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Research Article


# Modeling the treatment of tumor cells in a solid tumor

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**Abstract**

It is well known that the theory of differential equations and some software packages are important tools for solving several actual problems from different real world domains.

The novelty of this paper is the fact that the mathematical model of evolution of leukemic cells is adapted to the case of tumor cells, from a solid tumor, together with the treatment of the solid homogeneous tumor.

Using the paper Dingli and Michor [D. Dingli, F. Michor, STEM-CELLS, 24 (2006), 2603–2610], we consider the model of evolution of a leukemic population for the case of solid tumors. ©2014 All rights reserved.

*Keywords:* Cauchy problem, mathematical model, solid tumor, tumor cells, system of differential equations.
*2010 MSC:* 92B05, 34C60, 34A12.

## 1. Introduction

In this paper we will first study the mathematical model of evolution of a population of tumor cells from a solid tumor [8] as it follows:

$$\begin{cases} N' = \frac{aN}{1+bN} - cN, \quad a, b, c > 0 \\ N(0) = N_0 \end{cases}$$

We will also study the system:

$$\begin{cases} N' = \frac{aN}{1+bN} - cN - \mu AN \\ A' = \alpha(t) - \lambda A - \gamma AN \end{cases}$$

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that models the chemotherapy treatment of a tumor using a constant infusion.

The importance of this approach is given by the following aspects. First of all, the solid tumor is a mass of newly formed tissue that evolves in an organism by the exaggerated and pathological multiplication of some cells. Secondly, the mathematical research in medicine and biology is very complex (see, e.g. [1]–[9]), since it requires an in-depth study and knowledge of the medical and biological field (medical and biological terms, methods specially created for the recovery treatment of the pacients) on which the research is done.

## 2. The growth model of a population of tumor cells from a solid tumor

The slow growth of a population of cells can provide a more precise and accurate description of how the tumor evolves, but the discrepancy appears when the tumor grows in size. In this moment, the battle for survival cannot be ignored anymore. Further, we will consider a special mathematical model named the growth model of a population of tumor cells from a solid tumor, taking into account the competition for resources (without specifying which are the resources).

We consider the following model:

$$\begin{cases} N' = \frac{aN}{1+bN} - cN \\ N(0) = N_0 \end{cases} ; \ a, b, c > 0 \tag{2.1}$$

where $N(t)-$ represents the number of cells from a solid tumor that modifies in time, the constants: $a-$ represents the growth rate of cells population, $c-$ the death rate of cells population and the coefficient $\frac{1}{1+bN}-$ models the crowding effect.
The differential equation has two equilibrium points $N_1 = 0$ and $N_2 = \frac{a-c}{bc} := d$. We consider $N_2 > 0$ if $a > c$.

**The solution of the problem in implicit form:**

The Cauchy Problem (2.1) is solvable and the solution in implicit form [5] can be emphasized. The solution is:

$$\frac{N(t)}{(N(t) - \frac{a-c}{bc})^{\frac{a}{c}}} = \frac{N_0}{(N_0 - \frac{a-c}{bc})^{\frac{a}{c}}} e^{(a-c)t}$$

The Maple commands (see, e.g.[6, 10]) for calculating the solution of problem (2.1) are represented above, considering the values $a = 1$, $b = 0.5$ and $c = 0.5$ :

$> restart;$
$> ec1 := diff(N(t), t) = (a * N(t)/(1 + b * N(t))) - c * N(t);$
$> sist := ec1;$
$> a := 1;$
$> b := 0.5;$
$> c := 0.5;$
$> with(DEtools) :$
$> with(plots) :$
$> dsolve(\{sist\}, \{N(t)\});$

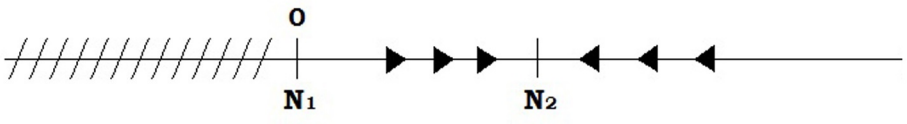
$$[\{N(t) = 2 - \frac{1}{2}\frac{(-1 + \sqrt{1 + 8e^{\frac{1}{2}t}\_C1})e^{-\frac{1}{2}t}}{\_C1}, N(t) = 2 + \frac{1}{2}\frac{e^{-\frac{1}{2}t}(1 + \sqrt{1 + 8e^{\frac{1}{2}t}\_C1})}{\_C1}\}]$$

Further, we will study the stationary solutions of the differential equation.
Next, we will study the stability of the equilibrium points.

