THE MODEL OF NUTRIENTS INFLUENCE ON THE TUMOR GROWTH

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Abstract. In this article a model of tumor growth is considered. The model is based on the reaction-diffusion equation that describes the distribution of nutrients within the tissue. Our aim was to predict the influence of nutrients on the tumor development. In the tissue the nutrients are transformed into energy, which supports the transfer of chemical and electrical signals and also transfer and copy the information in the tumor cells. We investigate, from a mathematical point of view, under which conditions this process takes place and how it affects the evolution of the tumor.

1. Introduction. In the recent years a variety of mathematical models for tumor growth have been developed and studied in the literature [3, 6, 9, 10, 17, 18, 19] and references therein. Many of the tumor models are based on the reaction-diffusion equations and mass conservation law. For example authors in [9], [10] study the changes of $\sigma(r, t)$, i.e. the nutrient concentration at radius $r$ and time $t$. It is assumed that the nutrient is consumed by tumor cells with constant rate $a$ by equation

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \sigma}{\partial r} \right) = a.$$ 

The changes of $R$ are governed by the mass conservation law, i.e.,

$$\frac{1}{4\pi} \frac{d}{dt} \left( \frac{4}{3} \pi R^3 \right) = S - Q,$$

where $R(t)$ is the outer tumor radius at time $t$, $S$ and $Q$ denote the net rates of proliferation and apoptosis, respectively.

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Authors in [6] consider the tumor model which is represented by equation
\[
\frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \sigma}{\partial r} \right) - \Gamma \sigma = 0, \quad 0 < r < R(t), \quad \Gamma > 0, \quad t > 0,
\]
and in the paper [18] authors investigate the equation
\[
d \frac{\partial \sigma}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \sigma}{\partial r} \right) - a, \quad 0 < r < R(t), \quad t > 0,
\]
where \( \sigma = \sigma(r, t) \) is concentration of nutrient, \( a \) is the consumption rate of nutrient, \( d \) is a constant, \( r \) is the radial space variable and \( R(t) \) is the radius of the tumor. The analysis of the tumor model is presented.

In [17] the author studies global stability of steady state solutions to one dimensional model
\[
\frac{\partial \sigma}{\partial t} = \frac{\partial^2 \sigma}{\partial z^2} - \lambda \sigma, \quad \text{in} \ B(t), \quad t > 0,
\]
\[
\frac{\partial \sigma}{\partial z}(0, t) = 0, \quad \sigma(R(t), t) = \sigma_1,
\]
\[
\sigma(z, 0) = \sigma_0(z), \quad \text{in} \ B(0),
\]
\[
\frac{\partial s}{\partial t} = \mu \int_0^{s(t)} (\sigma - \bar{\sigma}) \, dz, \quad t > 0,
\]
\[
s(0) = z_0,
\]
where \( B(t) = \{ z : 0 < z < s(t) \} \), \( s(t) \) which represents the growing boundary of the tumor is unknown function, \( \lambda, \mu \) are positive constants. Term \( \lambda \sigma \) is the consumption rate of nutrient in a unit volume, \( \sigma_1 \) denotes the external concentration of nutrients, which is assumed to be constant, \( c \) is the ratio of the nutrient diffusion time scale to the tumor growth time scale. The term
\[
\mu \int_0^{s(t)} \sigma \, dz
\]
is the total volume increase in a unit time interval induced by cell proliferation, the proliferation rate is \( \mu \sigma \). The term
\[
\mu \int_0^{s(t)} \bar{\sigma} \, dz
\]
is the total volume decrease in a unit time interval caused by natural death and the natural death rate is \( \mu \bar{\sigma} \).

For the tumor growth model the authors Byrne and Chaplain [3] are using the one-dimensional reaction-diffusion equation
\[
\frac{\partial \sigma(r, t)}{\partial t} = \frac{D_1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \sigma(r, t)}{\partial r} \right) + \Gamma (\sigma_B - \sigma(r, t)) - \lambda \sigma(r, t) - g_1(\sigma(r, t), \beta),
\]
where \( r, t \) are the spatial and temporal independent variables. For the survival of tumor, the nutrient is supplying via the capillary network at a rate \( \Gamma (\sigma - \sigma_B) \), where \( \sigma \) is the nutrient concentration in the tumor (or tissue), \( \sigma_B \) is the constant nutrient concentration in the tumor’s vasculature and constant \( \Gamma \) is the rate of blood-tissue transfer per unit length. Nutrient diffuses throughout the tumor with constant diffusion coefficient \( D_1 \) and is consumed at the rate \( \lambda \sigma \). The presence of inhibitor \( \beta \) in the tumor acts as a sink of nutrient at rate \( g_1(\sigma, \beta) \). The authors in [3] present the numerical simulations of the governing equations of the model.
In this paper we consider the equation
\[
\frac{\partial \sigma(x,t)}{\partial t} = d_1 \frac{\partial^2 \sigma(x,t)}{\partial x^2} + \gamma(x,t)[\sigma_1 - \sigma(x,t)] - \lambda(t-\tau) \frac{\partial f \left( \int_0^x (\sigma(s,t) - \sigma_1) \, ds \right)}{\partial x}, \quad 0 \leq x \leq a(t), \quad t \geq \tau > 0, \tag{1}
\]
where \(x, t\) are the spatial and temporal independent variables, \(\sigma(x,t)\) is the nutrient concentration in the tumor (or tissue), \(\sigma_1\) is the constant nutrient concentration in the tumor’s vasculature. The function \(\gamma(x,t)\) is the rate of blood-tissue transfer per unit length. The nutrient is supplying via the capillary network at a rate \(\gamma(x,t)[\sigma(x,t) - \sigma_1]\). Constant \(d_1\) is the diffusion coefficient. In \(\lambda(t-\tau)\), \(\tau\) is the time required to consume nutrients. The function \(a(t)\) represents the boundary of the tumor (cf.[17]). The term \(\frac{\partial f \left( \int_0^x (\sigma(s,t) - \sigma_1) \, ds \right)}{\partial x}\) reflects the rate of change of a total nutrient concentration on the segment \(0 \leq s \leq x, t \geq \tau\).

