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MATHEMATICAL MODELLING OF THE DEVELOPMENT OF A CYLINDRICAL TUMOUR

Algis Kavaliauskas, Aleksas Domarkas
Vilnius University, Faculty of Mathematics and Informatics, Lithuania
algis.kavaliauskas@mif.vu.lt, aleksas@ieva.mif.vu.lt

Abstract The article deals with interaction of tumour cells and leucocytes in the cylindrical cavities. This type of interaction is typical in the cases of development of a tumour in the intestine, blood vessel or in a bone cavity. Two cases are separated: the case of soft and hard tumour. In the case of a solid tumour, leucocytes can interact only with the surface cells of the tumour. This type of interaction is described by the system of two nonlinear first order differential equations. The expressions of stationary points are obtained and analysis of their stability is performed. In the case of a soft tumour, leucocytes interact with tumour cells in the whole volume. To describe this type of interaction the system of two partial differential equations with first order derivatives and initial and boundary conditions is proposed. An algorithm for computing the numeric solution of the mathematical model is applied. In this case the diffusion of leucocytes and their ability to reach the tumour cells in the whole volume of the tumour is included. The algorithm is constructed and the system is solved numerically. Bifurcation curve is obtained. It separates two qualitatively different regions on the two parameter plane. Under the same initial parameters in the first region development of the tumour cells cannot be stopped, whereas in the second region leukocytes defeat the tumour cells.

Keywords: mathematical modelling, diffusion, qualitative analysis, tumour.

Introduction

Cancer is one of the most difficult diseases and a leading cause of premature death. In the industrial nations it is the second fatal disease after the cardiovascular diseases (Araujo and McElwain, 2004). A great research effort is being devoted to find an effective and permanent cure for cancer. Much progress has been made in understanding the dynamic and tracking tumour and immune populations over time. As R. P. Araujo and D. L. S. MCElwain noticed in (Bellomo and Sleeman, 2006) ‘experimentalists and clinicians alike are becoming increasingly aware of the possibilities afforded by mathematical modelling, recognising that current medical techniques and experimental approaches are often unable to distinguish between various possible mechanisms underlying important aspects of tumour development’. N. Bellomo, N. K. Li and P. K. Maini in their review of selected topics related to the modelling of cancer (Araujo and McElwain, 2004) take up the position, that ‘mathematics alone cannot solve the problem of cancer. However, applied mathematics may be able to provide a framework in which experimental results can be interpreted, and a quantitative analysis of external actions to control neoplastic growth can be developed. Specifically, models and simulations can reduce the amount of experimentation necessary for drug and therapy development‘. Furthermore, ‘The

mathematical theory developed might not only provide a detailed description of the spatiotemporal evolution of the system, but may also help us understand and manipulate aspects of the process that are difficult to access experimentally'. (Araujo and McElwain, 2004).

Gatenby and Maini, (Bellomo et al., 2008) even suggest the development of a research line to be called *mathematical oncology*.

Enormous number of theoretical and experimental publications is devoted to solid tumour growth beginning with the early works by Burton (1966) and Greenspan, (1972) (Burton, 1966), (Greenspan, 1972) culminating in the most recent by Papadogiorgaki M. and others, developing a continuous three-dimensional model of avascular glioma spatio-temporal evolution (Papadogiorgaki et al., 2013), Verkman, performing mathematical modelling of slowed diffusion in the extracellular space (Verkman, 2013), Yang D, and others, analyzing the free boundary problem modelling tumour regrowth (Yang et al., 2013).

In this paper we have studied the special cases when tumour develops in the space of some certain form – cylindrical volume. For example, it can be blood vessel, intestine, or a bone cavity. Two mathematical models are proposed according to the possibilities to access the tumour cells. The type of interaction when leucocytes can access only the surface cells of the solid tumour is described by the system of two nonlinear first order differential equations. Some statements concerning stationary solutions are proved.

In case, when leucocytes are able to contact the tumour cells in the whole volume (soft tumour) the system of two partial differential equations with first order derivatives and initial and boundary conditions is proposed. Aiming to distinguish between the two regions in a two parameter space where the development of the tumour can be stopped by leucocytes and where the stopping fails we solve the system numerically. The bifurcation curve and numerical values of the parameters are provided.

