A Mechano-Chemical model for tumors growth

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Abstract

In this paper we present a study of local dynamics of the growth of cancer tumor and healthy cells considering the presence of nutrients in the system. We also analyze the evolution of system if we take indirectly into account the level of alkalinity (pH) in the system which shows that influences in tumor growth. The model consists in a set of differential equations of first order that involves a mechanical model added by a pair of differential equations for local oxygen and glucose.

Keywords: Tumor growth, Tumor cells, Healthy cells, Extracellular matrix, Extracellular liquid, Enzymes, Nutrients

1 Introduction

Cancer is a disease of uncontrolled cell proliferation [1]. These cells exhibit metabolic alterations [2] that distinguish them from healthy tissues and make their metabolic processes susceptible to pharmacological targeting [2]. Successful cell proliferation is dependent on a profound remodeling of cellular metabolism, required to support the biosynthetic needs of a growing cell [3]. In the literature we find that the conditions of the tumor microenvironment are important in the metabolism of the tumoral cells [2], this allows cells to use available nutrients such as glucose and glutamine [2, 1, 3, 4] for its survival and propagation. Some tumours show increased glucose uptake, that can be promoted by gene expression or oncogenic signalling changes [2, 3]. Signaling through oncogenes allows cancer cells to perpetually receive pro-growth stimuli, which for normal tissues are only transient in nature. As a consequence, cancer metabolism is constitutively geared toward supporting proliferation [3].

Some types of cancer show the nutrients are insufficient. In recent work has shown that cancer cells are able to overcome this nutrient insufficiency by scavenging alternative substrates as proteins and lipids [1].

Another problem that arises is the reduction of oxygen supply or hypoxia. Lack of sufficient oxygen has a profound effect on cellular metabolism as it inhibits those biochemical reactions in which oxygen is consumed [3]. One of the most important phenotypic changes is the cancer cells ability to change the extracellular acidity due to an altered glycolysis pathway. The ability to expel protons from cells and, therefore, change the extracellular pH provides an advantage to cancer cells [5].
In recent works it is clear that pH plays an important role in the survival mechanisms of cancer cells [5]. The acidic tumour microenvironment has also been associated with the degree of cancer aggressiveness. It has been reported that the lower the pH surrounding the cell, the more likely is the chance of malignancies with higher degree of invasiveness [5]. A recent therapeutic approach takes advantage of the altered acidity of the tumour microenvironment by using proton pump inhibitors (PPIs) to block the hydrogen transport out of the cell. The alteration of the extracellular pH kills tumour cells, reverses drug resistance, and reduces cancer metastasis. Targeting tumour pH can be therefore considered a therapeutic strategy [5].

2 Components of system.

A tumor is an example of a complex system composed of cells. Each of the the reproduced cells follows a set of rules and responds to local interactions with other cells either from the tumor or with healthy cells.

Extracellular matrix.
The Extracellular matrix (ECM) represents a network that includes to all organs, tissues and cells of the body, in this medium the cells survive, multiply and perform their vital functions [6]. The balance of extracellular matrix is maintained by a regulation between synthesis, training and reshuffle. Also the extracellular matrix provides oxygen and nutrients to the cell and the elimination of CO$_2$ and toxins under normal conditions [6].
The extracellular matrix of animals need to reorganize and also need a constant regeneration through of the degradation of components and the production of new components by cells. The degradation of ECM causes enzymes production such as metalloproteinases [7].

Extracellular liquid.
The extracellular liquid is body fluid not contained in cells. Often it is secreted by cells for a suitable environment. It is transported across the body in two stages, the first is the movement of blood by circulatory system; the second is movement between blood capillaries and cells. When blood flow through the capillaries, a large portion of the liquid containing is diffused into and out of interstitial liquid that found between cells, allowing the continuous exchange of substances between the cells and interstitial liquid and between the interstitial liquid and the blood.

Source of nutrients in the extracellular liquid.
- The respiratory system, it provides oxygen to the body and removes carbon dioxide.
- The digestive system, digests food and absorbs nutrients including carbohydrates, fatty acids, and amino acids, for to bring into the extracellular liquid.

The blood.
Transports nutrients, electrolytes, hormones, vitamins, antibodies, heat and oxygen, its composed of plasma, red and white blood cells, platelets. The principal function of red blood cells, transports oxygen and carbon dioxide. Glucose is a sugar which comes of food we eat, this glucose is stored in the body, is the main source of energy for body cells and reaches every cells through the bloodstream.
3 Mathematical model

We consider a mixture in which the essential components are cells, extracellular matrix, and extracellular liquid with dissolved chemicals. Hypotheses that are assumed are as follows:

- The components of the extracellular matrix form a complex network and move together.
- Cells respond mechanically to compression from cells around, regardless of the type of cell.
- The presence of nutrients in the mixture is essential for growth and vital functions of cells [8].

