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Existence and stability of a constant stationary solution for a simplified tumor growth model

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Abstract

The aim of this paper is to study a problem of existence and stability related to a tumor growth mathematical model. Based on a classical mathematical model for tumor growth describing proliferating, quiescent and necrotic cells, we propose to calculate explicitly the stationary solution and discuss the stability with respect to these three cells. Some open problems are presented in the conclusion.

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1 Introduction

The cancer modeling represents a complex multi step phenomenon and remains highly discussed in the literature. To study the tumor evolution, different PDE models have been presented and developed in the literature [1, 2, 3, 4, 5]. The growth of tumors can be represented by three basic stages (avascular, vascular and metastasis) and its modeling depends on these stages considered. The avascular stage, which can also be studied using both discrete or continuum models [7], is characterized by a limited diffusion in the sense that nutrient diffusion is not sufficient to assure the development of the tumor. In order to grow, an angiogenesis process is added to the system considered implying blood vessel formation (vascular stage) [6]. Finally, the metastasis stage is well known to be difficult to treat and is characterized by a propagation of tumor cells in different parts of the body. Basically, these different models are based on mass conservation laws and reaction diffusion processes.

In this work, we consider a mixed continuous avascular model, including proliferating and quiescent cells (the living cells) and necrotic cells (dead cells), denoted respectively by P, Q and D. These different densities are depending on a nutrient concentration C satisfying a diffusion equation. On the other part, the densities P, Q and D are time depending and are governing by rate coefficients denoted K_{ij} such that K_{PP} represents the rate of cell birth, K_{PD} is the death rate of proliferating cells, K_{PQ} the rate at which proliferating cells become quiescent and K_{QP} describes the transformation of Q to P, and K_{QD} is the rate death of quiescent cells. Finally, the dead cells are removed outside the tumor domain Ω and this mechanism is governed by a rate coefficient $k > 0$ independent of the nutrient C. More precisely, the general trend of this dependence verifies the fact that K_{PP}, K_{QP} increase when the nutrient concentration C increases, and K_{PD},K_{QD},K_{PQ} decrease when the nutrient concentration C increases. The originality of this work, is that we have supposed a linear dependance of these coefficients K_{ij} with respect to the densities P, Q, D and we have studied the existence and discussed the stability of a solution derived from the new system obtained.

This paper is organized as follows: in section 2, we review a classical mathematical formulation of tumor growth describing proliferating, quiescent and necrotic cells. We propose in section 3, a reformulation of the tumor growth model by considering a linear relation relying the rate coefficients K_{ij} and the densities P, Q, D. Some results concerning the existence and the stability of the stationary solution are also given in this section. Finally, we conclude in section 4 by recalling the main results and giving some open issues.

2 Preliminary Notes

By assuming that the total density of cells in the tumor is constant and that all the cells have the same size and density, we have

$$P + Q + D = constant = N.$$

The mathematical modeling of the three population cells is formulated by

$$\frac{\partial P}{\partial t} + div(Pv) =$$

$$(K_{PP}(C) - K_{PQ}(C) - K_{PD}(C))P + K_{QP}(C)Q, \tag{1}$$

$$\frac{\partial Q}{\partial t} + div(Qv) =$$

$$K_{PQ}(C)P - (K_{QP}(C) + K_{QD}(C))Q, \tag{2}$$

$$\frac{\partial D}{\partial t} + div(Dv) =$$

$$K_{PD}(C)P + K_{QD}(C)Q - kD, \tag{3}$$

with v the velocity of cell movements.

By scaling the densities $p = \frac{P}{N}$, $q = \frac{Q}{N}$ and $d = \frac{D}{N}$, the value 1 corresponds to a completely close packed population. We obtain for $x \in \Omega(t), t > 0$

$$\frac{\partial p}{\partial t} + div(pv) =$$

$$(K_{pp}(c) - K_{pq}(c) - K_{pd}(c))p + K_{qp}(c)q, \tag{4}$$

$$\frac{\partial q}{\partial t} + div(qv) =$$

$$K_{pq}(c)p - (K_{qp}(c) + K_{qd}(c))q, \tag{5}$$

$$\frac{\partial d}{\partial t} + div(dv) =$$

$$K_{pd}(c)p + K_{qd}(c)q - kd, \tag{6}$$

with $c = \frac{C}{C_0}$, where C_0 is the nutrient value at the tumor surface.

