Dense discrete phase model for tumor cell growth analysis in fluid environments

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Abstract

Cell-cell and cell-extracellular matrix interactions play a major role in tumor growth, which involves complex molecular intercommunications. We have developed a single-cell computational model in which fluid dynamics and cell-cell interaction are coupled to evaluate the growth of cancer cells in fluidic environments. The results demonstrate that, once the cell concentration increases, the cell-cell interaction increases, decreasing cell maturation time and increasing tumor growth rate.

Introduction

The suitability of in-vitro models to physiological conditions is critical for the development of new reliable cancer therapies [1]. It is challenging to achieve effective results because of the complex interactions between cells and extracellular matrix (ECM) [2,3]. The use of computational models could provide new perspectives and relevant information by evaluating and characterizing the main factors contributing to the growth, metastasis, and development of drug resistance [4]. To study cancer cell growth, we developed a new hybrid computational model that combines single-cell and fluid dynamics. In such case, cancer cell mechanics has been defined in a Discrete Particle Model (DPM), through the implementation of Used Defined Functions in Fluent (Ansys). The model has been validated and compared with experimental results.

Methods

Cell motility is defined by the coupling of the fluid-particle dynamics, as well as the acting forces on the cell (Fig. 1) [5]:

$$m\,\frac{dv}{dt} = \mathbf{F}_{drag} + \mathbf{F}_{r} + \mathbf{F}_{grav} + \mathbf{F}_{ij}, \qquad (1)$$

where m is the cell mass. $\mathbf{F}_{drag}$, $\mathbf{F}_{r}$, and $\mathbf{F}_{grav}$ are the contributions of the drag forces, mesh motion, and gravity, respectively. Finally, $\mathbf{F}_{ij}$ represents the contact forces between cells and walls of the domain, which can be calculated as (see Fig. 1):

$$\mathbf{F}_{ij} = \sum\left[\left[k\,\delta^{3/2} + \gamma(v_{ij}\,e_{ij})\right]\right]\left(e_{ij} + \mu\widehat{e_{ij}}\right), \qquad (2)$$

where k is the stiffness of the contact, δ is the cell interpenetration, and γ is the loss factor, which denotes the non-elasticity of the cell contact. v_{ij} is the relative velocity of the collision, and μ is the cell friction coefficient. Finally, e_{ij} and $\widehat{e_{ij}}$ are unit vectors corresponding to the normal and tangential contact directions, respectively.

The cell's perturbation is transmitted to the fluid flow as an external force, $\mathbf{F}_{ex}$, which is defined as:

$$\mathbf{F}_{ex} = \sum\left[\frac{18\,\mu_f\,C_D Re}{24\,\rho_c(2\,R_c)^2}\left(v_c - v_f\right)\right]\frac{dm}{dt}\Delta t, \qquad (3)$$

where μ_f is the ECM viscosity, C_D is the drag coefficient, Re is the Reynolds number, ρ_c is the cell density, R_c is the cell radius, v_c and v_f are the cell and fluid velocity, respectively.

This force is icorporated into the fluid dynamic resolution via the general equation for the momentum conservation of the continuous phase as:

$$\frac{\delta}{\delta t}\left(\rho_f\,\mathbf{v}\right) + \left(\rho_f \mathbf{v}\,\mathbf{v}\right) = -\nabla p + \nabla\tau + \rho_f\,\mathbf{g} + \mathbf{F}_{ex}, \qquad (4)$$

where p is the static pressure, ρ_f is the continuous phase density, $\mathbf{g}$ is the gravitational acceleration, $\mathbf{v}$ is the fluid velocity, and τ is the contribution of the stress tensor given by:

$$\tau = \mu\left[\left(\nabla\,\mathbf{v} + \nabla\,\mathbf{v}^T\right) - \frac{2}{3}\nabla\,\mathbf{v}\,I\right], \qquad (5)$$

where I is the unit tensor.