With respect to \(1\) throughout we will assume the following conditions: \(d_1, \sigma_1, \tau \in (0, \infty), \sigma : [0, \infty) \times [0, \infty) \to (0, \infty)\), is two times continuously differentiable function in \(x\) and continuously differentiable in \(t\), \(\gamma : [0, \infty) \times [0, \infty) \to (0, \infty)\), is continuously differentiable in \(x\) and continuous in \(t\), \(\lambda \in C([\tau, \infty), (0, \infty)), a \in C^1([0, \infty), (0, \infty))\), \(f(x,t)\) is continuously differentiable function in \(x\) and continuous in \(t\), \(f(0,t) = 0, f\) is a nondecreasing function. According to boundary conditions
\[
\sigma(a(t),t) = q(t), \quad t \geq \tau,
\]
\[
\frac{\partial \sigma(a(t),t)}{\partial x} - \frac{\partial \sigma(0,t)}{\partial x} = g(t), \quad t \geq \tau,
\]
\[
\int_0^{a(t)} \frac{\partial \gamma(x,t)}{\partial x} \int_0^x \sigma(s,t) \, ds \, dx = r(t), \quad t \geq \tau,
\]
where \(q \in C([0, \infty), (0, \infty))\), \(g, r \in C([0, \infty), R)\), we can rewrite \(1\) in the following way.

Integrating \(1\) we obtain
\[
\int_0^{a(t)} \frac{\partial \sigma(x,t)}{\partial t} \, dx = d_1 \left( \frac{\partial \sigma(a(t),t)}{\partial x} - \frac{\partial \sigma(0,t)}{\partial x} \right) + \sigma_1 \int_0^{a(t)} \gamma(x,t) \, dx
\]
\[- \int_0^{a(t)} \gamma(x,t) \sigma(x,t) \, dx - \int_0^{a(t)} \lambda(t-\tau) \frac{\partial f \left( \int_0^x (\sigma(s,t) - \sigma_1) \, ds \right)}{\partial x} \, dx, \quad t \geq \tau.
\]
We put
\[
N(t) = \int_0^{a(t)} \sigma(x,t) \, dx.
\]
Then we get
\[
N'(t) = a'(t)\sigma(a(t),t) + \int_0^{a(t)} \frac{\partial \sigma(x,t)}{\partial t} \, dx = a'(t)q(t) + \int_0^{a(t)} \frac{\partial \sigma(x,t)}{\partial t} \, dx,
\]
\[
\int_0^{a(t)} \gamma(x,t) \sigma(x,t) \, dx = \gamma(a(t),t)N(t) - \int_0^{a(t)} \frac{\partial \gamma(x,t)}{\partial x} \int_0^x \sigma(s,t) \, ds \, dx,
\]
\[
\int_0^{a(t)} \lambda(t-\tau) \frac{\partial f \left( \int_0^x (\sigma(s,t) - \sigma_1) \, ds \right)}{\partial x} \, dx
\]
\[
= \lambda(t-\tau)[f\int_0^{a(t)} (\sigma(s,t) - \sigma_1) \, ds) - f(0,t)] = \lambda(t-\tau)f(N(t) - \sigma_1a(t)),
\]
We consider the map

\[ S \]

Let

\[ t \]

Then equation 2 has a positive solution which is bounded by the functions v, w and bounded functions \( v, w \) and nonempty subset of a Banach space \((Schauder's \ Fixed \ Point \ Theorem)\)

Theorem 1.1. Let \( \Omega \) be a closed, convex and nonempty subset of a Banach space \( X \). Let \( S : \Omega \to \Omega \) be a continuous mapping such that \( S\Omega \) is a relatively compact subset of \( X \). Then \( S \) has at least one fixed point in \( \Omega \). That is there exists an \( x \in \Omega \) such that \( Sx = x \).

