac{\alpha_2+3\alpha_5}{3}\ \mathbf{u_5}\right) = L_A^3(\mathcal{H}_2^3) + \left(\alpha_1\mathbf{u_1} + \frac{\alpha_2+3\alpha_5}{3}\ \mathbf{u_5}\right)$ holds. In particular, for the SODE (**3.4**), we have $\boldsymbol{\xi_2} = \begin{pmatrix} \dfrac{d_0}{2}\ q_1^3 + \dfrac{(c_0^2 - 3c_0 - e_0)d_0^2}{2}\ q_1^2q_2 + (2e_0 - e_0c_0)d_0^3\ q_1q_2^2 \\ \dfrac{(c_0 - 2)d_0}{2}\ q_1^2q_2 + (1 - e_0)d_0^2\ q_1q_2^2 \end{pmatrix}$, i.e. $\alpha_1 = \alpha_4 = \alpha_8 = 0,\ \alpha_2 = (c_0 - 2)d_0/2,\ \alpha_3 = (1 - e_0)d_0^2,\ \alpha_5 = d_0/2,\ \alpha_6 = (c_0^2 - 3c_0 - e_0)d_0^2/2,\ \alpha_7 = (2e_0 - e_0c_0)d_0^3$, leading to

$$\mathbf{h} = \begin{pmatrix} \dfrac{(1-3c_0+c_0^2-2e_0)d_0^2}{6}q_1^3 + \dfrac{(2e_0-e_0c_0)d_0^3}{2}q_1^2q_2 \\ \dfrac{(c_0-2)d_0}{6}q_1^3 + \dfrac{(1-e_0)d_0^2}{2}q_1^2q_2 \end{pmatrix}.$$

Consequently, the transformation $\mathbf{q} = \mathbf{r} + \mathbf{h}(\mathbf{r})$ reads

$$\begin{cases} q_1 = r_1 + \dfrac{(1-3c_0+c_0^2-2e_0)d_0^2}{6}r_1^3 + \dfrac{(2e_0-e_0c_0)d_0^3}{2}r_1^2r_2, \\ q_2 = r_2 + \dfrac{(c_0-2)d_0}{6}r_1^3 + \dfrac{(1-e_0)d_0^2}{2}r_1^2r_2, \end{cases}$$

and replaced into (**3.4**) yields (**3.6**). □

Theorem 3.1. *The SODE (3.6) is the normal form of order two for the SODE (3.1). The equilibrium* $(0,\ y_0)$ *is a Bogdanov-Takens degenerated singularity.*

Proof. The form (**3.6**) is a particular case of a general result [1]. □

Corollary 3.1. *The SODE (3.6) is of the form*

$$\begin{cases} \dot{r}_1 = r_2 + r_1^2\Phi_1(r_1), \\ \dot{r}_2 = r_1^2\Phi_2(r_1), \end{cases}$$

where $\Phi_1(r_1),\ \Phi_2(r_1)$ *are polynomials of degree* $k-2,\ k \geq 2$.

$\mathbf{l{=}c{=}0,\ b{=}0, e{\neq}0; b{=}c{=}0, l{=}0, e{\neq}0}$ **and** $\mathbf{l{=}b{=}c{=}0, e{\neq}0, y_0{=}1}$. In all these three cases the nonhyperbolic equilibrium point is $(0,\ 1)$. The coordinate transformation $u_1 = x,\ u_2 = y-1,\ e_1 = e - e_0$ carry the equilibrium $(0,\ 1)$ from $(x,\ y)$ plane into $(0,\ 0)$ from $(u_1,\ u_2)$ plane and SODE (**2.2**) into

$$\begin{cases} \dot{u}_1 = -u_1^2 + u_1u_2, \\ \dot{u}_2 = -(e_1+e_0)u_1 - (e_1+e_0)u_1^2. \end{cases} \quad \textbf{(3.7)}$$

The matrix, associated with the system linearized around $(0,\ 0)$, is $A = \begin{pmatrix} 0 & 0 \\ -e_1-e_0 & 0 \end{pmatrix} \neq \mathbf{0}_2$. For $\mathbf{u} = \mathbf{0}$, we have $detA = 0,\ trA = 0$ and $p_\pm = 0$. Therefore, $(0,\ 1)$ is a double-zero singularity. Let $\mathbf{v}_+ = (0,\ 1),\ \mathbf{v}_- = (-1/e_0,\ 0)$ be two linearly independent eigenvector and associated eigenvector of A and consider the transformation $\mathbf{u} = P\mathbf{n}$ changing the canonical base of $\mathbb{R}^2$ into the base $\{\mathbf{v}_+,\ \mathbf{v}_-\}$, where $P = \{\mathbf{v}_+,\ \mathbf{v}_- |\ A\mathbf{v}_+ = 0,\ A\mathbf{v}_- = \mathbf{v}_+, \langle \mathbf{v}_+,\ \mathbf{v}_- \rangle = 0\}$. Then A assumes the canonical form $P^{-1}AP$. Correspondingly, the system (**3.7**) becomes