For this model is defined \( \phi \in [0, 1] \) as the volume occupied by cells and either \( m \in [0, 1] \) as the volume occupied by extracellular matrix. The mixture is saturated if the remaining space is filled with extracellular liquid then we define \( l \in [0, 1] \) as the volume occupied by extracellular liquid. Considering normalized amounts for the sample volume we have:

\[
\phi + m + l = 1 \tag{1}
\]

In the cellular component of tissue, the differential equation that describes the change in mass of the cellular component is

\[
\frac{\partial \phi}{\partial t} + \nabla \cdot (\phi \vec{v}_\phi) = \Gamma_\phi \tag{2}
\]

which considers that cell density is constant ([9], [10], [11]). Here \( \Gamma_\phi \) corresponds to rapid growth or death for cell mass, \( \vec{v}_\phi \) is the cell rate and the term \( \nabla \cdot (\phi \vec{v}_\phi) \) it is associated with the flow of cell component

In the same way, the corresponding equations for the components of the mixture

\[
\frac{\partial \phi_i}{\partial t} + \nabla \cdot (\phi_i \vec{v}_i) = \Gamma_{\phi_i}, \quad i = n, t, \tag{3}
\]

\[
\frac{\partial m}{\partial t} + \nabla \cdot (m \vec{v}_m) = \Gamma_m \tag{4}
\]

\[
\frac{\partial l}{\partial t} + \nabla \cdot (l \vec{v}_l) = \Gamma_l. \tag{5}
\]

For the system of interest it is needed to distinguish different types of cells such as tumor cells, endothelial, epithelial, fibroblasts, etc. However, for simplicity, in the cell mass only we only distinguish two subpopulations that correspond to healthy cells and tumor cells. In the extracellular matrix components all are considered as a single assembly.

\[
\frac{\partial \phi_i}{\partial t} + \nabla \cdot (\phi_i \vec{v}_i) = \Gamma_{\phi_i}, \quad i = n, t, \tag{6}
\]

and considering the result obtained in [9] and [10], cell velocity is:

\[
\vec{v}_i = -K_{im} \left(1 - \frac{\sigma_{im}}{\nabla \cdot (\phi_i \vec{T}_\phi)}\right) \nabla(\phi_i \vec{T}_\phi) \quad i = n, t. \tag{7}
\]

In this equation it is considered \( \sigma_{im} = 0 \) ([11]), that is associated with frictional forces and it is expected to depends on adhesion mechanisms of volume occupied by cells. Also it is supposed that the coefficient of mobility \( K_{im} = K_i \) is constant, while the term \( \vec{T}_\phi \) expresses stress to which the cells are subjected.
Now if we divide the sample volume in small cubes in which only there is a cell population healthy or tumor, then $\phi_i$ is constant in each cube, and in this way the cell velocity can be expressed as

$$\vec{v} i = -K_i \nabla (\phi_i \mathbf{T}_\phi) \quad i = n, t$$  \hspace{1cm} (8)

where, the term associated with the flow can be expressed as follows

$$\nabla \cdot (\phi_i \vec{v}) = -\phi_i K_i \nabla^2 (\phi_i \mathbf{T} \phi_i).$$  \hspace{1cm} (9)

It is necessary an equation that describes the response of cells and extracellular matrix to stress, this equation is constructed assuming that they behaves like an elastic fluid ([9], [12], [13], [10]), so we consider

$$\mathbf{T}_\phi = -\Sigma I,$$  \hspace{1cm} (10)

and for the function $\Sigma$, we use the expression proposed by Chaplain et. al. [11]

$$\Sigma(\psi) = \left(2 - \frac{\psi_0}{1 - \psi_0}\right) \left(\frac{\psi - \psi_0}{1 - \psi}\right),$$  \hspace{1cm} (11)

where $\psi = \phi_n + \phi_t + m$, measure indirectly, the free space available locally and it can be use for calculate the stress exerted by the environment on cellular matter. Also $\psi_0 \in (0, 1)$, is identified as the volume free of stress.

### 3.1 Term of growth or death cell.

Cells live in a crowd environment and they perceive the presence of other cells. This fact is fundamental in controlling cell concentration and implies to stop mitosis (cellular division) when the volume exceeds a threshold, so the behavior of cells in terms of growth and movement depends crucially on how they perceive the presence of other cells and its signal is translated.