1. Mathematical model of the interaction of tumour cells and leucocytes on the tumour surface.

Let's say that two types of cells are in interaction – tumour cells and leucocytes. Suppose the interaction is possible only on the surface of the tumour. This model can be described by two simple differential equations.

Denote:
L – number of leucocytes on the tumour surface,
A – total number of tumour cells including its surface,
A_s – number of the tumour cells on its surface,
$\tilde{A}_s$ – number of tumour surface cells undamaged by leucocytes,
$\tilde{A}$ – total number of undamaged tumour cells (on its surface and inside).

Let's make a system of two differential equations considering the variables L and A as the key variables. All other variables will be expressed with respect to them.

Then we have

$$\dot{L} = g(L) + \bar{A}_s \Phi(L). \tag{1}$$

Here the speed of reproduction of leucocytes consists of two summands. The first one – *g(L)* – describes the usual speed of leucocytes reproduction. In general it is negative and such that

$$g(0) = 0,\ g(L) < 0,\ g'(L) < 0. \tag{2}$$

The second summand reflects the reproduction of leucocytes under the stimulation of the presence of tumour cells. (It is described in (Yang et al., 2013)).

Equation of the reproduction of tumour cells is

$$\dot{A} = G(\bar{A}) - \alpha \bar{A}_s \Phi_1(L). \tag{3}$$

The function *G* defines the own speed of the reproduction of the tumour cells. Let's say that

$$G(0) = 0, \quad G(\bar{A}) \geq 0. \tag{4}$$

The member $\alpha \bar{A}_s \Phi_1(L)$ defines the impact of leucocytes on the reproduction speed of the tumour cells.

Let's eliminate the supplementary variables $\bar{A}$ and $\bar{A}_s$ from these main equations. Then we have:

$$\begin{aligned} \bar{A} &= A - \frac{f(A)F(L)}{1+F(L)}, \\ \bar{A}_s &= \frac{f(A)}{1+F(L)}. \end{aligned} \tag{5}$$

The function *f* defines connection between the number of tumour cells A_s on the tumour surface and the number of all tumour cells *A*, i.e. $A_s = f(A)$. This function depends on the shape of the tumour. Always $f(0) = 0$. The function *F* describes here the influence of leucocytes on the connection of tumour cells. Suppose $F(0) = 0$ and $F'(L) > 0$.

Rewriting $\bar{A}$ and $\bar{A}_s$ in terms of A and L, as it was done in (Yang et al., 2013), we have:

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

Suppose leukocytes can fuse together with tumour cells only on the surface of the tumour and suppose the tumour is allocated in a cylindrical cavity. It could be a blood vessel, intestine, or a bone cavity. Let's analyze the system of differential equations (6) and concretize the functions:

$$g(L) = -l_1 L, \quad G(A) = l_2 A, \quad \Phi(L) = k_1 L, \quad F(L) = k_2 L \ \ and \ \ \Phi(L) = \Phi_1(L).$$

After substitution in (6) we have:

$$\begin{cases} \dot{L} = -l_1 L + \dfrac{(aA^{\frac{1}{2}} + bA)k_1 L}{1 + k_2 L}, \\ \dot{A} = l_2 A - \dfrac{(aA^{\frac{1}{2}} + bA)}{1 + k_2 L}(k_2 l_2 + \alpha k_1)L. \end{cases} \tag{7}$$

In the system (7) we have additional function $f(A) = aA^{\frac{1}{2}} + bA$ which reflects the shape of the tumour. This function is derived in (Yang et al., 2013). It is used in the case when the development of a tumour goes in the direction of the cylinder radius. Namely this case is analyzed below.

Let us define the new variables:

$$x = k_2 L, \ \ y = A, \quad c = \frac{k_2 l + \alpha k_1}{k_2}, \quad k_1 = d. \tag{8}$$

Then the system (7) can be written as:

$$\begin{cases} \dot{x} = -l_1 x + (ay^{\frac{1}{2}} + by)d\dfrac{x}{1+x} = F_1(x, y), \\ \dot{y} = l_2 y - (ay^{\frac{1}{2}} + by)c\dfrac{x}{1+x} = F_2(x, y). \end{cases} \tag{9}$$

Statement.