Proposition 2.1 *For $t > 0$, we have the equivalence*

$$p + q + d = 1 \Longleftrightarrow div(v) = K_{pp}(c)p - kd,$$

with the initial condition

$$p_0 + q_0 + d_0 = 1.$$

Proof 2.2 *Using the equations (4), (5) and (6), we obtain the relation*

$$div(v) = K_{pp}(c) - kd, \quad \Omega(t), t > 0. \tag{7}$$

Conversely, using the equations (1), (2) and (3) with equal motility for the three different cells, we deduce that

$$\frac{\partial}{\partial t}(P + Q + D) + v\nabla(P + Q + D) + (P + Q + D)div(v) =$$

$$K_{PP}P - kD.$$

From equation (7), we deduce the following relation

$$\frac{\partial}{\partial t}(P + Q + D) + v\nabla(P + Q + D) =$$

$$\frac{1}{N}(K_{PP} - KD)(N - (P + Q + D)),$$

yields to the equation

$$p + q + d = 1.$$

3 Main Results

We propose in this section to modify the system describing the different population cells. In fact, our idea is the following First, we assume that there is no dependance of both K_{pp} and K_{pd} with effects in relation with the system in p, q and d. In conclusion, we can suppose that these two coefficients are depending only of c. Second, we assume that K_{pq} has a linear dependence with p and that K_{qp} has a linear dependence with q. Finally, K_{qd} depends of both p and q, then we can assume that there exists a linear dependence related K_{qd} to $p+q$. We deduce that there exists $k_{ij} > 0$ such that $K_{pp} = k_{pp}, K_{pd} = k_{pd}, K_{pq} = k_{pq}p, K_{qp} = k_{qp}q$, and $K_{qd} = k_{qd}(p+q)$ which gives the following system

$$\frac{\partial p}{\partial t} + div(pv) = (k_{pp} - k_{pq}p - k_{pd})p + k_{qp}q^2, \tag{8}$$

$$\frac{\partial q}{\partial t} + div(qv) = k_{pq}p^2 - (k_{qp}q + k_{qd}(p+q))q, \tag{9}$$

$$\frac{\partial d}{\partial t} + div(dv) = k_{pd}p + k_{qd}pq + k_{qd}q^2 - kd. \tag{10}$$

Proposition 3.1 *Under previous assumptions, and by supposing that the natural cells which will be removed out of the proposed process, corresponding to a natural death is neglected, then the system (8-10) has exactly two stationary solutions.*

Proof 3.2 *As*

$$0 = k_{pp}p - k_{pq}p^2 + k_{qp}q^2, \tag{11}$$

$$0 = k_{pq}p^2 - k_{qp}q^2 - k_{qd}pq - k_{qd}q^2, \tag{12}$$

$$0 = k_{qd}pq + k_{qd}q^2 - kd, \tag{13}$$

then, we obtain

$$k_{pp}p - kd = 0.$$

By assuming that $p, q, d \neq 0$, *we have*

$$d = \frac{k_{pp}p}{k}. \tag{14}$$

Using the equation (13) and the relation (14), we deduce the following equation

$$k_{qd}pq + k_{qd}q^2 - k_{pp}p = 0,$$

implying that

$$p = \frac{k_{qd}q^2}{k_{pp} - k_{qd}q}. \tag{15}$$

Finally using equation (11), we obtain

$$\frac{k_{pp}k_{qd}q^2}{k_{pp}-k_{qd}q}-k_{pq}\left(\frac{k_{qd}q^2}{k_{pp}-k_{qd}q}\right)^2+k_{qp}q^2=0,$$

which gives a fourth order equation in q defined by

$$\left(k_{qd}^2\left(k_{qp}-k_{pq}\right)\right)q^4-\left(k_{pp}(\,k_{qd}^2+2k_{qd}k_{qp}\,)\right)q^3+$$

$$\left(k_{pp}^2\left(k_{qp}+k_{qd}\right)\right)q^2=0.$$

As $q\neq 0$ then

$$\left(k_{qd}^2\left(k_{qp}-k_{pq}\right)\right)q^2-$$

$$\left(k_{pp}(\,k_{qd}^2+2k_{qd}k_{qp}\,)\right)q+\left(k_{pp}^2\left(k_{qp}+k_{qd}\right)\right)=0. \tag{16}$$

Solving the equation (16) which possesses a positive discriminant given by

$$k_{qd}^2k_{pp}^2\left(4k_{qd}k_{pq}+4k_{pq}k_{qp}+k_{qd}^2\right) \tag{17}$$

we obtain the two solutions

$$q_1=\frac{k_{pp}\left(k_{qd}+2k_{qp}\right)+k_{pp}\sqrt{4k_{pq}\left(k_{qd}+k_{qp}\right)+k_{qd}^2}}{2k_{qd}\left(k_{qp}-k_{pq}\right)} \tag{18}$$

$$q_2=\frac{k_{pp}\left(k_{qd}+2k_{qp}\right)-k_{pp}\sqrt{4k_{pq}\left(k_{qd}+k_{qp}\right)+k_{qd}^2}}{2k_{qd}\left(k_{qp}-k_{pq}\right)}. \tag{19}$$

Let us deduce the following properties of the solutions q_1 and q_2.