2. The existence theorems. In this section we investigate the existence of positive solution for the equation 2.

Theorem 2.1. Suppose that there exists a bounded function \( a \in C^1([0, \infty), (0, \infty)) \) and bounded functions \( v, w \in C^1([0, \infty), (0, \infty)) \), constant \( K \geq 0 \) such that

\[ v(t) \leq w(t), \quad t \geq 0, \quad (3) \]
\[ w(t) - w(\tau) - v(t) + v(\tau) \geq 0, \quad 0 \leq t \leq \tau, \quad (4) \]
\[ \frac{1}{w(t)} \left( K + \int_{t}^{\infty} \left[ \gamma(a(s), s)w(s) + \lambda(s - \tau)f(w(s) - \sigma_1a(s)) - r(s) - a'(s)q(s) \right. \right. \\
\[ \left. - d_1g(s) - \sigma_1h(s) \right] ds \right) \leq 1 \leq \frac{1}{v(t)} \left( K + \int_{t}^{\infty} \left[ \gamma(a(s), s)v(s) + \lambda(s - \tau) \right. \right. \\
\[ \left. - f(v(s) - \sigma_1a(s)) - r(s) - a'(s)q(s) - d_1g(s) - \sigma_1h(s) \right] ds \right), \quad t \geq \tau. \quad (5) \]

Then equation 2 has a positive solution which is bounded by the functions \( v(t), w(t), t \geq \tau \).

Proof. Let \( B = \{ N \in C([0, \infty), (0, \infty)) \} \) be the Banach space with the norm \( ||N|| = \sup_{0 \leq t} |N(t)| < \infty \). We define a closed, bounded and convex subset \( \Omega \) of \( B \) as follows

\[ \Omega = \{ N = N(t) \in B : v(t) \leq N(t) \leq w(t), \quad t \geq 0 \}. \]

We consider the map \( S : \Omega \to B \) as follows

\[ (SN)(t) = \begin{cases} 
K + \int_{t}^{\infty} \left[ \gamma(a(s), s)N(s) + \lambda(s - \tau)f(N(s) - \sigma_1a(s)) \right. \\
\left. - r(s) - a'(s)q(s) - d_1g(s) - \sigma_1h(s) \right] ds, \quad t \geq \tau, \\
(SN)(\tau) + w(t) - w(\tau), \quad 0 \leq t \leq \tau.
\end{cases} \]

We will show that for any \( N \in \Omega \) we have \( SN \in \Omega \). For every \( N \in \Omega \) and \( t \geq \tau \), we obtain

\[ \int_{0}^{\alpha(t)} \gamma(x, t) \, dx = h(t). \]
(SN)(t) ≤ K + \int_t^\infty \left[ \gamma(a(s), s)w(s) + \lambda(s - \tau)f(w(s) - \sigma_1a(s)) - r(s) \\
-a'(s)q(s) - d_1g(s) - \sigma_1h(s) \right] ds ≤ w(t). \hspace{1cm} (6)

Since \((SN)(\tau) ≤ w(\tau), for t \in [0, \tau]\) we get
\[
(SN)(t) = (SN)(\tau) + w(t) - w(\tau) ≤ w(\tau) + w(t) - w(\tau) = w(t).
\]

Furthermore for \(N \in \Omega, t ≥ \tau\), we obtain
\[
(SN)(t) ≥ K + \int_t^\infty \left[ \gamma(a(s), s)v(s) + \lambda(s - \tau)f(v(s) - \sigma_1a(s)) \\
-r(s) - a'(s)q(s) - d_1g(s) - \sigma_1h(s) \right] ds ≥ v(t).
\]

Since for \(t \in [0, \tau]\), \(w(t) - w(\tau) + v(\tau) ≥ v(t)\) and \((SN)(\tau) ≥ v(\tau)\), we get
\[
(SN)(t) = (SN)(\tau) + w(t) - w(\tau) ≥ v(\tau) + w(t) - w(\tau) ≥ v(t).
\]

Thus we have proved that \(SN \in \Omega\) for any \(N \in \Omega\).

We now show that \(S\) is completely continuous. First we will show that \(S\) is continuous. Let \(N_k(t) \in \Omega\) be such that \(N_k(t) \to N(t)\) as \(k \to \infty\). Because \(\Omega\) is closed, \(N = N(t) \in \Omega\). For \(t ≥ \tau\) we get
\[
\| (SN_k)(t) - (SN)(t) \| = | \int_0^\tau (\gamma(a(s), s)[N_k(s) - N(s)] + \lambda(s - \tau)[f(N_k(s) - \sigma_1a(s)) \\
-f(N(s) - \sigma_1a(s))] ) ds | ≤ \int_0^\tau (\gamma(a(s), s)[N_k(s) - N(s)] \\
+\lambda(s - \tau)[f(N_k(s) - \sigma_1a(s)) - f(N(s) - \sigma_1a(s))]) ds.
\]

With regard to 6 and since \(w(t)\) is bounded, it follows that
\[
\int_\tau^\infty \left[ \gamma(a(s), s)w(s) + \lambda(s - \tau)f(w(s) - \sigma_1a(s)) - r(s) \\
-a'(s)q(s) - d_1g(s) - \sigma_1h(s) \right] ds < \infty, \hspace{1cm} (7)
\]

and since \(|N_k(s) - N(s)| \to 0\) as \(k \to \infty\), by applying the Lebesgue dominated convergence theorem we obtain
\[
\lim_{k \to \infty} \| (SN_k)(t) - (SN)(t) \| = 0.
\]

This means that \(S\) is continuous.