System of differential equations (9) always has at least one nontrivial stationary solution. To be more specific, when $bk - l_1 < 0$ the system (9) has two nontrivial stationary solutions. When $bk - l_1 > 0$ it has one nontrivial stationary solution.

Proof.

Stationary solutions of the system of differential equations (9) are obtained from the system of equations

$$\begin{cases} F_1(x, y) = 0, \\ F_2(x, y) = 0. \end{cases} \tag{10}$$

Multiplying the first equation of the system (10) by *c* and the second equation by *d* and adding them together we have:

$$-l_1 cx + l_2 dy = 0, \tag{11}$$

or

$$y = \frac{l_1 c}{l_2 d} x. \tag{12}$$

If we denote $\frac{l_1 c}{l_2 d} = k,$ then $y=kx.$

After elimination of y from the first equation of the system (10) we have:

$$x((bk - l_1)x + ak^{\frac{1}{2}} x^{\frac{1}{2}} - l_1) = 0. \tag{13}$$

The equation has one trivial solution x=0, y=0. The other solutions can be obtained after solving the quadratic equation

$$(bk - l_1)x + ak^{\frac{1}{2}} x^{\frac{1}{2}} - l_1 = 0. \tag{14}$$

When $D = a^2 k + 4l_1(bk - l_1) > 0$ the equation has two real solutions

$$x_{1,2}^{\frac{1}{2}} = \frac{-ak^{\frac{1}{2}} \pm \sqrt{D}}{2(bk - l_1)} \tag{15}$$

if only the right side of the equation is non negative.

So, when $bk - l_1 < 0 \ \ and \ \ -ak^{\frac{1}{2}} + \sqrt{D} < 0$ we have two real non trivial stationary solutions.

When $bk - l_1 > 0 \ \ and \ \ -ak^{\frac{1}{2}} + \sqrt{D} < 0$ the equation has no real solutions.

Finally when $bk - l_1 > 0 \ \ and \ \ -ak^{\frac{1}{2}} + \sqrt{D} > 0$ the equation has the only real solution

$$x^{\frac{1}{2}} = \frac{-ak^{\frac{1}{2}} + \sqrt{D}}{2(bk - l_1)}. \tag{16}$$

Lemma.

For every value of the parameters the following is valid:

$$(bk - l_1)(-ak^{\frac{1}{2}} + \sqrt{D}) > 0. \tag{17}$$

Proof.

Let's make some equivalent reorganization which proves the lemma:

$$-ak^{\frac{1}{2}} + \sqrt{D} < 0 \ \Leftrightarrow \ \sqrt{D} < ak^{\frac{1}{2}} \ \Leftrightarrow \ D < a^2 k \ \Leftrightarrow \ a^2 k + 4l_1(bk - l_1) < a^2 k \ \Leftrightarrow \ bk - l_1 < 0.$$

According to the lemma, the case that the quadratic equation analyzed above has no solutions is impossible.

Finalizing we have:

1. When $bk - l_1 < 0$ the system (10) has two stationary nontrivial solutions

$$\left(\frac{(ak^{\frac{1}{2}} + \sqrt{D})^2}{4(bk - l_1)^2}; k\frac{(ak^{\frac{1}{2}} + \sqrt{D})^2}{4(bk - l_1)^2} \right); \quad \left(\frac{(-ak^{\frac{1}{2}} + \sqrt{D})^2}{4(bk - l_1)^2}; k\frac{(-ak^{\frac{1}{2}} + \sqrt{D})^2}{4(bk - l_1)^2} \right). \tag{18}$$

2. When $bk - l_1 > 0$ the system has one stationary solution

$$\left(\frac{(-ak^{\frac{1}{2}} + \sqrt{D})^2}{4(bk - l_1)^2}; k\frac{(-ak^{\frac{1}{2}} + \sqrt{D})^2}{4(bk - l_1)^2} \right). \tag{19}$$

In this way the statement is proved.