We denote: $f(N) = \frac{aN}{1+bN} - cN$

**Case I:** If $a - c \geq 0$, then we obtain the following table and the corresponding phase portrait:

| $N$ | $-\infty$ | | | $N_1 = 0$ | | | | $N_2 = \frac{a-c}{bc} = d$ | | | $+\infty$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $f(N)$ | $-$ | $-$ | $-$ | $0$ | $+$ | $+$ | $+$ | $0$ | $-$ | $-$ | $-$ |



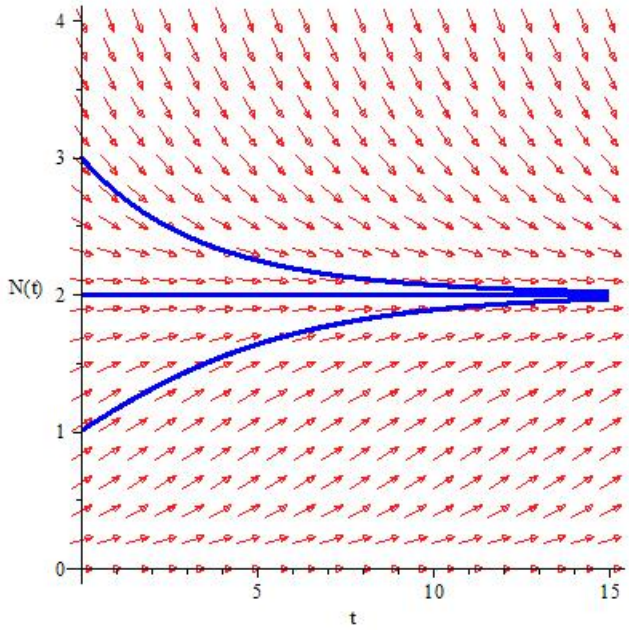

In this case, we have two stationary solutions $N_1 = 0$, $N_2 = d$, and their stability is: $N_1-$ unstable and $N_2-$ asymptotically stable, which means that for any initial positive value of the malign cells, the total number of these is stabilized at the value $N_2(t) = d$.

The graph with the Maple commands (see, e.g.[6, 10]) of the function $N$ is represented for the values $a = 1$, $b = 0.5$ and $c = 0.5$ :

$> restart;$
$> ec1 := diff(N(t), t) = (a * N(t)/(1 + b * N(t))) - c * N(t);$
$> sist := ec1;$
$> a := 1;$
$> b := 0.5;$
$> c := 0.5;$
$> with(DEtools) :$
$> with(plots) :$
$> dsolve(\{sist\}, \{N(t)\});$

$$[\{N(t) = 2 - \frac{1}{2}\frac{(-1 + \sqrt{1 + 8e^{\frac{1}{2}t}\_C1})e^{-\frac{1}{2}t}}{\_C1}, N(t) = 2 + \frac{1}{2}\frac{e^{-\frac{1}{2}t}(1 + \sqrt{1 + 8e^{\frac{1}{2}t}\_C1})}{\_C1}\}]$$

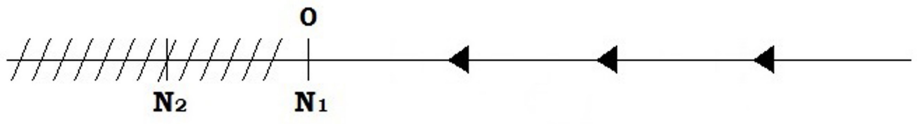
$> DEplot([sist], [N(t)], t = 0..15, N = 0..4, [[N(0) = 1], [N(0) = 2], [N(0) = 3]], arrows = medium, linecolor = blue, stepsize = 0.01);$



*Remark* 2.1. In the case of $a = c$ then $N_1 = N_2 = 0$, so in the sign table the interval $[N_1; N_2]$ disappears and the differential equation has only one equilibrium point $N^* = 0$ which is asymptotically stable.