We now show that \(S\Omega\) is relatively compact. It is sufficient to show by the Arzela-Ascoli theorem that the family of functions \(\{SN : N \in \Omega\}\) is uniformly bounded and equicontinuous on \([0, \infty)\). The uniform boundedness follows from the definition of \(\Omega\) and 7. For the equicontinuity we only need to show, according to Levitan’s result [11] that for any given \(\varepsilon > 0\) the interval \([0, \infty)\) can be decomposed into finite subintervals in such a way that on each subinterval all functions of the family have a change of amplitude less than \(\varepsilon\). Then with regard to condition 7, for \(N \in \Omega\) and
any \( \varepsilon > 0 \) we take \( t^* \geq \tau \) large enough so that

\[
\int_{t^*}^{\infty} \left[ \gamma(a(s), s)N(s) + \lambda(s - \tau)f(N(s) - \sigma_1 a(s)) - r(s) - a'(s)q(s) - d_1 g(s) - \sigma_1 h(s) \right] ds < \frac{\varepsilon}{2}.
\]

Then for \( N \in \Omega, \ T_2 > T_1 \geq t^* \), we get

\[
|\langle SN \rangle(T_2) - \langle SN \rangle(T_1)\rangle \leq |\langle SN \rangle(T_2)\rangle + |\langle SN \rangle(T_1)\rangle < \frac{\varepsilon}{2} + \frac{\varepsilon}{2} = \varepsilon.
\]

For \( N \in \Omega, \ \tau \leq T_1 < T_2 \leq t^* \), we obtain

\[
|\langle SN \rangle(T_2) - \langle SN \rangle(T_1)\rangle \leq \int_{T_1}^{T_2} \left| \gamma(a(s), s)N(s) + \lambda(s - \tau)f(N(s) - \sigma_1 a(s)) - r(s) - a'(s)q(s) - d_1 g(s) - \sigma_1 h(s) \right| ds
\]

\[
\leq \max_{\tau \leq s \leq t^*} \left\{ \left| \gamma(a(s), s)N(s) + \lambda(s - \tau)f(N(s) - \sigma_1 a(s)) - r(s) - a'(s)q(s) - d_1 g(s) - \sigma_1 h(s) \right| \right\}(T_2 - T_1).
\]

Thus there exists \( \delta_1 = \varepsilon/M \), where

\[
M = \max_{\tau \leq s \leq t^*} \left\{ \left| \gamma(a(s), s)N(s) + \lambda(s - \tau)f(N(s) - \sigma_1 a(s)) - r(s) - a'(s)q(s) - d_1 g(s) - \sigma_1 h(s) \right| \right\},
\]

such that \( |\langle SN \rangle(T_2) - \langle SN \rangle(T_1)\rangle \leq M(T_2 - T_1) < M\delta_1 = \varepsilon \) if \( 0 < T_2 - T_1 < \delta_1 \).

Finally for any \( N \in \Omega, \ 0 \leq T_1 < T_2 \leq \tau \), there exists a \( \delta_2 = \varepsilon/M_1 \), where

\[
M_1 = \max_{0 \leq s \leq \tau} \{|w'(s)|\},
\]

such that \( |\langle SN \rangle(T_2) - \langle SN \rangle(T_1)\rangle = |w(T_2) - w(T_1)|\)

\[
= \left| \int_{T_1}^{T_2} w'(s) ds \right| \leq \max_{0 \leq s \leq \tau} \{|w'(s)|\}(T_2 - T_1) = M_1(T_2 - T_1)
\]

\[
< M_1\delta_2 = \varepsilon \quad \text{if} \quad 0 < T_2 - T_1 < \delta_2.
\]

Then \( \{SN : N \in \Omega\} \) is uniformly bounded and equicontinuous on \([0, \infty)\) and hence \( S\Omega \) is relatively compact subset of \( B \). Therefore \( S \) is completely continuous. By Theorem 1.1 there is an \( N_0 \in \Omega \) such that \( SN_0 = N_0 \). We see that \( N_0(t) \) is a positive solution of 2 which is bounded by the functions \( v(t), \ w(t) \).