In order to make the qualitative analysis of the stationary solutions let us construct characteristic equation of the system (9):

$$\begin{vmatrix} \frac{\partial F_1}{\partial x} - \lambda & \frac{\partial F_1}{\partial y} \\ \frac{\partial F_1}{\partial x} & \frac{\partial F_1}{\partial y} - \lambda \end{vmatrix} = \lambda^2 + \sigma\lambda + \Delta = 0, \tag{20}$$

Here the partial derivatives

$$\begin{aligned} \frac{\partial F_1}{\partial x} &= -l_1 + (ay^{\frac{1}{2}} + by)\frac{d}{(1+x)^2}, \\ \frac{\partial F_1}{\partial y} &= (\frac{1}{2}ay^{-\frac{1}{2}} + b)\frac{dx}{1+x}, \\ \frac{\partial F_2}{\partial x} &= -(ay^{\frac{1}{2}} + by)\frac{c}{(1+x)^2}, \\ \frac{\partial F_2}{\partial y} &= l_2 - (\frac{1}{2}ay^{-\frac{1}{2}} + b)\frac{cx}{1+x}. \end{aligned} \tag{21}$$

are calculated at the stationary point (x_0, y_0).

This way we have:

$$\sigma(x,y) = -\left(\frac{\partial F_1}{\partial x} + \frac{\partial F_2}{\partial y}\right) = l_1 - l_2 - (ay^{\frac{1}{2}} + by)(1+x)^{-2}d + (\frac{1}{2}ay^{-\frac{1}{2}} + b)(1+x)^{-1}cx, \tag{22}$$

$$\Delta(x,y) = \begin{vmatrix} -l_1 + (ay^{\frac{1}{2}} + by)d(1+x)^{-2} & (\frac{1}{2}ay^{-\frac{1}{2}} + b)dx(1+x)^{-1} \\ -(ay^{\frac{1}{2}} + by)\dfrac{c}{(1+x)^2} & l_2 - (\frac{1}{2}ay^{-\frac{1}{2}} + b)cx(1+x)^{-1} \end{vmatrix}. \tag{23}$$

Let's calculate the determinant:

$$\Delta = -l_1 l_2 + l_2(ay^{\frac{1}{2}} + by)d(1+x)^{-2} + l_1(\frac{1}{2}ay^{-\frac{1}{2}} + b)cx(1+x)^{-1}. \tag{24}$$

Statement

Characteristic equation has real solutions in nontrivial stationary points when

$$l_1 + l_2 - AB'd - A'Bc \geq 2\sqrt{ABA'B'cd} \ . \tag{25}$$

Here $A(y) = A = ay^{\frac{1}{2}} + by, \quad B(x) = B = \dfrac{x}{1+x}.$

Proof

Whereas

$$A'_y = A' = \frac{1}{2}ay^{-\frac{1}{2}} + b, \quad B'_x = B' = \frac{1}{(1+x)^2} \tag{26}$$

and $\sigma = l_1 - l_2 - AB'd + A'Bc$, (27)

$$\Delta = -l_1 l_2 + l_2 AB'd + l_1 A'Bc \tag{28}$$

the discriminant of the quadratic equation can be written down as

$$D = \sigma^2 - 4\Delta = l_1^2 + l_2^2 + d^2A^2B'^2 + c^2A'^2B^2 + 2l_1l_2 - 2l_1dAB' - 2l_1cA'B - 2l_2dAB' - 2l_2cA'B - 2ABA'B'cd. \tag{29}$$

Therefore $D = (l_1 + l_2 - AB'd - A'Bc)^2 - 4ABA'B'cd$.

Whenever $x_0 > 0$ *and* $y_0 > 0$,

we have $A(y_0) > 0, \ B(x_0) > 0, \ A'(y_0) > 0$ *and* $B'(x_0) > 0.$

When $D \geq 0$, the characteristic equation has real roots. When $D<0$, its roots are in the set of complex numbers.

The statement is proved.

Now some conclusions can be drawn concerning nontrivial points. When $\Delta < 0$, the stationary point is a saddle point and therefore it is unstable. When $D < 0$, the stationary point is a focus point. It means that it is stable when $\sigma > 0$ and it is unstable when $\sigma < 0$. When $D > 0$, the stationary point is a nod point. It is stable when $\Delta > 0$ and $\sigma < 0$.