$$\begin{cases} \dot{n}_1 = \dfrac{e_1+e_0}{e_0}n_2 - \dfrac{e_1+e_0}{e_0^2}n_2^2, \\ \dot{n}_2 = n_1n_2 + \dfrac{1}{e_0}n_2^2, \end{cases}$$

in a neighborhood of equilibrium point $(0,\ 0)$ and

$$\begin{cases} \dot{n}_1 = n_2 - \dfrac{1}{e_0} n_2^2, \\ \dot{n}_2 = n_1 n_2 + \dfrac{1}{e_0} n_2^2, \end{cases} \tag{3.8}$$

at the origin, namely for $e_1 = 0$.

Theorem 3.2. *The equilibrium point* $(0,\ 1)$ *is a Bogdanov-Takens degenerated singularity. In this case the normal form of the system (**2.2**) is*

$$\begin{cases} \dot{r}_1 = r_2 + \dfrac{1}{2} r_1^2 + O(|\mathbf{r}|^3), \\ \dot{r}_2 = O(|\mathbf{r}|^4). \end{cases} \tag{3.9}$$

Proof. In a similar way we deduced the transformations allowing us to eliminate the non-resonant terms. In the following we present only the results of our study, namely the nonlinear transformations used to determine the normal form (**3.9**), that is

- $$\begin{cases} n_1 = q_1 + \dfrac{1}{2e_0} q_1^3 - \dfrac{1}{e_0} q_1 q_2, \\ n_2 = q_2 + \dfrac{1}{2} q_1^2 + \dfrac{1}{e_0} q_1 q_2, \end{cases}$$
  which transforms the SODE in $\mathbf{n}$ into the SODE in $\mathbf{q}$ and
- $$\begin{cases} q_1 = r_1 - \dfrac{1}{3e_0} r_1^3, \\ q_2 = r_2 + \dfrac{2}{3e_0} r_1^3 + \dfrac{2 - e_0}{2e_0^2} r_1^2 r_2 + \dfrac{1}{e_0^2} r_2^3, \end{cases}$$
  which transforms the SODE in $\mathbf{q}$ into the SODE in $\mathbf{r}$.

□

$\mathbf{e = l = b = 0,\ c \neq 0,\ y_0 = 1}$ **and** $\mathbf{e = b = 0,\ l = 0,\ c \neq 0}$. In all these cases, the singularity $(0,\ 1)$ is of the BT type. The changes $u_1 = x,\ u_2 = y - 1, c_1 = c - c_0$ carry the equilibrium $(0,\ 1)$ at $(0,\ 0)$ and the system (**2.2**) into

$$\begin{cases} \dot{u}_1 = -u_1^2 + u_1 u_2, \\ \dot{u}_2 = (c_1 + c_0) u_1 + (c_1 + c_0) u_1 u_2. \end{cases} \tag{3.10}$$

For $c_1 = 0$ the matrix A is characterized by $detA(\mathbf{0},\ 0) = 0,\ trA(\mathbf{0},\ 0) = 0$ and $p_\pm = 0$. The eigenvector and generalized vector, corresponding to the double-zero eigenvalues, are $\mathbf{v}_+ = (0,\ 1)$ and $\mathbf{v}_- = (1/c_0,\ 0)$ and they satisfy the relations $A\mathbf{v}_+ = 0,\ A\mathbf{v}_- = \mathbf{v}_+,\ \langle \mathbf{v}_+,\ \mathbf{v}_- \rangle = 0$. Thus, we change the canonical base using the transformation $u_1 = n_2/c_0,\ u_2 = n_1$. The system (**3.10**) becomes

$$\begin{cases} \dot{n}_1 = n_2 + n_1 n_2, \\ \dot{n}_2 = n_1 n_2 - n_2^2/c_0. \end{cases} \tag{3.11}$$

Theorem 3.3. *The equilibrium point* $(0,\ 1)$ *is a Bogdanov-Takens degenerated singularity. The normal form of SODE (**2.2**) is*

$$\begin{cases} \dot{r}_1 = r_2 + \dfrac{1}{2}\, r_1^2 + O(|\mathbf{r}|^3), \\ \dot{r}_2 = O(|\mathbf{r}|^4). \end{cases} \tag{3.12}$$

Proof. Similarly, the transformations used to determine the normal form are:

- $$\begin{cases} n_1 = q_1 + \dfrac{c_0 - 1}{2c_0}\, q_1^2, \\ n_2 = q_2 + \dfrac{1}{2}\, q_1^2 - \dfrac{1}{c_0}\, q_1 q_2, \end{cases}$$
  which transforms the SODE in $\mathbf{n}$ into the SODE in $\mathbf{q}$ and
- $$\begin{cases} q_1 = r_1 + \left(\dfrac{1}{6} + \dfrac{1}{3c_0^2} - \dfrac{1}{2c_0}\right) r_1^3, \\ q_2 = r_2 + \dfrac{c_0 - 4}{6c_0}\, r_1^3 + \dfrac{1}{c_0^2}\, r_1^2 r_2, \end{cases}$$
  which transforms the SODE in $\mathbf{q}$ into the SODE in $\mathbf{r}$.

