AGENT-BASED MODELING OF SPHEROID-ECM INTERACTION AND EVOLUTION UNDER FLUID FLOW

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Introduction

A spheroid is a group of cells, usually embedded in a hydrogel, with a quasi-spherical geometry. They are intended to mimic key cellular processes, such as communication, differentiation, migration and signaling, between others [1]. Given the 3D nature of spheroids, they are good *in vitro* models for the study of tumors, since they represent very well the proliferative dynamics present in cancer as well as their heterogeneity in terms of quiescence, hypoxic and necrotic regions found in spheroids [1-2]. In this work, we have developed a 3D agent-based model of spheroid evolution, based on the previous works developed in 2D [2], in which we have added the effect of the extracellular matrix (ECM) and laminar flow, in order to analyze the growth of the spheroid under different scenarios.

Methods

With respect to the mathematical model, nutrient diffusion from the medium to the spheroid nucleus and the dynamics of cell proliferation and death are considered. Depending on the concentration of nutrients, ω (eq. (1)), a cell can be in a proliferative state, if $\omega_q < \omega \leq 1$, quiescent, if $\omega_h < \omega \leq \omega_q$, hypoxic, if $\omega \leq \omega_h$ or necrotic. Different forces are considered in the model, namely, mechanical, between spheroid cells and between spheroid cells with ECM particles (F_i^m and $F_i^{m,ECM}$, respectively); random (F_i^r); surface tension (F_i^s) and laminar flow (F_i^f), see eq. (2). $\boldsymbol{x}_i$ is the cell position in eqs. (1)-(4). When a proliferative cell completes its cell cycle (T_i, eq. (3)), it gives rise to a daughter cell and when a hypoxic cell remains in this state for a certain time ($\tilde{T}_i$, eq. (4)), it becomes necrotic. In eqs. (1)-(4), D_ω is the coefficient for nutrient diffusion, κ is the nutrient consumption rate, ν is the damping coefficient and δ and $\mathcal{H}$ are the Delta and Heaviside functions, respectively. The parameter values are detailed in [2]:

$$\frac{\partial \omega}{\partial t} = D_\omega \nabla^2 \omega - \kappa \omega \sum_i \delta(\boldsymbol{x} - \boldsymbol{x}_i) \quad (1)$$

$$\nu \frac{d\boldsymbol{x}_i}{dt} = \boldsymbol{F}_i^m + \boldsymbol{F}_i^r + \boldsymbol{F}_i^s + \boldsymbol{F}_i^{m,ECM} + \boldsymbol{F}_i^f \quad (2)$$

$$\frac{dT_i}{dt} = \mathcal{H}\big(\omega(\boldsymbol{x}, t) - \omega_q\big) \quad (3)$$

$$\frac{d\tilde{T}_i}{dt} = \mathcal{H}\big(\omega_h - \omega(\boldsymbol{x}, t)\big) \quad (4)$$

Results

In this work, we have considered the following case studies: (i) the spheroid is partially immersed in the ECM in the absence of flow, and (ii) the spheroid has its upper (free) part subjected to a laminar flow, without considering the mechanical interaction with the matrix (Fig. 1):

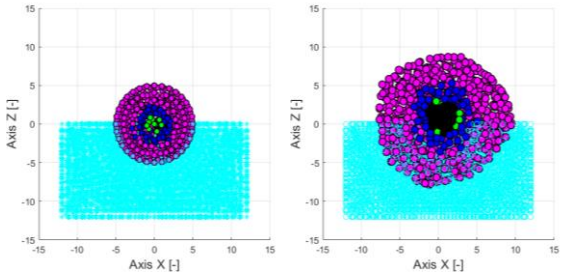

Figure 1: Left: initial conditions in which the spheroid is composed of 816 cells and the ECM of 10127 particles. Right: spheroid subjected to a laminar flow velocity of $1 \cdot 10^{-2} \frac{\mu m}{s}$ *in the upper region and null ECM interaction. The spheroid consists of 1679 cells, of which 77 form the necrotic core. The proliferative layer is magenta, the quiescent is blue, the hypoxic is green and the necrotic is black. The simulations are fully 3D and they correspond to 1000-time steps.*

Discussion

From the simulations performed, we have observed that the shape of the spheroid is conditioned by the mechanical environment. In this case, the matrix induces a stiffer microenvironment to cells, thus decreasing its compressed state and increasing proliferation, due to the translation and expansion of the spheroid towards the more rigid zone, increasing the thickness of the proliferative layer. In addition, the cells tend to move in the direction of flow, because of the tangential component (Fig. 1). These results are in agreement, qualitatively, with other *in vitro* studies in the literature [3-4]. These preliminary results will allow us to develop models of increasing complexity to recreate, *in silico*, the behavior and evolution of *in vitro* experiments of organoids [5].

References

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