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A Finite element method for Shear Stress study on cancer cell proliferation

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***Abstract*—Metastatic progression of tumors requires the coordinated dissemination of cancerous cells through interstitial tissues and their replication in distant body locations. Despite their importance in cancer treatment decisions, key factors, such as cell shape adaptation and the role it plays in dense tissue invasion by cancerous cells, are not well understood. With this work, we will continue further work on the study of the effect of shear stress on cancer cell proliferation. We present a coupled Keller-Segel and Darcy–Brinkman model implemented in finite elements to obtain numerical results.**

***Index Terms*—Keller-Segel; Darcy–Brinkman; incompressible; shear stress; interstitial flow; cancer, Finite Element Methods**

I. Introduction

When cancer cells grow and divide, they can move from where they started to other areas of the body. One of the ways for cancer proliferation is bloodstream spread, or hematogenous spread, which means that cancer cells break away from the primary tumour, enter the blood and travel to a new place in the body [1].

The migrative properties of cells and their chemotactic abilities, i.e, their directing movement towards zones of high concentration of certain chemical stimuli [2], are thus key when it comes to understanding the development of metastases in several kinds of cancer.

The immune system usually attacks and destroys cancer cells that travel through the blood, however this process is not completely effective, [3] and [4].

During this process there is also a proliferation of cells that are subject to mechanical forces due to fluid shear stress, [5], hydrostatic pressure, tension and compression forces generated by blood flow in the vascular microenvironment [6], or those generated by interstitial flows in the tumour microenvironment.

In this paper, we are interested in studying the main biological phenomenon responsible for their formations through mathematical modelling. Models for the aggregative behaviour of cells in the extracellular matrix can be continuous models typically based on ordinary differential equations or partial differential equations [7].

We present a new mathematical model based on the Keller-Segel model, for proliferation (source terms) and propagation due to the presence of a chemoattractant for cancer cell, adapted to take account the stresses generated by interstitial flows.

This is a continuation work on the study of the shear stress effect on the cancer cells membrane [8]. Now we focus on the effect produced by these forces over cell proliferation .

In order to achieve this we begin introduce the differential equation system model involving cancer cells and its propagation due to the presence of a chemoattractant. This proliferation model will be changed to take account stresses generated by interstitial and blood flows, [9].

We start by introducing the coupled mathematical models. We explain the numerical discretization by

a finite element method and numerical results at Section IV .

Finally, concluding remarks are made in the conclusion at Section V .

II. Materials and Methods

A. Identification of the model

We assume that a group of cells detaches from the main site and moves in an interstitial medium towards a chemical attractant.

Chemotaxis has attracted significant interest due to its critical role in a wide range of biological phenomena. In general, organism or cell moves from a lower concentration towards a higher concentration of the chemo attractant, which is known as positive chemotaxis. The easiest model is that the average velocity with which the cells respond to the gradient is proportional to the gradient. Therefore the flux should be proportional to the product of the gradient and the density of cells.

III. Mathematical Formulation

We consider that there is a change in cell number density ρ due to dispersion, arising from random locomotion and we take $\varphi(\rho)$ as the cell motility function, characterising how cells would disperse from higher to lower densities, [9].

In addition, the important features that the nonlinearity of the random motility captures are the finite speed of dispersion as well as the preservation of initial conditions of compact support. This means that if the initial cancer cells are localized in a finite region then at all subsequent times it will be confined to a finite region whose size however could change over time.

For governing interstitial flow between boundaries we will consider the Darcy–Brinkman equation (1-2), with the velocity $\vec{u}$ and pressure p, as in [10].

The Keller-Segel model takes into account cell motility, proliferation and propagation due to the presence of a chemoattractant c (3-4) using [2].

Additionally, we consider the effect of shear stress on the proliferation of cells from the environment in which they are inserted (5), [11]. Based on information from the experiment in [8], we assume the force due to the fluid shear stress [3], acting to the cells agglomeration in movement, collapses the cells when this magnitude is larger than τ_M.

$$-\nu\Delta\vec{u} + \frac{\nu}{k}\vec{u} + \nabla p = 0 \quad (1)$$

$$\nabla \cdot \vec{u} = 0 \quad (2)$$

$$\frac{\partial \rho}{\partial t} - D\Delta\rho + \nabla \cdot (\varphi(\rho)\nabla c) - r\rho(\rho_M - \rho) = \chi(\rho) \quad (3)$$

$$\frac{\partial c}{\partial t} - \Delta c - s\left(\frac{\rho}{\rho_M} - c\right) = 0 \quad (4)$$

With

$$\chi(\rho) = (\tau - \tau_M)\rho \quad (5)$$

and

$$\varphi(\rho) = \left(1 - \frac{\rho}{\rho_M}\right)\rho \quad (6)$$

Where τ_M is the critical value for the shear stress from [8] after what the the membrane collapse is achieved, where $D > 0$ is the diffusion rate, $r > 0$ is a proliferation rate and $\rho_M = 100$ is the threshold cell density. The quantity c is the concentration of chemoattractant (or chemorepellent according to the sign of $\varphi(\rho)$. The parameter $s > 0$ is a reaction rate for the substance c. Additionally the function φ regulates the direction of attraction of chemical species, if $\varphi(\rho) > 0$ the chemical species act as attractors and otherwise as repellers.

One consider two boundaries for the coupled problem, one internal defined as the cell cluster contour Γ_I, and the other one as the inbeding's domain limit Γ_E.