**Corollary 1.** Suppose that there exists a bounded function \( a \in C^1([0, \infty), (0, \infty)) \) and bounded functions \( v, w \in C^1([0, \infty), (0, \infty)), \) constant \( K \geq 0 \) such that 3, 5 hold and

\[
w'(t) - v'(t) \leq 0, \quad 0 \leq t \leq \tau.
\]

Then 2 has a positive solution which is bounded by the functions \( v, w \).

**Proof.** We only need to prove that condition 8 implies 4. Let \( t \in [0, \tau] \) and set

\[
H(t) = w(t) - w(\tau) - v(t) + v(\tau).
\]

Then with regard to 8, it follows that

\[
H'(t) = w'(t) - v'(t) \leq 0, \quad 0 \leq t \leq \tau.
\]

Since \( H(\tau) = 0 \) and \( H'(t) \leq 0 \) for \( t \in [0, \tau], \) this implies that

\[
H(t) = w(t) - w(\tau) - v(t) + v(\tau) \geq 0, \quad 0 \leq t \leq \tau.
\]
Remark 1. The conditions 3 and 4 enable that the total nutrient concentration $N$.

Corollary 3. Suppose that there exists a bounded function $a \in C^1([0, \infty), (0, \infty))$ and bounded function $w \in C^1([0, \infty), (0, \infty))$, constant $K \geq 0$ such that

$$1 = \frac{1}{w(t)} \left( K + \int_{t}^{\infty} \left[ \gamma(a(s), s)N(s) + \lambda(s - \tau)f(w(s) - \sigma_1 a(s)) - r(s) \right. \right. $$

$$\left. \left. -a'(s)q(s) - d_1 g(s) - \sigma_1 h(s) \right] ds \right), \quad t \geq \tau. \quad (9)$$

Then 2 has a solution $N(t) = w(t)$, $t \geq \tau$.

Proof. We put $v(t) = w(t)$ and apply Theorem 2.1.

Theorem 2.2. Suppose that there exists a bounded function $a \in C^1([0, \infty), (0, \infty))$ and bounded functions $v, w \in C^1([0, \infty), (0, \infty))$, constant $K \geq 0$ such that 3-5 hold and

$$\lim_{t \to \infty} w(t) = \lim_{t \to \infty} v(t) = k \geq 0. \quad (10)$$

Then equation 2 has a positive solution which is bounded by the functions $v(t)$, $w(t)$ and tends to $k \geq 0$ as $t \to \infty$.

Proof. The conclusion follows from Theorem 2.1 and condition 10.

Corollary 3. Suppose that there exists a bounded function $a \in C^1([0, \infty), (0, \infty))$ and bounded function $w \in C^1([0, \infty), (0, \infty))$, constant $K \geq 0$ such that $9$ holds and

$$\lim_{t \to \infty} w(t) = k \geq 0.$$

Then 2 has a solution $N(t) = w(t)$ which tends to $k \geq 0$ as $t \to \infty$.

Proof. We put $v(t) = w(t)$ and apply Theorem 2.2.

Remark 1. The conditions 3 and 4 enable that the total nutrient concentration $N(t)$ remains between the bounded functions $v(t)$ and $w(t)$ for $t \geq \tau$.

The uniqueness of the solution of the equation 2 is an open problem.

The next example illustrates the result of Theorem 2.1.

Example. Consider the differential equation

$$N'(t) = -\gamma(a(t), t)N(t) - \lambda(t - \tau)f(N(t) - \sigma_1 a(t)) + r(t) + a'(t)q(t) + d_1 g(t) + \sigma_1 h(t), \quad t \geq \tau > 0, \quad (11)$$

where $a(t) = be^{-0.5t}$, $b > 0$, $\gamma(x, t) = 2xe^{-t}$, $x > 0$, $\lambda(t) = e^{-t}$, $f(u) = u^3$, $r(t) = ce^{-t}$, $c > 0$, $q(t) = e^{-0.5t}$, $g(t) = e^{-t}$, $h(t) = b^2e^{-2t}$, $d_1, \sigma_1 \in (0, \infty)$.
We show that the conditions of Theorem 2.1 are satisfied. For $K = 0$, $w(t) = c_2 e^{-t}$, $c_2 > 0$, we get
\[
\frac{1}{w(t)} \int_t^\infty \left( \gamma(a(s), s) w(s) + \lambda(s - \tau) [w(s) - \sigma_1 a(s)]^3 - r(s) - a'(s) q(s) \right) \, ds = \frac{1}{c_2} e^t \int_t^\infty \left( 2b c_2 e^{-2.5s} + e^{t - 2.5s} (2c_2^3 e^{-1.5s}
\right.
\]
\[
-3c_2^2 \sigma_1 b e^{-s} + 3c_2^2 \sigma_1 b^2 e^{-0.5s} - \sigma_1^2 b^3 \right) + (0.5b - c - d_1) e^{-t} - \sigma_1 b^2 e^{-2s} \right) \, ds
\]
\[
= \frac{1}{c_2} e^t \left[ \frac{4}{5} b c_2 e^{-2.5t} + e^t \left( \frac{1}{4} c_2^4 e^{-6t} - 6 \frac{7}{5} c_2 \sigma_1 b e^{-3.5t} + 2 \sigma_1^2 b^2 e^{-3t} - \frac{2}{5} \sigma_1^2 b^3 e^{-2.5t} \right) \right] \left. \right] = \frac{1}{c_2} (0.5b - c - d_1)
\]
\[
+ \frac{4}{5} b e^{-1.5t} + e^t \left( \frac{1}{4} c_2^4 e^{-6t} - 6 \frac{7}{5} c_2 \sigma_1 b e^{-2.5t} + \sigma_1^2 b^2 e^{-2t} - \frac{2}{5} \sigma_1^3 b^3 e^{-1.5t} \right) \]
\[
- \frac{1}{2c_2} \sigma_1 b^2 e^{-t}.
\]