Stability of the stationary solution can be compared with a tumour which has stopped growing. It does not change in time. In our case the reason of its stability would be the stable equilibrium in the contest between leucocytes and tumour cells.

2. Mathematical model of the interaction of leucocytes and tumour cells in the whole volume of the tumour (in a cylindrical cavity).

Denote $u_1(t,x)$ – the density of leucocytes at the cross-section of a target tissue at the distance of x units from the origin of coordinates at the moment t,

$u_2(t,x)$ – the density of tumour cells.

Let's analyze the system of differential equations

$$\begin{cases} \dfrac{\partial u_1}{\partial t} = D_1 \dfrac{\partial^2 u_1}{\partial x^2} - k_1 u_1 u_2, \\ \dfrac{\partial u_2}{\partial t} = D_2 \dfrac{\partial^2 u_2}{\partial x^2} - k_1 u_1 u_2 + k_2 u_2. \end{cases} \tag{30}$$

In the first equation the reproduction speed of leucocytes consists of two summands. The first one is the diffusion speed at which leucocytes penetrate into the tumour. It is proportional to D_1. The second summand reflects the losses of leucocytes when they contact the tumour cells.

The second equation describes the reproduction speed of the tumour cells. The right side of it consists of three summands. The first one describes diffusion of the tumour cells.

The second summand describes losses of the tumour cells which they suffer because of the activity of leucocytes. Consider that the fusion of a tumour cell and a leukocyte results in death of both cells. For this reason the constant of proportionality k_1 is the same as in the first equation.

The last summand $k_2 u_2$ shows the reproduction speed of the tumour cells.

Let's define the following initial conditions

$$\begin{aligned} &u_1(0,x) = u_{10} = const, \\ &u_2(0,x) = \varphi(x), \ if \ 0 < x < d, \end{aligned} \tag{31}$$

and boundary conditions

$$
\begin{aligned}
&u_1(t,0) = \bar{u}_{10},\\
&u_1(t,d) = \bar{u}_{10},\\
&u_2(t,0) = \bar{u}_{20},\\
&u_2(t,d) = \bar{u}_{20},\\
&\frac{\partial u_2(t,0)}{\partial x} = \bar{u}_{21},\\
&\frac{\partial u_2(t,d)}{\partial x} = \bar{u}_{21}.
\end{aligned}
\tag{32}
$$

Consider $\bar{u}_{10} = const,\ \bar{u}_{20} = 0,\ \bar{u}_{21} = 0.$

Let us distinguish two key parameters. One of them is k_1. It characterizes the magnitude of interaction between leucocytes and tumour cells. The parameter depends on immunity of an organism and it varies subject to different means of treatment.

Another key parameter is $u_{10} = u_0$. It indicates the initial number of leucocytes. The parameter characterizes reaction of an organism to the appearance of tumour cells.

The main task of this paragraph is to find the bifurcation curve which divides the plane of those two key parameters into two regions. In one of them the development of a tumour cells cannot be stopped, in another – the number of tumour cells decreases in time.

To solve the problem numerically the software MAPLE was used. The total number of tumour cells was taken into account

$$u_2(t) = \int_0^d u_2(t,x)dx \tag{33}$$

and two cases were observed: $u_2(+\infty) = 0$ or $u_2(+\infty) = \infty$. The curve separating these two cases is shown in the chart below.

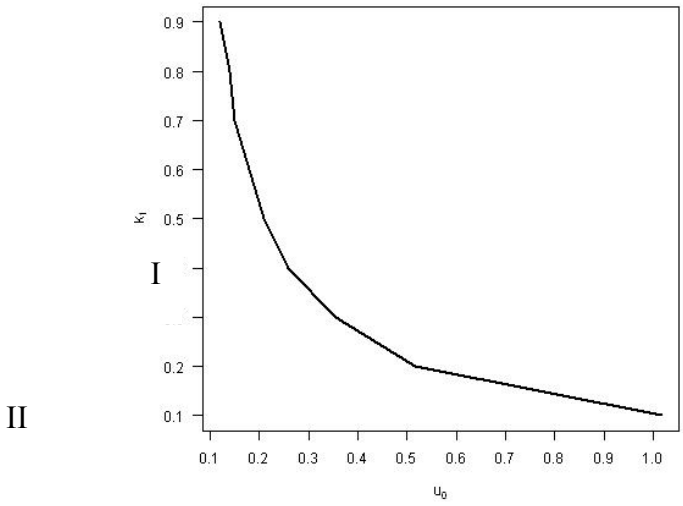

Figure 1. The bifurcation curve in the plane of parameters k_1 and u_0.