Schematically, we start with the formulation of the coupled problem on the initial region that will be altered as a function of the concentration of cancer cells. The process starts by solving the Keller-Segel problem in a discretized region as in Fig. 1 and from the result obtained for the density of cells we obtain the meshes with an interior boundary Γ_I obtained from the contour of the density obtained, as in Fig. 2. In the new region we solve the problem Darcy–Brinkman and iterate. We consider an initial Gaussian distribution for the substance c centred at the region. For the Darcy–Brinkman problem we take the two boundaries: Γ_I and Γ_E.

Briefly, the procedure is, for each instant t:

1) Using the cell density ρ,produce an adapted mesh, (for $t = 0$ we use the c quantity)on a region Ω_k;
2) Solve the Keller-Segel problem on Ω_k;
3) Using the contour line for the cell density, produce a new region Ω_{k+1} and a new interior boundary;
4) Solve Darcy–Brinkman problem on Ω_{k+1};
5) iterate t.

Tables I and II have the parameters for the coupled problems. We use a finite element discretization to solve this problem over and a backward Euler method to solve the evolutionary problem, in a FreeFem++ implementation [12].

TABLE I
KELLER-SEGEL MODEL PARAMETERS VALUES.

The critical shear stress value	τ_M	0.55dyn/cm^2 [8]
The diffusion rate	D	1
The proliferation rate	r	0.1
The reaction rate c	s	10

TABLE II
DARCY–BRINKMAN MODEL BOUNDARY CONDITIONS AND PARAMETERS VALUES.

Boundary Conditions	$\vec{u}_h = \vec{0}\ \mu s^{-1}$ on Γ_E $\vec{u}_h = (1,0)\ \mu s^{-1}$ on Γ_I [8]
The Permeability k	3.5×10^{-3} [4]
The Viscosity ν	5×10^{-6} [1]

IV. RESULTS

In this section, we breef present some numerical experiments to predict the effect of fluid shear stress on cancer cells displacement on the interstitial region to assess its metastatic behaviour.

As control results we have the ones presented at figures 3-4. Here we can observe the cell density evolution without considering the effect of shear stress with parameter $\tau_M = 0$, between $t = 0$ and $t = 19$.

Using the parameters from tables I and II and the above procedure we get, after 19 iterations, the results shown at figures 5-6, where we observe the collapse for some cancer cells under the shear stress effect.

In order to quantify the effect of shear stress we used the function defined at 7 with which we generate the graph at the figure 7, where the black line and the red lines graphs the cell concentration for the cases $\tau_M = 0$ and $\tau_M \neq 0$ respectively. We can observe the decay of cell concentration by the effect of shear stress comparing the cells concentration for each instant.

$$V(\rho) = \int_\Omega \rho \, d\omega \tag{7}$$

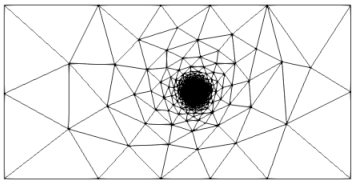

Fig. 1. Mesh at $t = 1$ for KS model.

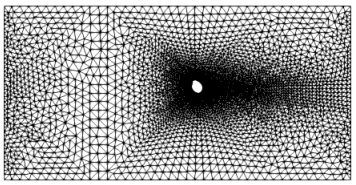

Fig. 2. Mesh at $t = 12$ for KS model.

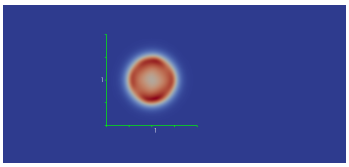

Fig. 3. $t = 1$.

V. CONCLUSIONS

The present manuscript has provided a new model for cancer cell proliferation in a metastatic

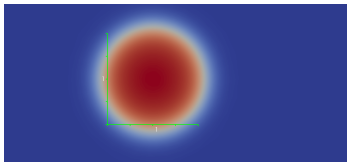

Fig. 4. $t = 19$.

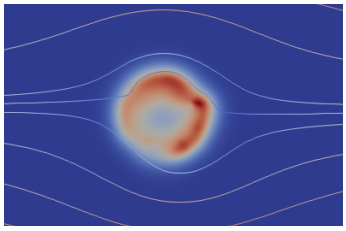

Fig. 5. $t = 1$.

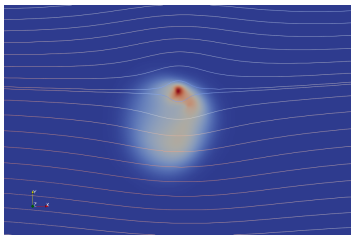

Fig. 6. $t = 19$.

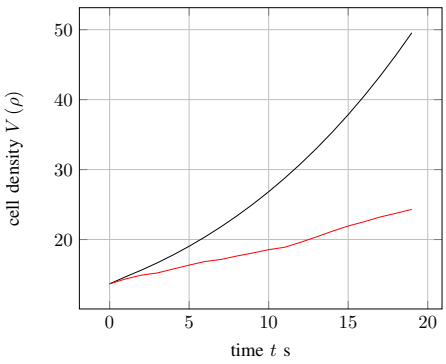

Fig. 7. Comparison of the evolution of cell density with the shear stress effect, the red line, and without, the black line.

process on an interstitial medium in the presence of a shear stress due the fluid forces.

The methodology presented can be enhanced when combined with a complementary therapy strictly targeted at the most resistant cells, thus reducing the amount of drugs needed in the considered time interval.

The model presented also stands out for its parameterization and consequent adaptation to various types of cancer.

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