□

4. Discussions

The obtained results concerning the evolution in time of the populations x (free lymphocytes) and y (tumor cells) for the cases described above and provided by the corresponding theoretical classical theorems [5] agree with the numerical results in Figs. (1-3).

In the case when only the parameter e (the coefficient of efficiency of medical cure) varies, then x and y decrease. More precisely, the lymphocytes number decreases very rapidly comparative to tumor cells population, tending to zero. At a certain time, the tumor cells population becomes stable such that the tumor is in dormancy state.

If the free and bound lymphocytes number is equal to 1/maximum lymphocytes number, i.e., $c = 1$, then the evolution of antigens increases and is represented in the plane $(x,\ T)$ by an ascending curve. The same phenomenon is observed at the tumor cells population at less time. Hence, at some time, between lymphocytes and malignant cells dominate the population of tumor cells, i.e., a tumor growth takes place.

If e and c vary simultaneously, then both populations present a decreased evolution in time. Therefore, at a certain time, the malignant cells are in an equilibrium state such that the tumor does not develop.

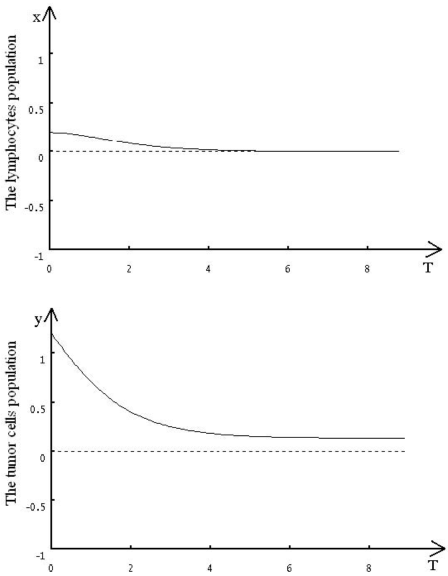

Fig.1. Evolution of the lymphocytes and malignant cells populations for $x_0 = 0.2$, $y_0 = 1.2$, $e = 2.25$.

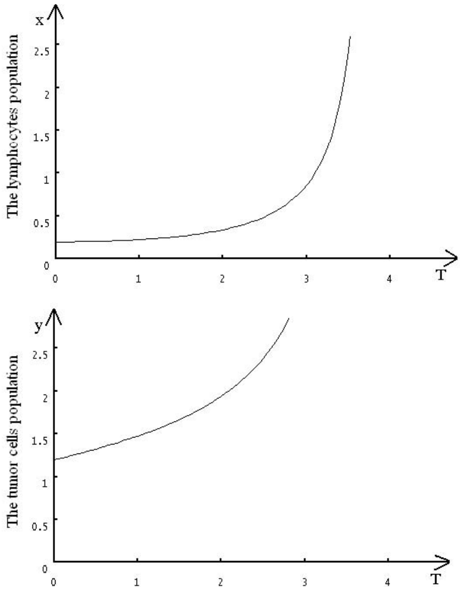

Fig. 2. Evolution of the lymphocytes and malignant cells populations for $x_0 = 0.2$, $y_0 = 1.2$, $c = 1$.

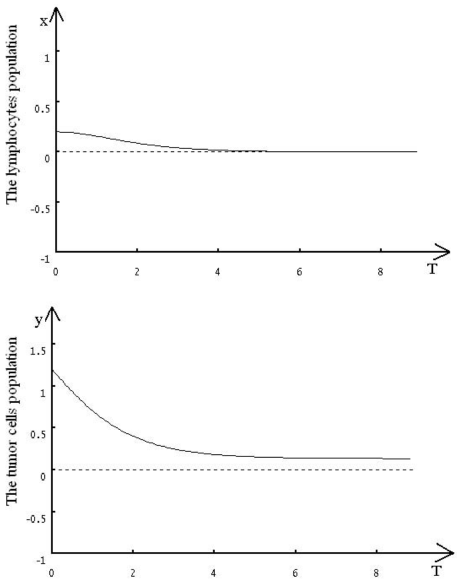

Fig. 3. Evolution of the lymphocytes and malignant cells populations for $x_0 = 0.2$, $y_0 = 1.2$, $e = 2.25$, $c = 1$.

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