Nonlinear Analysis: Modelling and Control, 2003, Vol. 8, No. 2, 55–63

# Analysis of One Model of the Immune System

**A. Kavaliauskas**

Vilnius University
Vilnius Gediminas Technical University
algis.kavaliauskas@mif.vu.lt

Received: 26.07.2003
Accepted: 30.08.2003

**Abstract.** The article deals with development of a tumor in the cylindrical space. A model with two parameters – lymphocytes and tumor cells – described in [1] is taken as a base of the research. Some generalization of the model is done. The research, results of which are described in [2, 3], was continued. The relationship between the surface and volumetric tumor cells of classical forms is obtained. It turns out, that even in general case the trivial stationary point is of a saddle type.

The article particularly deals with the development of a cylindrical tumor. It is considered, that lymphocytes and the medical intervention (chemotherapy or irradiation) keeps down the cell fission of the tumor. Some special parameter is introduced to indicate the influence of the medical cure. In respect of that parameter the bifurcation values of the system are surveyed using the theory of [1, 4]. Some results of the survey are tested with the help of the software package MAPLE.

**Keywords:** immune system, tumor cells, cylindrical surrounding, Hopf bifurcation.

## 1 Model

Let us consider the interaction of two kinds of cells – tumor cells and lymphocytes. Assume, that it takes place only on the surface of the tumor. Lymphocytes multiply without any delay. Denote:

$L$ – a number of free lymphocytes on the tumor surface,

$A$ – a number of tumor cells inside the tumor and on its surface,

$A_S$ – a number of tumor cells on the tumor surface,

$\bar{A}_S$ – a number of tumor cells on the tumor surface, which are not connected to the lymphocytes,

$\bar{A}$ – a number of tumor cells inside the tumor and on its surface, which are not connected to the lymphocytes.

The system of two differential equations is constructed. The variables $L$ and $A$ are treated as the main variables. The other variables can be expressed via the main ones under the following assumptions:

1. Consider function $f$ as a connection of tumor cells on the tumor surface $A_S$ and all the tumor cells $A$:

$$A_S = f(A). \tag{1}$$

The function itself will be analyzed a bit later.

2. Consider the relation between the number of the connected tumor cells $A_S - \bar{A}$ (the connection takes place only on the surface of the tumor) and the number of free tumor surface cells to be defined as:

$$A_S - \bar{A}_S = \bar{A}_S F(L). \tag{2}$$

The function $F$ corresponds here the influence of lymphocytes to the connection of tumor cells. Let's say, that

$$F(0) = 0 \quad \text{and} \quad F'(L) > 0.$$

3. The multiplication speed of the lymphocytes is influenced by two factors: the decline speed of the lymphocytes $g(L),\ \big(g(L) < 0,\ g(L)' < 0,$ $g(0) = 0\big)$ and the growth stimulation speed of the lymphocytes $\bar{A}_S\Phi(L)$. Then

$$L = g(L) + \bar{A}_S\Phi(L). \tag{3}$$

4. The multiplication speed of the tumor cells consists of the growth speed of the tumor cells $G(\bar{A})$ in absence of lymphocytes $\big(G(0) = 0,\ G(A) \geq$

$0\big)$ and the influence of lymphocytes on the tumor cells on its surface $\alpha\bar{A}_S\Phi_1(L)$. It means, that

$$A = G(\bar{A}) - \alpha\bar{A}_S\Phi_1(L). \tag{4}$$

The assumptions (1), (2) and the equation of the balance of the cells $A = \bar{A} + A_S - \bar{A}_S$ result:

$$\bar{A}_S = \frac{f(A)}{1+F(L)}, \quad \bar{A} = A - \frac{f(A)F(L)}{1+F(L)}. \tag{5}$$

After embedding (5) into the system of equations (3), (4) we obtain:

$$\begin{cases} \dot{L} = g(L) + \dfrac{f(A)\Phi(L)}{1+F(L)}, \\ \dot{A} = G\Big(A - \dfrac{f(A)F(L)}{1+F(L)}\Big) - \alpha\,\dfrac{f(A)\Phi_1(L)}{1+F(L)} + H(L,t). \end{cases} \tag{6}$$

In the model [1] we have $g(L) = -\lambda_1 L,\ G(A) = \lambda_2 A,\ f(A) = k_1 A^{2/3}$. $\Phi(L) = \alpha_1 L(1 - L/L_M),\ H(L,t) = 0,\ \Phi_1(L) = \alpha_2 L,\ F(L) = k_2 L$. Let's consider in the future, that $\Phi(L) = \Phi_1(L)$.