For the terms of growth, we consider ([9], [11], [10]), the next

$$\Gamma_i = [\gamma_i H_\sigma(\psi - \psi_i) - \delta_i(\psi)] \phi_i, \quad i = n, t$$  \hspace{1cm} (12)

where $H_\sigma(\psi - \psi_i)$ is a amendment to step function, and it is equal to 1 for $\psi$ smaller that the threshold value $\psi_i$ and is equal to zero for $\psi > \psi_i + \sigma$. Also it must be satisfied that $\psi_n < \psi_t$, and we consider constants $\delta_i$, and $\gamma_i > 0$ which represent coefficients of death and cell reproduction respectively. The parameter $\sigma > 0$ controls the transition between $H_\sigma(s) = 1$, and $H_\sigma(s) = 0$ ([11]), therefore it controls the transition on/off in the cells reproduction, so the expression used in this work is

$$H_\sigma(s) = \begin{cases} 
1, & \text{if } s \leq 0 \\
0, & \text{if } s > \sigma \\
1 - \frac{s}{\sigma}, & \text{another case.}
\end{cases}$$  \hspace{1cm} (13)

### 3.2 Remodeling of the extracellular matrix.

As mentioned on the biological part of extracellular matrix, now we consider a concentration of enzymes that degrades the ECM. The enzymes are produced by tumor or healthy cells [7] and so the process of remodelling can be described by the equation for $m$ as follows:

$$\frac{\partial m}{\partial t} = \mu_n \phi_n \Sigma(\psi) + \mu_t \phi_t \Sigma(\psi) - \nu m.$$  \hspace{1cm} (14)
Here $\mu_n$ and $\mu_t$ corresponds to speed of production in the extracellular matrix by healthy or tumor cells respectively, $\nu$ is the degradation coefficient due to action of enzymes that degrade the matrix and $e$ is the concentration of said enzymes \[9\].

Now, we introduce an reaction-diffusion equation which aims to describe the evolution in concentration of enzymes that degrade the extracellular matrix

$$
\frac{\partial e}{\partial t} = \kappa \nabla^2 e + \pi_n \phi_n \Sigma(\psi) + \pi_t \phi_t \Sigma(\psi) - \frac{e}{\tau}. \tag{15}
$$

In this equation $\pi_n$ and $\pi_t$ correspond to the rapid production of enzymes that degrade the extracellular matrix produced by healthy and tumor cells respectively; $\tau$ is the average lifetime and $\kappa$ the diffusion coefficient of enzymes \[9\].

### 3.3 Nutrients.

In tumor growth, as well as vital functions of an healthy cell it is necessary the presence of dissolved chemicals in the liquid component of the mixture considered, such as nutrients, growth factors, etc. These chemicals are “absorbed” by cell populations to perform some vital functions such as proliferation, growth or intercellular communication \[9\]. For the consideration of nutrients will assume that there is a source that supplies the nutrients, that is to say, there is a capillary in which blood flow is constant that transports nutrients.

Considering only oxygen and glucose \[8\], we propose the following equations \[10\]:

$$
\frac{\partial c}{\partial t} = D_c \nabla^2 c - \beta_n \phi_n c + f_c \tag{16}
$$

$$
\frac{\partial g}{\partial t} = D_g \nabla^2 g - \beta_t \phi_t g + f_g \tag{17}
$$

in which $c \in [0,1]$ is the oxygen concentration and $g \in [0,1]$ is the glucose concentration with $D_i$ ($i = c, g$) are the diffusion coefficients of nutrients and $\beta_j$ ($j = n, t$) corresponds to the absorption rate. Also $f_i$ represents the continuous supply of nutrients (i.e. a source). In the supply of nutrients must be met $f_c + f_g < 1$.

Considering the nutrients that influence in the evolution of cell population, we assume that the rate of reproduction in cells is proportional to nutrients concentration, that would result replace $\gamma_n$ by $c \gamma_n$ ($\gamma_n \longrightarrow c \gamma_n$) for healthy cells and $\gamma_t \longrightarrow g \gamma_t$ for tumor cells, in the case of rate cell death is obtained $\delta_n \longrightarrow (1 - c) \delta_n$ and $\delta_t \longrightarrow (1 - g) \delta_t$ for healthy and tumor cells respectively, the reason for these substitutions is that for example if considered to healthy cells, with an optimal concentration of oxygen these are reproduced and the term of rate of death must decrease, this situation is described by the term $(1 - c)$. We must mention that competition is not considered between cell populations for nutrients. Thus, the complete mathematical model for the simulation
of the system it is as follows:

\[
\begin{align*}
\frac{\partial \phi_n}{\partial t} &= \phi_n K_n \nabla^2 (\phi_n \Sigma(\psi)) + c \gamma_n \phi_n H_\sigma(\psi - \psi_n) - (1 - c) \delta_n \phi_n \\
\frac{\partial \phi_t}{\partial t} &= \phi_t K_t \nabla^2 (\phi_t \Sigma(\psi)) + g \gamma_t \phi_t H_\sigma(\psi - \psi_t) - (1 - g) \delta_t \phi_t \\
\frac{\partial m}{\partial t} &= \mu_n \phi_n \Sigma(\psi) + \mu_t \phi_t \Sigma(\psi) - \nu m \\
\frac{\partial e}{\partial t} &= \kappa \nabla^2 e + \pi_n \phi_n \Sigma(\psi) + \pi_t \phi_t \Sigma(\psi) - \frac{e}{\tau} \\
\frac{\partial c}{\partial t} &= D \nabla^2 c - \beta_n \phi_n c + f_c \\
\frac{\partial g}{\partial t} &= D \nabla^2 g - \beta_t \phi_t g + f_g.
\end{align*}
\]

which will be solved in an homogeneous space.

4 Results

In this section we show the results of numerical solution for the system of equations obtained, some parameters were obtained from [11], and we propose some parameters for the simulations. We consider the cell population is approximately 50%, the extracellular matrix occupies a 20% and extracellular liquid a 30% of the total volume.

We will take as reference the following parameters:

\[
\begin{array}{|c|c|c|c|c|}
\hline
\phi_n &= 0.45 & \phi_t &= 0.005 & m &= 0.2 \\
\psi_n &= 0.6 & \delta_n &= 0.1 & \mu_n &= 0.1 \\
\beta_n &= 1.2 & \gamma_n &= 0.746 & \psi_t &= 0.8 \\
\gamma_t &= 0.97 & \delta_t &= 0.03 & \mu_t &= 0.05 \\
\beta_t &= 1.3 & \pi_n &= 6000000 & \pi_t &= 3000000 \\
\nu &= 0.000016 & \kappa &= 0.00000734 & \tau &= 0.005 \\
D &= 1.0 & \psi_0 &= 0.75 & f_c &= 0.25 \\
f_g &= 0.16 & \hline
\end{array}
\]

Table 1: Initial condition.

| $K_n$ | $\gamma_n$ | $\psi_n$ | $\delta_n$ | $\mu_n$ | $\beta_n$ | $K_t$ | $\gamma_t$ | $\psi_t$ | $\pi_n$ | $\pi_t$ | $\nu$ | $\kappa$ | $\tau$ | $D$ | $\psi_0$ | $f_c$ | $f_g$ |
|-------|------------|----------|------------|----------|-----------|-------|------------|----------|-------|-------|------|--------|-------|-----|--------|------|------|
| 0.1   | 0.746     | 0.6      | 0.1        | 0.1      | 1.2       | 0.3   | 0.97       | 0.8      | 6000000 | 3000000 | 0.000016 | 0.00000734 | 0.005 | 1.0 | 0.75   | 0.25 | 0.16 |

Table 2: Set of parameters.

Following graphs show the results of the local dynamics of the system considered. Figures 1 and 2 show dependence of cell populations in nutrient uptake, for which is varied the absorption rate of tumor and healthy cells.

In the graphs 3, 4, correspond to growth of cell population, varing the concentration of oxygen, also we considered that $f_g = 0.1$. 


The parameters used in the simulation remain constant. But if we consider the parameters of the source for oxygen and glucose (which are associated with pH levels), these parameters may vary depending on the diet in each person. For this situation we use uniform random numbers for these parameters, only in the interval [0, 0.5].

5 Conclusions

From the numerical results that we get can say the following: the model presented in this paper is congruent with Gompertz’s model for tumor cells, in which it is observed a stage of uncontrolled growth and then they stabilize at a value, also can be seen in graphics that they are susceptible to the presence of nutrients, these are two cases, if the absorption rate is low the occupied volume increases and if absorption rate is high the occupied volume is less. With respect to the variation in the oxygen concentration, can be seen two situations, if the local concentration of
oxygen is low, the volume in stabilizing the tumor cells is high and when the local concentration of oxygen is high the volume of tumor cells is lower compared to the previous situation, this suggests that can intervene in tumor growth increasing the local concentration of oxygen in the system.

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