For $c_2 = 2$, $b = 2$, $c = d_1 = 0.1$, $\sigma_1 = 0.25$, $\tau = 1$, we obtain
\[
0.4 + \frac{8}{5} e^{-1.5t} + e^t \left( e^{-3t} - \frac{6}{5} e^{-2.5t} + 0.25 e^{-2t} - \frac{1}{40} e^{-1.5t} \right)
\]
\[
-0.25 e^{-t} < 0.686 < 1, \quad t \geq \tau = 1.
\]

For $v(t) = c_1 e^{-t}$, $c_1 > 0$, we get
\[
\frac{1}{v(t)} \int_t^\infty \left( \gamma(a(s), s) v(s) + \lambda(s - \tau) [v(s) - \sigma_1 a(s)]^3 - r(s) - a'(s) q(s) \right) \, ds = \frac{1}{c_1} (0.5b - c - d_1)
\]
\[
+ \frac{4}{5} b e^{-1.5t} + e^t \left( \frac{1}{4} c_1^4 e^{-6t} - 6 \frac{7}{5} c_1 \sigma_1 b e^{-3.5t} + \sigma_1^2 b^2 e^{-3t} - \frac{2}{5} \sigma_1^2 b^3 e^{-2.5t} \right) \]
\[
- \frac{1}{2c_1} \sigma_1 b^2 e^{-t}.
\]

For $c_1 = 0.5$ we obtain
\[
1.6 + \frac{8}{5} e^{-1.5t} + e^t \left( \frac{1}{16} e^{-3t} - \frac{3}{14} e^{-2.5t} + \frac{1}{4} e^{-2t} - \frac{1}{10} e^{-1.5t} \right)
\]
\[
- e^{-t} > 1.53 > 1, \quad t \geq \tau = 1.
\]

Thus the condition 5 of Theorem 2.1 is satisfied. Conditions 3, 4 also hold. Then equation 11 has a positive solution $N(t)$ which is bounded by functions $v(t) = 0.5 e^{-t}$, $w(t) = 2 e^{-t}$, $t \geq 1$.

3. Applications. In this section we investigate the influence of nutrient concentration on the evolution of the tumor boundary.

We say that the boundary $a(t)$ diminishes, if $a'(t) < 0$ and spreads, if $a'(t) > 0$, $t \geq \tau$. We denote by
\[
N(t) = \int_0^{a(t)} \sigma(x, t) \, dx
\]
the total nutrient concentration on the segment $0 \leq x \leq a(t)$, $t \geq \tau$.

We consider the modification of the McKendric-Foster equation
\[
\frac{\partial \sigma(x, t)}{\partial t} + \frac{\partial \sigma(x, t)}{\partial x} = -\mu \sigma(x, t), \quad \mu > 0, \quad 0 \leq x \leq a(t), \quad t \geq \tau,
\]
or the inequalities
\[ \frac{\partial \sigma(x,t)}{\partial t} + \frac{\partial \sigma(x,t)}{\partial x} \geq -\mu \sigma(x,t), \quad \mu > 0, \quad 0 \leq x \leq a(t), \quad t \geq \tau, \quad (12) \]
\[ \frac{\partial \sigma(x,t)}{\partial t} + \frac{\partial \sigma(x,t)}{\partial x} \leq -\mu \sigma(x,t), \quad \mu > 0, \quad 0 \leq x \leq a(t), \quad t \geq \tau. \quad (13) \]

Constant \( \mu > 0 \) is the decrease rate of nutrient concentration.

**Theorem 3.1.** Suppose that the conditions of Theorem 2.1 are satisfied, \( \sigma(x,t) \) satisfies 12 and \( N'(t) < 0, \quad t \geq \tau, \)
\[ N(t) \leq \frac{1}{\mu} [\sigma(0,t) - \sigma(a(t),t)], \quad \mu > 0, \quad t \geq \tau. \]
Then \( N(t) \) exists and \( a'(t) < 0, \quad t \geq \tau, \) i.e. the boundary \( a(t) \) diminishes.