The influence of medical cure is reflected by the term

$$H(L,t) = -\gamma(L) sin^2 \omega t.$$

Here $\omega$ – frequency of the medical cure. The term $\gamma(L)$ defines the efficiency of the medical cure. Next try to make some analysis of the second equation from the system (6) after striking an average by the active time $t$.

$$\frac{1}{T}\int_0^T \dots dt, \quad T = \frac{2\pi}{\omega}.$$

It means, that in some sense the influence of the medical cure or irradiation will be taken into account:

$$\begin{cases} \dot{L} = g(L) + \dfrac{f(A)\Phi(L)}{1+F(L)}, \\ \dot{A} = G\Big(A - \dfrac{f(A)F(L)}{1+F(L)}\Big) - \alpha\,\dfrac{f(A)\Phi(L)}{1+F(L)} - \dfrac{\gamma(L)}{2}. \end{cases} \tag{7}$$

## 2 The trivial stationary point

The conditions $g(0) = 0,\ f(0) = 0,\ G(0) = 0$ and $\gamma(0) = 0$ show, that the system (7) has a trivial stationary point. Consider, that the type of the point is determined by the linear part of the system (7):

$$W(L,A) = \begin{bmatrix} g' + H'_L & H'_A \\ G' \cdot \dfrac{f(A)F'(L)}{\big(F(L)+1\big)^2} - \alpha H'_L - \dfrac{\gamma'}{2} & G' \cdot \left(1 - \dfrac{f'(A)F(L)}{1+F(L)}\right) - \alpha H'_A \end{bmatrix},$$

where

$$H(L,A) = \frac{f(A)\Phi(L)}{1+F(L)}, \quad \Phi'_L = \frac{\partial \Phi}{\partial L}, \quad \Phi'_A = \frac{\partial \Phi}{\partial A}.$$

The characteristic equation of it can be written as $\det[W - \lambda e] = \lambda^2 + \sigma\lambda + \Delta = 0$. $\Delta(0,0) = g'G' < 0$ causes, that the stationary point will be of a saddle type. The line $L = 0$ $\big($ if $\Phi(0) = 0\big)$ is the solution of the system (7), for which $A > 0$, i.e. the axis OA is the separatriss of the saddle, along which the solutions of the system recede from the point $(0,0)$. In the other words, in the surrounding of the point the tumor cells multiply most actively.

## 3 Function $f(A)$ in the case, when the tumor growth speed is different in various directions

Let's compare two cases.

**Case 1.** The shape of the tumor is close to the rectangular parallelepiped with the sides $a_0$ and $b_0$ (when $t = 0$) and the height $h_0$. Suppose at the moment of the growth of the tumor $a = a_0 t^\alpha,\ b = b_0 t^\beta,\ h = h_0 t^\gamma$. If $k_s$ – the number of tumor cells in the area unit and $k_v$ – the number of tumor cells in the volume unit, then

$$A_S = 2k_S(a_0 b_0 t^{\alpha+\beta} + b_0 h_0 t^{\beta+\gamma} + a_0 h_0 t^{\gamma+\alpha}),$$
$$A = k_v a_0 b_0 h_0 t^{\alpha+\beta+\gamma}.$$

After elimination of $t$ we obtain:

$$\begin{aligned} &A_S = f(A) = aA^{\frac{\alpha+\beta}{\alpha+\beta+\gamma}} + bA^{\frac{\beta+\gamma}{\alpha+\beta+\gamma}} + cA^{\frac{\alpha+\gamma}{\alpha+\beta+\gamma}}, \\ &a = \frac{2k_s a_0 b_0}{(k_v a_0 b_0 h_0)^{\frac{\alpha+\beta}{\alpha+\beta+\gamma}}}, \quad b = \frac{2k_s b_0 h_0}{(k_v a_0 b_0 h_0)^{\frac{\beta+\gamma}{\alpha+\beta+\gamma}}}, \\ &c = \frac{2k_s a_0 h_0}{(k_v a_0 b_0 h_0)^{\frac{\alpha+\gamma}{\alpha+\beta+\gamma}}}. \end{aligned}$$

If the growth of the tumor is equal in every direction ($\alpha = \beta = \gamma$), then $f(A) = (a + b + c)A^{2/3}$. If the tumor grows only in the direction $h$, ($\alpha = \beta = 0$), then $f(A) = a + (b + c)A$. When $\gamma = 0$ and $\alpha = C$, we have $f(A) = aA + (b + c)A^{1/2}$.