In the region II the tumour cells overcome leucocytes. In the region I leucocytes win.

This problem was solved, when $\varphi(x) = 2,\ 0 < x < 1,\ d = 1,\ k_2 = 0.1,\ D_1 = 1,\ D_2 = 0.1.$

Calculations were done for k_1 varying in the interval [0;1]. Exact values are provided in the table 1:

Table 1. Calculations k_1 varying in the interval [0;1].

k_1	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
u_o	1.0168	0.516	0.355	0.26	0.21	0.18	0.15	0.14	0.12

Conclusions

In this article mathematical models of solid and soft tumour in a cylindrical cavity were proposed and analyzed. In the case of a solid tumour the conditions of stabilization of the development of the tumour were determined. It happens (from the mathematical point of view) when non trivial stationary points – focus point and node point – are obtained.

Stability of the non-zero stationary solution can be compared with a tumour which has stopped growing. In a sense of physiology, development of the tumour stops at some certain level. One of the possible mathematical interpretations of this phenomenon is the stability of the stationary solution. Thus under some certain conditions even the growth of a malignant tumour can be stopped.

In the case of a soft tumour the stabilization of its development was not observed. The numerical results of the mathematical modelling demonstrate two possible outcomes: either the tumour extends or disappears.

The curve presented in the article shows under which value of the parameter k_1 having fixed parameter $u_{10} = u_0$ (which indicates the number of leucocytes) the qualitative change of the development of the tumour happens, i.e., transition from $u_2(+\infty) = \infty$ to $u_2(+\infty) = 0$.

On the other hand increase of the parameter k_1 is caused by variety of physical, biological and chemical factors.

This model encountering the diffusion of cells is to be developed in the future together with the specialists of the corresponding field of medicine.

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A. Kavaliauskas is associate professor at the department of Differential Equations and Numerical Mathematics in Vilnius University. He gives courses of Qualitative theory of differential equations and Calculus. His scientific interests include application of the qualitative theory of differential equations in medicine and biology as well as in the stability analysis of electromechanical systems.

A. Domarkas is associate professor at the department of Differential Equations and Numerical Mathematics in Vilnius University. He gives several courses in the field of differential equations and algebra. He is a co-author of the "Equations of Mathematical Physics" textbook. His scientific interests include methods of computer algebra, nonlinear Schrödinger equations.

CILINDRINIO AUGLIO VYSTYMOSI MATEMATINIS MODELIAVIMAS

Algis Kavaliauskas, Aleksas Domarkas

Santrauka

Straipsnyje nagrinėjama auglio ląstelių ir leukocitų tarpusavio sąveika cilindrinės formos ertmėse. Tokio tipo sąveika būdinga tuo atveju, kai auglys vystosi žarnoje, kraujagyslėje arba kaulo ertmėje. Išskiriami du atvejai: kieto ir minkšto auglio. Kieto auglio atveju leukocitai gali sąveikauti su auglio ląstelėmis tik ant auglio paviršiaus. Šis atvejis aprašomas dviejų netiesinių pirmojo laipsnio paprastųjų diferencialinių lygčių sistema. Gaunamos stacionariųjų taškų išraiškos, atliekama jų stabilumo analizė. Minkšto auglio atveju sistemą sudaro dvi diferencialinės lygtys dalinėmis išvestinėmis. Šiuo atveju įskaitoma leukocitų difuzija ir galimybė leukocitams pasiekti auglio ląsteles visame auglio užimame tūryje. Sudaromas algoritmas ir skaitiniu būdu išsprendžiama sistema. Gaunama bifurkacinė kreivė dviejų parametrų plokštumoje.

Pagrindiniai žodžiai: matematinis modeliavimas, difuzija, kokybinė analizė, auglys.