**Proof.** The existence of \( N(t) \) follows from Theorem 2.1. According to condition \( N'(t) < 0 \) we get
\[ N'(t) = a'(t)\sigma(a(t),t) + \int_{0}^{a(t)} \frac{\partial \sigma(x,t)}{\partial t} \, dx < 0, \]
\[ a'(t)\sigma(a(t),t) < -\int_{0}^{a(t)} \frac{\partial \sigma(x,t)}{\partial t} \, dx, \quad t \geq \tau. \]
Applying 12 we get
\[ -\int_{0}^{a(t)} \frac{\partial \sigma(x,t)}{\partial t} \, dx \leq \int_{0}^{a(t)} \left( \frac{\partial \sigma(x,t)}{\partial x} + \mu \sigma(x,t) \right) \, dx \]
\[ = \sigma(a(t),t) - \sigma(0,t) + \mu \int_{0}^{a(t)} \sigma(x,t) \, dx \]
\[ = \sigma(a(t),t) - \sigma(0,t) + \mu N(t) \leq 0, \quad t \geq \tau. \]
We conclude that \( a'(t)\sigma(a(t),t) < 0 \) and \( a'(t) < 0, \quad t \geq \tau. \)

**Theorem 3.2.** Assume that the conditions of Theorem 2.1 are satisfied, \( \sigma(x,t) \) satisfies 13 and \( N'(t) > 0, \quad t \geq \tau, \)
\[ N(t) \geq \frac{1}{\mu} [\sigma(0,t) - \sigma(a(t),t)], \quad \mu > 0, \quad t \geq \tau. \]
Then \( N(t) \) exists and \( a'(t) > 0, \quad t \geq \tau, \) i.e. the boundary \( a(t) \) spreads.

**Proof.** We obtain
\[ a'(t)\sigma(a(t),t) > -\int_{0}^{a(t)} \frac{\partial \sigma(x,t)}{\partial t} \, dx \geq \int_{0}^{a(t)} \left( \frac{\partial \sigma(x,t)}{\partial x} + \mu \sigma(x,t) \right) \, dx \]
\[ = \sigma(a(t),t) - \sigma(0,t) + \mu N(t) \geq 0, \quad t \geq \tau. \]
It follows that \( a'(t) > 0, \quad t \geq \tau. \)

4. **Stability of the positive solution.** In this section we consider the exponential stability of the positive solution of equation (2). We denote \( N(t) \) and \( N_1(t) \) for the positive solutions of (2). Let \( y(t) = N(t) - N_1(t), \quad t \geq \tau. \) Then we get
\[ y'(t) = N'(t) - N'_1(t) = -\gamma(a(t),t)N(t) + \lambda(t - \tau)f(N(t) - \sigma_1 a(t)) \]
\[ + \gamma(a(t),t)N_1(t) - \lambda(t - \tau)f(N_1(t) - \sigma_1 a(t)) = -\gamma(a(t),t)y(t) \]
\[ -\lambda(t - \tau)[f(N(t) - \sigma_1 a(t)) - f(N_1(t) - \sigma_1 a(t))], \quad t \geq \tau. \]
Lemma 4.1. Assume that $K$

Definition 4.2. Let $N(t)$ of the positive solution $\alpha$

Then there exists $\alpha \in (0,1]$ such that

$x - \gamma(x,t) - d\lambda(t - \tau) < 0$, for $t \geq \tau$.

Proof. Define a continuous function $F(u)$ by

By hypothesis we get

$F(0) = \sup_{\tau \geq \tau}\{-\gamma(a(t),t) - d\lambda(t - \tau)\} < 0.$

With respect to continuity of $F(u)$ and $F(0) < 0$, there exists $\alpha \in (0,1]$ such that $F(\alpha) < 0$, that is

$\alpha - \gamma(a(t),t) - d\lambda(t - \tau) < 0$, for $t \geq \tau$.

Definition 4.2. Let $N_1(t)$ be a positive solution of 2 and there exist constants $K_{N_1}$, $\alpha > 0$ such that for every solution $N(t)$ of 2

$|N(t) - N_1(t)| < K_{N_1}^{-\alpha t}$ for all $t > \tau$.

Then $N_1(t)$ is said to be exponentially stable.

In the next lemma we establish sufficient conditions for the exponential stability of the positive solution $N_1(t)$ of 2.

Lemma 4.3. Suppose that $\dot{f}(N(t) - \sigma_1 a(t)) \geq d \geq 0$, $t \geq \tau$ and

$\sup_{\tau \geq \tau}\{-\gamma(a(t),t) - d\lambda(t - \tau)\} < 0.$

Then there exists $\alpha \in (0,1]$ such that

$|N(t) - N_1(t)| < K_{N_1}e^{-\alpha t}$, $t > \tau$.

where $K_{N_1} = e^{\alpha\tau}|y(\tau)| + 1$.

Proof. We consider the Lyapunov function

$L(t) = |y(t)|e^{\alpha t}$, $\alpha \in (0,1]$, $t \geq \tau$.