Results & Conclusions

For the model validation, a series of experiments where cell sedimentation and cell proliferation are

prepared, evaluated, and compared with in-vitro results. The obtained results are consistent with those reported in the bibliography [5-9].

Cell sedimentation has been studied in a 4.5 mm height matrix for 120 min, in which the cells are randomly distributed along within the domain. Then, cell proliferation has been calibrated with in-vitro results. Once validated and calibrated, the model was used to study cell proliferation for 6 days with various initial cell concentrations. Finally, cell aggregate formation has been studied in 21 days of culture. Initially, cells are seeded into groups of 15-20 cells, which promotes cell-cell interaction. The results show that the cells remain attached once they proliferate, which increases cell maturation rate and, consequently, cell proliferation and tumor growth. As the number of cells in the group increases, tumor aggregates (at least 30 cells) grow in size (Fig. 2).

Acknowledgments

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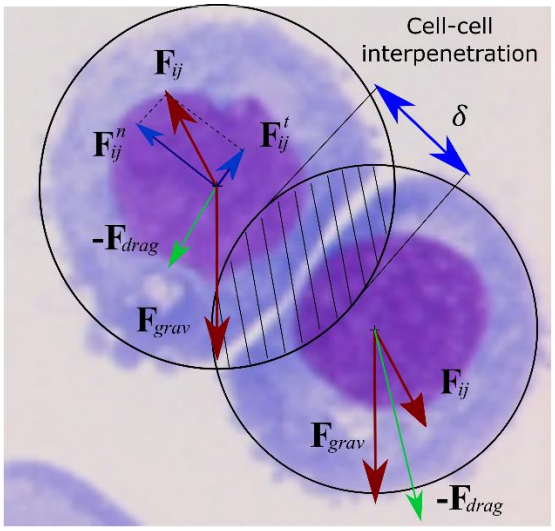

Fig. 1. Cell-cell interaction forces. Cells in a fluid environment are mainly driven by drag and gravity forces. Cell interaction forces are dependent on the interpenetration distance, δ, and the cell stiffness, k .

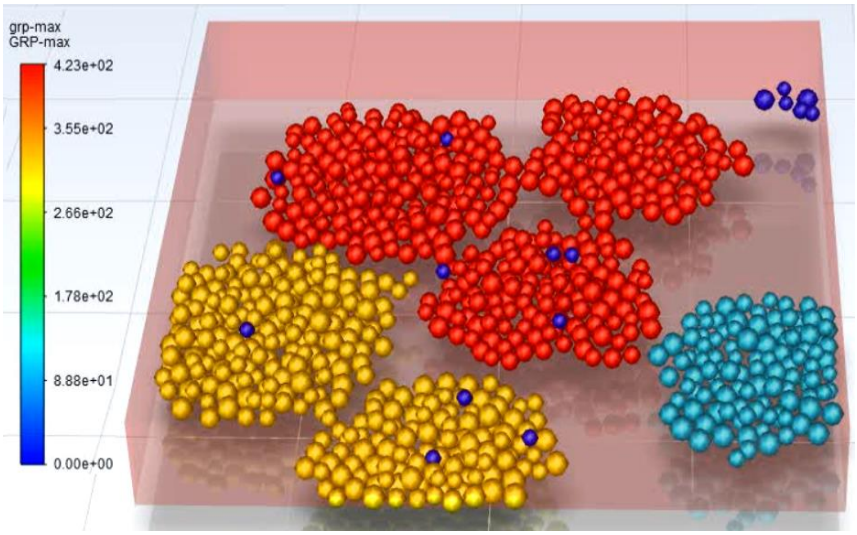

Fig. 2. Cancer cell aggregates after 77 hr. Starting with groups of 15-20 cells, cells interact and proliferate. Groups of cells increase their number and form cell aggregates (at least 30 cells). After 75 hours these aggregates start to merge with surrounding groups, obtaining one cell aggregate with 400 cells.