**Case II:** If $a - c < 0$, then we will obtain the following table with the corresponding phase portrait:

| $N$ | $-\infty$ | | | $N_2 = \frac{a-c}{bc} = d$ | | | | $N_1 = 0$ | | | $+\infty$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $f(N)$ | $-$ | $-$ | $-$ | $0$ | $+$ | $+$ | $+$ | $0$ | $-$ | $-$ | $-$ |




In this case, we have a unique positive stationary solution $N_1 = 0$ which is asymptotically stable (this means that for any initial value of the malign cells, the total number of these decreases to $N_1 = 0$, so they disappear in time).

The graph with the Maple commands (see, e.g.[6, 10]) of the function $N$ is represented for the values $a = 2$, $b = 0.5$ and $c = 3$ :

$> restart;$

$> ec1 := diff(N(t), t) = (a * N(t)/(1 + b * N(t))) - c * N(t);$

$> sist := ec1;$

$> a := 2;$

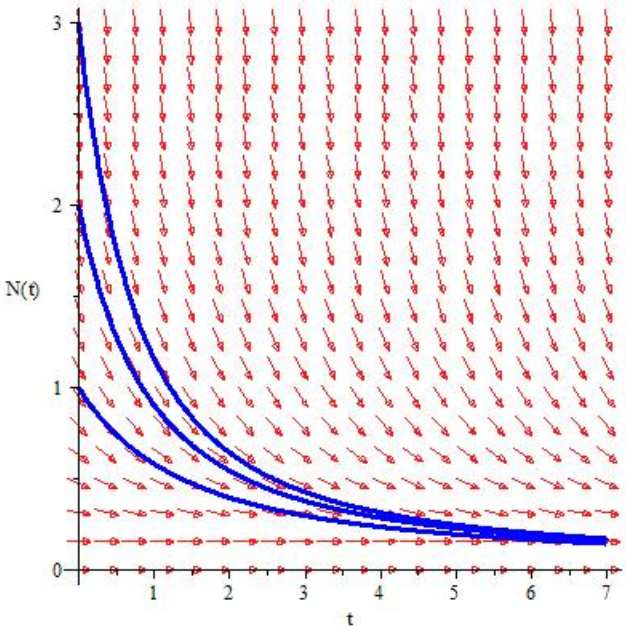
$> b := 0.5;$

$> c := 3;$

$> with(DEtools) :$

$> with(plots) :$

$> DEplot([sist], [N(t)], t = 0..4, N = 0..3, [[N(0) = 1], [N(0) = 2], [N(0) = 3]], arrows = medium, linecolor = blue, stepsize = 0.01);$




When the number of malign cells is stabilized, there exists the posibility to operate the tumor and the patients can be cured, along with the chemotherapeutic procedures. Following the chemotherapeutic treatment after the operation increases the death rate, more precisely the parameter $c$ so as to be greater than the parameter $a$, which coresponds to the situation when the solution $N_1 = 0$ is asymptotically stable, even if after the operation still remain malign cells. In this context, these cells will disappear in time.