**Case 2.** The shape of the tumor is cylinder. Suppose, its radius varies like $r = r_0 t^{\alpha}$, and its height $h = h_0 t^{\beta}$. Then we have

$$\begin{aligned} &A_S = f(A) = \widetilde{a}A^{\frac{\alpha+\beta}{2\alpha+\beta}} + \widetilde{b}A^{\frac{2\alpha}{2\alpha+\beta}}, \quad \text{where} \\ &\widetilde{a} = \frac{2\pi k_s a_0 h_0}{(\pi k_v a_0^2 h_0)^{\frac{\alpha+\beta}{2\alpha+\beta}}}, \quad \widetilde{b} = \frac{2\pi k_s a_0^2}{(\pi k_v a_0^2 h_0)^{\frac{2\alpha}{2\alpha+\beta}}}. \end{aligned}$$

When $\alpha = \beta$, i.e. the growth of the tumor is equal in the directions $R$ and $H$, then $f(A) = (\widetilde{a} + \widetilde{b})A^{2/3}$. If the tumor grows in the $h$ direction ($\alpha = 0$), then $f(A) = \widetilde{a}A + \widetilde{b}$. When the tumor grows in the $R$ direction ($\beta = 0$), then $f(A) = \widetilde{a}A^{1/2} + \widetilde{b}A$.

The tumor growth in the cylindrical surrounding $f(A) = aA + b$ basically corresponds its one direction growth in the case of rectangular parallelepiped. That's why the wide spectrum of tumor growth cases will be overwhelmed by the analysis of the liner function $f$.

## 4 Development of a tumor in the cylindrical surrounding

Blood vessels, guts or the interior of a bone have a shape, which is close to the cylinder. This consideration let us give the problem some practical approach. At the same time, when $f(A) = aA + b$, (i.e. $f(A)$ – linear function) we deal with wider spectrum of surfaces, than cylinders (Section 4).

Suppose $g(L) = -l_1 L,\ G(A) = l_2 A,\ \gamma(L) = 2\varepsilon L$. Then we have a system:

$$\begin{cases} \dot{L} = -l_1 L + \dfrac{(aA+b)\Phi(L)}{1+F(L)}, \\ \dot{A} = -\varepsilon L + l_2 A - \dfrac{(aA+b)}{1+F(L)}\big(l_2 F(L) + \alpha\Phi(L)\big). \end{cases} \tag{8}$$

Let's concretize the connection functions $\Phi(L) = L,\ F(L) = kL$. The number of parameters can be reduced by introducing the following replacements: $x = kL,\ y = A$. Denote $\varepsilon/k = e,\ (l_2 k + \alpha)/k = c$. Then the following system can be obtained

$$\begin{cases} \dot{x} = -l_1 x + (ay+b)\,\dfrac{x}{1+x}, \\ \dot{y} = -ex + l_2 y - (ay+b)\,c\,\dfrac{x}{1+x}. \end{cases} \tag{9}$$

The system (9) has either two stationary values $(0,0)$ and $(x_0, y_0)$ or one of them $(0,0)$. Here

$$x_0 = \frac{l_1 l_2 - b l_2}{ea + l_1 ca - l_1 l_2}, \quad y_0 = \frac{(e + l_1 c)(l_1 - b)}{ea + l_1 ca - l_1 l_2}. \tag{10}$$

They are positive, when

$$\text{a)} \begin{cases} l_1 > b, \\ ea + l_1 ca - l_1 l_2 > 0, \end{cases} \quad \text{or} \quad \text{b)} \begin{cases} l_1 < b, \\ \varepsilon a + l_1 ca - l_1 l_2 < 0. \end{cases} \tag{11}$$