We claim that $L(t) < K_{N_1}$ for $t > \tau$. In order to prove it, assume that there exists $t_*$ such that $L(t) = K_{N_1}$ and $L(t) < K_{N_1}$ for $t \in [\tau, t_*)$. Calculating the upper left derivative of $L(t)$ along the solution $y(t)$ of 14, we obtain

$D^-(L(t)) \leq -[\gamma(a(t),t) + \lambda(t - \tau)\dot{f}(N_*(t) - \sigma_1 a(t))]y(t)|e^{\alpha t}$

$+ \alpha|y(t)|e^{\alpha t}$, $t \geq \tau$. 
For $t = t_*$ and applying Lemma 4.1, we get

$$0 \leq D^- (L(t_*)) \leq [\alpha - \gamma(a(t_*), t_*) - d\lambda(t_* - \tau)]|y(t_*)|e^{\lambda t_*},$$

which is a contradiction. Therefore we obtain

$$L(t) = |y(t)|e^{\alpha t} < K_{N_1}$$

for $t > \tau$ and for some $\alpha \in (0, 1]$. \hfill \Box

**Theorem 4.4.** In addition to conditions of Theorem 2.1 we suppose that

$$\dot{f}(N(t) - \sigma_1 a(t)) \geq d \geq 0, \quad t \geq \tau$$

and

$$\sup_{t \geq \tau} \{-\gamma(a(t), t) - d\lambda(t - \tau)\} < 0.$$

Then 2 has a positive solution which is exponentially stable.

**Proof.** The proof follows from the Theorem 2.1 and Lemma 4.3. \hfill \Box

5. **Conclusion.** Our results indicate that the decreasing of the concentration of nutrients is not sufficient to reduce the tumor. It is necessary, that the total concentration has dropped below a certain level (Theorem 3.1).

6. **Discussion.** Increased utilization of mathematical modeling in biology is the result of both demand for quantifying and analyzing highly complex data obtained by biologists as well as development in the field of mathematical models. Indeed, various mathematical models for the tumor growth have been generated and used lately [3, 6, 9, 10, 17, 18, 19]. In order to obtain more accurate results which could be interpreted correctly, several factors have to be taken into consideration. Biological variables used as an input data for the calculations are approximations obtained by measurement methods with limited accuracy. Also, to solve the problem from mathematical perspective one has to understand the biology of the studied system and the limitations of collected data. Majority of the tumors are highly complex, non-coherent, heterogeneous entities with dynamic qualitative and quantitative spatio-temporal development and interaction with organism, especially with its immune system. The heterogeneity is present on several levels - from gene expression alterations, DNA/mutation status, karyotype alterations, cytological composition, up to structural differences in tumor and also a treatment status. For the illustration: It has been observed in surgical specimens that the tumor lesions or lymphadenopathies have different gene expression in different sites [20]. Another work [12] pointed out the role of the over-expression of particular chemokine ligands or interleukin molecules in sub-clones with enhanced growth. Cancer genome sequencing studies indicate that there is a strong evidence for the existence of genetically distinct subclones within the same tumor. This intratumor clonal heterogeneity has been reported for a wide range of malignancies, ranging from hematopoietic cancers to different types of solid tumors [4, 5, 14]. It is believed that intratumor clonal heterogeneity is one of the factors underlying therapeutic resistance [14]. Also, when a single nucleus sequencing (SNS) was employed to investigate tumor subpopulation structures, significant differences in ploidity were observed [2], [13]. Further, tumor itself does not consist only of malignant neoplastic cells. Number of different somatic cell types and extracellular matrix are involved in its architecture. Multiple subtypes of immune cells have been shown to infiltrate microenvironment of the
tumors. For example: CD3+, CD4+, CD8+, CD20+, FOXP3+ tumor infiltrating lymphocytes (TILs); CD163+, CD68+ tumor infiltrating macrophages (TIMs), CD83+ dendritic cells, tumor infiltrating natural killers (TI-NK), tumor infiltrating neutrophils (TINs) [1]. Besides the immune cells, endothelial cells creating tumor vascular system are another major factor. Vascularization of the tumor is influencing distribution of oxygen thus its deficiency is responsible for formation of hypoxic areas and necrosis later on. Moreover, quality of vascular system affects the transfer of nutrients directly [7]. Another important cell types are cancer-associated fibroblasts (CAFs) and cancer-associated adipocytes (CAAs) that are believed to play a role in tumor grow and progression [15]. Morphological structures, localization of the tumor and interaction with surrounding tissues or even efficiency of drug penetration into the tumor can also increase the heterogeneity. All of this can alter a distribution and utilization of nutrients in the tumor tissue and therefore the particular location of measurement or sample collection can influence obtained data significantly. Thus, viewing tumor as a homogenous mass of rapidly proliferating cells is very reductive and incorrect. On the other hand, tumor structures are in the most cases very distinctive from normal, healthy tissue and clear, well-defined borders can be demarcated. Total input and output of such object can be monitored and analyzed. Application of model like ours can be a great asset both in cancer research as well as in clinical practice and prediction of disease development.

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