## 3. The treatment of the homogeneous solid tumor

Considering a tumor developed in vitro, which increases in the absence of terapeutic intervention and follows a growth on a growing tumor cells population mathematical model from a solid tumor. A medicine which destroys the malign cells is injected to the patient. We note $N(t)$ the number of cells at the moment $t$ and $A(t)$ the average concentration of medicine and we suppose that:

$$N' = \frac{aN}{1+bN} - cN - \mu AN \equiv f(N, A) \tag{3.1}$$

$$A' = \alpha(t) - \lambda A - \gamma AN \equiv g(N, A) \tag{3.2}$$

with the initial conditions,

$$\begin{cases} N(0) = N_0 \\ A(0) = A_0 \end{cases}$$

where:

$\mu-$ represents the rate with which the medicine destroys the malign cells;

$\lambda-$ represents the descreasing rate of the concentration of the medicine;

$\gamma-$ represents the rate at which the medicine destroys the malign cells;

$\alpha(t)-$ represents the rate with which the medicine is injected in the organism. We consider a single delivery mode by constant infusion: $\alpha(t) = \alpha_\infty, \forall t \geq 0$.

When $\alpha_\infty = 0$ (no medicine is administered), therefore $N(t) \to d$, $t \to \infty$, then we apply the treatment in case $a > c$. When the tumor is in a continuously mode exposed to a cytostatic medicine, the concentration of the tumor and the concentration of the medicine will evolve to equilibrium values. To study the impact of the continuous infusion of medicine, we will identify and classify the equilibrium solutions of the equations (3.1) and (3.2), taking into account how they depend on $\alpha_\infty$ (and, therefore, the quantity of the administered medicine).

When $\gamma = 0$ (the medicine keeps its efficiency effect), the system consisting of the equations (3.1) and (3.2) has the following form:

$$\begin{cases} N' = \frac{aN}{1+bN} - cN - \mu AN = f_1(N, A) \\ A' = \alpha_\infty - \lambda A = f_2(N, A) \end{cases} ; \ a, b, c, \mu > 0,$$

In the first equation, the constants $a, b$ respective $c$ denote the proliferation rate, i.e. the ability of tumor cells to carry when the medicine is not administered and $\mu$ represents the rate with which the medicine kills the cancer cells. In the second equation, $\alpha_\infty$ represents the quantity of drug administered by infusion and $\lambda$ represents the rate of decomposition.

Next, we will determine the equilibrium points by solving the system:

$$\begin{cases} \alpha_\infty - \lambda A = 0 \\ \frac{aN}{1+bN} - cN - \mu AN = 0 \end{cases}$$

By calculation results: we have the equilibrium points $X_1(N_1^*, A^*)$ and $X_2(N_2^*, A^*)$ where

$$A^* = \frac{\alpha_\infty}{\lambda}, \ N_1^* = 0 \text{ and } N_2^* = \frac{a - c - \mu A^*}{b(\mu A^* + c)}.$$

We will study the stability of the equilibrium points through the first approximation method:

The Jacobian matrix is:

$$J_f(N, A) = \begin{pmatrix} \frac{\partial f_1}{\partial N}(N, A) & \frac{\partial f_1}{\partial A}(N, A) \\ \frac{\partial f_2}{\partial N}(N, A) & \frac{\partial f_2}{\partial A}(N, A) \end{pmatrix} = \begin{pmatrix} \frac{a}{(1+bN)^2} - c - \mu A & -\mu N \\ 0 & -\lambda \end{pmatrix}$$

For $X_1^*(0, \frac{\alpha_\infty}{\lambda})$ :

$$J_f(0, \frac{\alpha_\infty}{\lambda}) = \begin{pmatrix} a - c - \frac{\mu\alpha_\infty}{\lambda} & 0 \\ 0 & -\lambda \end{pmatrix}$$

and

$$\begin{cases} \eta_1 = a - c - \frac{\mu\alpha_\infty}{\lambda} \\ \eta_2 = -\lambda < 0 \end{cases}$$

If $a - c < \frac{\mu\alpha_\infty}{\lambda}$ then the point $X_1^*(0, \frac{\alpha_\infty}{\lambda})$ is asymptotically stable, so the treatment succeeds.
If $a - c > \frac{\mu\alpha_\infty}{\lambda}$ then the point $X_1^*(0, \frac{\alpha_\infty}{\lambda})$ is unstable.