Let's make the characteristic equation of (9) at the point $(x_0, y_0)$:

$$\lambda^2 + \sigma\lambda + \Delta = 0, \tag{12}$$

$$\sigma = l_1 - l_2 - \frac{ay_0 + b}{(1+x_0)^2} + \frac{acx_0}{1+x_0}, \tag{13}$$

$$\Delta = -l_1 l_2 - \frac{ay_0 + b}{(1+x_0)^2} l_2 + \frac{l_1 acx_0 + eax_0}{1+x_0}. \tag{14}$$

At the point $(0,0)$ the $\Delta = l_2(b - l_1)$ has a type of a saddle, when $b < l_1$. If $b > l_1$ , then $\sigma < 0$, this stationary point is an unstable focus or a node. This result is different from that in the Section 2, because here we have $f(0) \neq 0$.

At the nontrivial stationary point (14)

$$\Delta = \frac{x_0}{1+x_0}(-l_1 l_2 + l_1 ac + ea).$$

Therefore in the case b) of (11) this point will be of a saddle type. Let's analyze it in a more detailed way in the case a) of (11). In this case the stationary point $(0,0)$ is of a saddle type (because $l_1 > b$). Let's observe the system change, which depends on the parameter $e$. Suppose all the other parameters are fixed. Physiologically it means, that the influence of medical cure on the tumor will be observed.

## 5 Bifurcation value of the parameter $e$

Let's apply the theorem about Hopf bifurcation [1] to the system (9). Consider $e$ as a variable parameter. The real part of the root of the characteristic equation (12) can be written as

$$\mathrm{Re}\lambda_{1,2}(e) = -\frac{\sigma}{2}.$$

The bifurcation value $e_0$ can be found from

$$\mathrm{Re}\lambda_{1,2}(e) = 0 \iff e_0 = \frac{l_1^2 - bl_1 + bl_2 - abc}{a}.$$

It should be kept in mind here, that the roots are complex. In that case $l_1 - l_2 + ac > 0$ should be satisfied. The condition

$$\frac{d}{de}\mathrm{Re}\lambda_{1,2}\big|_{l=l_0} > 0.$$

is satisfied, when $l_1 > b$, because

$$\frac{d}{de}\mathrm{Re}\lambda_{1,2}(e) = \frac{l_2 a(l_1 - b)(ac + l_1)}{2(ea + l_1 ca - bl_2)^2}.$$

Let's move the stationary point $(x_0, y_0)$ into the origin of coordinates by introducing the replacement $x = x_1 + x_0,\ y = y_1 + y_0$. Then (9) turns into

$$\begin{cases} \dot{x}_1 = -l_1 x - l_1 x_0 + \dfrac{(ay_1 + ay_0 + b)(x_1 + x_0)}{1 + x_1 + x_0}, \\ \dot{y}_1 = -ex_1 - ex_0 + l_2 y_1 + l_2 y_0 - \dfrac{c\,(ay_1 + ay_0 + b)(x_1 + x_0)}{1 + x_1 + x_0}. \end{cases} \tag{15}$$

In order to satisfy the last condition of the theorem that the stationary point $(0,0)$ of the system (15) is asymptotically stable when $e = e_0$, the theory of indices will be applied. Denote the linear part of the system (15) at the point $(0,0)$ as $A$ and turn the system into canonic form:

$$M^{-1}AM = B, \tag{16}$$

$$B=\begin{bmatrix} 0 & \omega_0 \\ -\omega_0 & 0 \end{bmatrix}, \quad \omega_0 \mathrm{Im}\lambda_{1,2}\big|_{e=e_0} = (l_1-b)\sqrt{\frac{l_2(-l_2+ac+l_1)}{(l_1-b)(l_2+ac)}}.$$

From the system of equations (16) the matrix $M$ can be found:

$$M = \begin{bmatrix} -\omega_0 & a_{11} \\ 0 & a_{21} \end{bmatrix},$$

where $a_{11}$ and $a_{21}$ – the coefficients of the matrix $A$:

$$a_{11} = -l_1 + \frac{b+ay_0}{(1+x_0)^2}, \quad a_{21} = -e_0 - \frac{(b+ay_0)c}{(1+x_0)^2}.$$