If $k_{qp}<k_{pq}$ then the solution q_1 is rejected, which explain that necessary the rate at which proliferating cells become quiescent is strictly less than the rate at which cells return to the proliferative state from the quiescent one. Then, in the following, we suppose that $k_{pq}<k_{qp}$. On the other part, as all the rate coefficients are strictly positive, then we have

$$\begin{aligned}
k_{pq}<k_{qp} &\implies (k_{qp}-k_{pq})(k_{qp}+k_{qd})>0,\\
&\implies k_{qp}(k_{qp}-k_{pq})+k_{qd}(k_{qp}-k_{pq})>0,\\
&\implies k_{qp}^2+k_{qp}k_{qd}-k_{pq}k_{qd}-k_{pq}k_{qp}>0,\\
&\implies (k_{qd}+2k_{qp})^2>4k_{pq}(k_{qd}+k_{qp})+k_{qd}^2,
\end{aligned}$$

assuring that that solution q_2 is well defined. Finally, using the relation (11) we deduce that $p>\frac{k_{pp}}{k_{pq}}$. The explicit expressions of p_1,p_2, are then easily deduced form (15).

Let us remark that for f, g, h defined by

$$\begin{aligned} f(p,q,d) &= k_{pp}p - k_{pq}p^2 + k_{qp}q^2, \\ g(p,q,d) &= k_{pq}p^2 - k_{qp}q^2 - k_{qd}pq - k_{qd}q^2, \\ h(p,q,d) &= k_{qd}pq + k_{qd}q^2 - kd, \end{aligned}$$

the Jacobian matrix at $(0,0,0)$ is given by

$$J = \begin{pmatrix} k_{pp} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & -k \end{pmatrix}$$

yields to a non stability.

Now, let us study the conditions under which we have an uniqueness of the stationary solution. First, the equation (17) assumes that $k_{pp} = 0$ or $k_{qd} = 0$.

Using the equations (11-13), we deduce that if $q \neq 0$ then the case $k_{pp} = 0$ implies trivially that $k_{qd} = 0$ and $d = 0$. This case is equivalent to the particular model given in [3], in which the author have supposed that the rate k is very large so that dead cells are instantly removed, and then we have $p + q = 1$.

By taking $p + q = 1$ we obtain the following second order equation in p

$$(k_{pq} - k_{qp})\, p^2 + 2k_{qp}p - k_{qp} = 0,$$

and then by adding the conditions $k_{qp} \neq 0$ and $k_{qp} = k_{pq}$ we obtain the unique stationary solution $p = q = \frac{1}{2}$, otherwise (if $k_{pq} \neq k_{qp}$), we have the two solutions

$$\begin{aligned} p_1 &= -\frac{1}{k_{pq} - k_{qp}} \left(k_{qp} - \sqrt{k_{pq}k_{qp}} \right), \\ p_2 &= -\frac{1}{k_{pq} - k_{qp}} \left(k_{qp} + \sqrt{k_{pq}k_{qp}} \right). \end{aligned}$$

In this case, the Jacobian matrix associated to the functions f, g, h is given by

$$J = \begin{pmatrix} 0 & k_{pq} & 0 \\ k_{pq} & -k_{pq} & 0 \\ 0 & 0 & -k \end{pmatrix}$$

and then admits an eigenvalue which vanishes, implying an unstable state.

Conversely, if $k_{qd} = 0$ then $k_{pp} = 0$ and $d = 0$, giving the same result as previously.

Now, by supposing that all cells are proliferating as the model proposed by [3], giving the solution $p = 1$, we obtain an unstable state too, because the eigenvalues of the Jacobian matrix associated to f, g, h are $-k$ and 0.

In the model developed in this section, we have neglected the rate k_{pd}. More generally, if we suppose that this rate does not vanish, then the Jacobian matrix associated to f, g, h is given by

$$J = \begin{pmatrix} -k_{pd} & k_{pq} & 0 \\ k_{pq} & -k_{pq} & 0 \\ k_{pd} & 0 & -k \end{pmatrix}.$$

It is easy to see that it suffices to take $k_{pq} < k_{pd}$ to assure the stability.

To conclude, a model of tumor growth has been investigated in this work. More precisely, we have presented a partial differential equations model giving the evolution of proliferating, quiescent and necrotic cells, and have proposed and discussed the existence and the stability of a stationary solution. Some attention should be devoted to the nutrient concentration, which does not considered in this work. In fact, in [8, 9], J.P Ward *et al.* have explained how the nutrient concentration is consumed with a rate proportional to the proliferating and quiescent cells. This proportionality will naturally effect the solution and will change the behavior of the evolution of proliferating and quiescent curves. On the other part, it is interested too, to view the impact of Random effect on the PDE solution if a white noise is added to the nutrient concentration. We propose to discuss these two points of view in a forthcoming paper. We have supposed in the present work that all cells have the same velocity. For real life applications, this point should be generalized by considering different velocities. Another mathematical challenge generally noted is that the size of the tumor is naturally changing over the time, implying a tumor domain depending on the time. This natural property of the tumor evolution gives a free boundary problem and we intend to apply topological optimization which will be a good alternative to determine the geometry of the tumor and make numerical simulations with a low cost computation.

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