For $X_2^*(\frac{a-c-\mu A^*}{b(\mu A^*+c)}, \frac{\alpha_\infty}{\lambda})$ :

$$J_f(\frac{a - c - \mu A^*}{b(\mu A^* + c)}, \frac{\alpha_\infty}{\lambda}) = \begin{pmatrix} -\frac{ca\lambda^2+\mu\alpha_\infty a\lambda-c^2\lambda^2-2c\lambda\mu\alpha_\infty-\mu^2\alpha_\infty^2}{a\lambda^2} & -\frac{\mu(a\lambda-c\lambda-\mu\alpha_\infty)}{b(c\lambda+\mu\alpha_\infty)} \\ 0 & -\lambda \end{pmatrix}$$

$$det(\eta I_2 - J_f) = 0 \Longleftrightarrow \begin{cases} \eta_1 = -\frac{ca\lambda^2+\mu\alpha_\infty a\lambda-c^2\lambda^2-2c\lambda\mu\alpha_\infty-\mu^2\alpha_\infty^2}{a\lambda^2} \\ \eta_2 = -\lambda < 0 \end{cases}$$

If $a\lambda(c\lambda + \mu\alpha_\infty) > (c\lambda + \mu\alpha_\infty)^2 \Leftrightarrow a\lambda > c\lambda + \mu\alpha_\infty \Leftrightarrow a - c > \frac{\mu\alpha_\infty}{\lambda}$, then the point $X_2^*$ is asymptotically stable, so the malign cell population tends to $N_2^*$, meaning that the treatment does not succeeds.
If $ca\lambda^2 + \mu\alpha_\infty a\lambda < (c\lambda + \mu\alpha_\infty)^2 \Leftrightarrow a - c < \frac{\mu\alpha_\infty}{\lambda}$, then the point $X_2^*$ is unstable.

When $\gamma \neq 0$ (the medicine does not keeps its efficiency effect), for the determination of the equilibrium points, the equations (3.1) and (3.2) shall be reduced to:

$$0 = N(\frac{a}{1 + bN} - c - \mu A),$$
$$0 = \alpha_\infty - \lambda A - \gamma AN$$

therefore

$$N = 0 \; and \; A = \frac{\alpha_\infty}{\lambda},$$

or

$$0 = \gamma bcN^2 + (\gamma c + \lambda bc + \mu\alpha_\infty b)N + \mu\alpha_\infty - a \text{ and } A = \frac{\alpha_\infty}{\lambda + \gamma N} \tag{3.3}$$

Now for a specific tumor and for a particular medicine, the parameters $a, b, c, \mu, \lambda, \gamma$ are fixed, the only one parameter over which we will put certain conditions is $\alpha_\infty$, that will give us the bifurcation parameter.

Using elementary calculations on the equation (3.3) we obtain:

$\Delta = (\gamma c - \mu\alpha_\infty b)^2 + 2\gamma\lambda bc^2 + \lambda b^2c^2 + 2\mu\alpha_\infty\lambda b^2c + 4\gamma abc > 0$, thus we obtain two real distinct solution $N_1, N_2$.

We also have:

$$\begin{cases} N_1 + N_2 = -\frac{\gamma c+\lambda bc+\mu\alpha_\infty b}{\gamma bc} < 0 \\ N_1 \cdot N_2 = \frac{\mu\alpha_\infty - a}{\gamma bc} \end{cases}$$

Because we are interested only in the positive stationary solutions we will consider the situation $N_1 \cdot N_2 = \frac{\mu\alpha_\infty - a}{\gamma bc} < 0$ (because otherwise if $N_1 \cdot N_2 > 0 \Rightarrow N_1, N_2 < 0$).

**Case I:** If $\alpha_\infty < \frac{a}{\mu}$ will result that $N_1 \cdot N_2 < 0$, so $N_1$, $N_2$ will have different signs. Let $N_1 < 0$ this situation does not have biological signification, i.e. $N_2 > 0$ it will group together with $A_2 = \frac{\alpha_\infty}{\lambda + \gamma N_2} > 0$.

This situation is inconvenient because the number of diseased cells is positive, in this case we infer that the treatment does not have the desired effect if the point $(N_2, A_2)$ is stable.