After the change of variables in the system (15)

$$\begin{pmatrix} x_1 \\ y_1 \end{pmatrix} = M \begin{pmatrix} x_2 \\ y_2 \end{pmatrix}$$

we can result:

$$\begin{aligned}
\dot{x}_2 =& \left(\frac{a_{11}e_0}{a_{21}} - l_1\right)x_2 + \left(\frac{1}{\omega_0} - \frac{a_{11}c_0}{a_{21}\omega_0} + \frac{l_2}{\omega_0}\right)a_{11}y_2 \\
&+ \frac{l_1}{\omega_0}x_0 - \frac{e_0x_0a_{11}}{a_{21}\omega_0} + \frac{a_{11}l_2y_0}{a_{21}\omega_0} \\
&- \frac{(aa_{21}y_2+ay_0+b)(-\omega_0x_2+a_{11}y_2+x_0)}{1-\omega_0x_2+a_{11}y_2+x_0}\cdot\left(\frac{1}{\omega_0}+\frac{a_{11}c}{a_{21}\omega_0}\right),
\end{aligned} \tag{17}$$

$$\begin{aligned}
\dot{y}_2 =& \frac{e_0\omega_0}{a_{21}}x_2 + \left(l_2 - \frac{e_0a_{11}}{a_{21}}\right)y_2 - \frac{e_0x_0}{a_{21}} + \frac{l_2y_0}{a_{21}} \\
&- \frac{c\,(aa_{21}y_2+ay_0+b)(-\omega_0x_2+a_{11}y_2+x_0)}{(1-\omega_0x_2+a_{11}y_2+x_0)a_{21}}.
\end{aligned}$$

The stationary point $(0,0)$ is stable for those parameter values, for which the index

$$\begin{aligned}
I =& \omega_0(Y^1_{111} + Y^1_{122} + Y^2_{112} + Y^2_{222}) \\
&+ (Y^1_{11}Y^2_{11} - Y^1_{11}Y^2_{12} + Y^2_{11}Y^2_{12} + Y^2_{22}Y^2_{12} - Y^1_{22}Y^1_{12} - Y^1_{22}Y^2_{22})
\end{aligned} \tag{18}$$

is negative. The upper index in the formula (18) indicates, from which of the two equations (17) the left side is taken. The lower indices indicate the exponent and quantity of partial derivatives (1 means the derivative by $x_2$, 2 – the derivative by $y_2$). All the partial derivatives are calculated at the point $(0,0)$. Those quite long calculations are done by using the software package MAPLE. With help of this package the general expression (18) was obtained and also some particular cases were analyzed. One of them is given below.

The value of the index $I$ is negative for the parameters $l_1=3,\ l_2=1,\ a=2,$ $b = 2,\ c = 0.1$. It can be also calculated, that in this case the parameter $e_0 = 2.3$ is Hopf bifurcation value.

With help of MAPLE was also checked, that the stationary point $(0,0)$ is a stable focus, when $e < e_0$ (for example, $e = 2.28$). When $e > e_0$ (for example $e = 2.31$), it turns into unstable focus. Physiologically it means, that the system (9) has a stable position $(x_0, y_0)$, when $e > e_0$. In this case the growth of the tumor is stopped by lymphocytes and the medical cure. After extension of influence of the medical cure (the parameter $e$) the stable equilibrium is lost and the tumor starts "oscillate". Because of those "oscillations" the tumor can disappear or the patient can dye.

## References

1. Errousmit D., Pleis K. *Obyknovennye differencial'nye uravneniya. Kachestvennaya teoriya s prilozheniyami,* Mir, Moscow, p. 239, 1986

2. Kavaliauskas A. "Sistemos nestabilumo srities nustatymas naudojant n-tosios eilės determinanto išreiškimą per k-tosios eilės determinantus", *LMD konferencijos darbai,* **41**, p. 200–205, 2001

3. Kavaliauskas A. "Imuninės sistemos tyrimas kokybiniais metodais", *LMD konferencijos darbai,* **42**, p. 651–655, 2002

4. Kuznetsov Y.A. *Elements of applied bifurcation theory,* Springer-Verlag, New York Inc., p. 515, 1995