**Case II:** If $\alpha_\infty > \frac{a}{\mu}$ will result that $\begin{cases} N_1 \cdot N_2 > 0 \\ N_1 + N_2 < 0 \end{cases} \Rightarrow N_1, N_2 < 0$ this situation does not have biological signification.

**Case III:** If $\alpha_\infty = \frac{a}{\mu}$ will result that $\begin{cases} N_1 \cdot N_2 = 0 \\ N_1 + N_2 < 0 \end{cases}$. Then $N_1 = 0$ will group together with $A = \frac{\alpha_\infty}{\lambda}$ (the equilibrium solution that coincides with the first solution found), i.e. $N_2 < 0$ this situation is not appropriate.

The unique solution that leads to the null solution of the diseased cells, meaning that the only chance that the treatment to take effect upon the diseased cells is in the Case III, when $X(0, \frac{\alpha_\infty}{\lambda})$.

We study further the case when the treatment succeeds, i.e., in which condition the point of equilibrium $X^*(0, \frac{\alpha_\infty}{\lambda})$ is asymptotically stable.

For Case III, when $\gamma > 0$ and $N^* = 0$, $A^* = \frac{\alpha_\infty}{\lambda}$ then:

$$f_1(N, A) = \frac{aN}{1 + bN} - cN - \mu AN$$

$$f_2(N, A) = \alpha_\infty - \lambda A - \gamma AN$$

The Jacobian matrix is:

$$J_{f=(f_1,f_2)}(N, A) = \begin{pmatrix} \frac{a-aNb}{(1+bN)^2} - c - \mu A & -\mu N \\ -\gamma A & -\lambda - \gamma N \end{pmatrix}$$

For $X^*(0, \frac{\alpha_\infty}{\lambda})$ :

$$J_f\left(0, \frac{\alpha_\infty}{\lambda}\right) = \begin{pmatrix} a - c - \mu\frac{\alpha_\infty}{\lambda} & 0 \\ -\gamma\frac{\alpha_\infty}{\lambda} & -\lambda \end{pmatrix}$$

and

$$\begin{cases} \eta_1 = a - c - \mu\frac{\alpha_\infty}{\lambda} \\ \eta_2 = -\lambda < 0 \end{cases}$$

If $a - c < \mu\frac{\alpha_\infty}{\lambda}$ then the point $X^*(0, \frac{\alpha_\infty}{\lambda})$ is asymptotically stable for $\eta_1 < 0$, so the treatment succeeds.

*Remark* 3.1. We have the same conclusion as in the case $\gamma = 0$ for the point of equilibrium $X_1^*(0, \frac{\alpha_\infty}{\lambda})$.

## 4. Conclusion:

This study on the stability of stationary solutions of the mathematical model of population growth of tumor cells in a solid tumor, was focused on the behavior of the solutions depending on the initial condition $N_0$ and the values of the parameters $a$, $b$, $c$, $\lambda$ and $\gamma$. When the diseased cell count becomes low, it is possible to operate the tumor and combined with chemotherapy procedures, the patient can heal. In the second part of the work, namely the homogeneous solid tumor treatment, we obtained specific solutions which are asymptotically stable. The unique solution which suits us as the treatment to succeed is that where the solution $N^* = 0$ is asymptotically stable. For the case in which the treatment does not keeps its efficiency effect, we determined the balance points and studied the stability of the equilibrium solution, by the method of the first approximation. We obtained certain conditions on the parameter of the model from where we could deduct if the treatment fails or not. We are interested only in the positive solutions, because the negative ones do not have biological significance.

This study gives us the opportunity to observe and analyze the evolution of these tumor cells in a solid tumor, and depending on the evolution of these cells it is possible to operate the tumor and combined with chemotherapy procedures (the treatment of the homogeneous, solid tumor), the patient can heal. Chemotherapy treatment after surgery practically increases the mortality rate of tumor cells, so even though there might remain diseased cells after surgery, they will disappear in time.

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