A MODEL FOR CELL/MATRIX GROWTH ON 3D SURFACES: A COUPLING OF LEVEL SET METHOD AND BRINKMAN EQUATION.

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Introduction

The kinetics of in vitro cell growth has been shown to depend on the local surface curvature of the substrate, an observation that lead to the description of curvature-controlled cell growth [1]. Additionally, Rumpler et al [1] proposed a 2D computational model capable of capturing in vitro cell growth with a curvature-driven velocity advecting the cell surface.

Inspired by the results of Rumpler et al, [1], the work presented here aims to extend their model to 3 dimensions to capture 3D in vitro cell growth, in this case applied for cell-seeded open porous scaffolds cultured under static conditions. To be able to simulate cell/matrix growth in a dynamics bioreactor environment and study the effect of fluid flow on the cell/matrix growth, this study also addresses for the first time a coupling of the proposed growth model to a fluid model.

Methods

To account for the curvature dependent nature of the mathematical model, an initial Level-Set function is computed all over the domain, with the zero-level corresponding to the cell/scaffold-culture medium interface. The curvature is computed at each time step and subsequently the Level-Set function is advected with a certain velocity. This velocity is a constant plus the curvature, resulting in a layer by layer growth as well as an acceleration of cell growth where the curvature is high.

The fluid part of the model is represented by the Brinkman equation which is a mix between the Darcy equation, characterising the flow profile in porous media (the matrix), and the Stokes equation. The model was implemented in FreeFem++ (http://www.freefem.org/), a dedicated language for Finite Element Analyses based on C++.[2]

Results

In a first step, this model was applied to simulate cell/matrix growth in cell-seeded regular scaffolds with different unit cells cultured under static conditions (7 unit cells in total including different geometries and pore sizes, Figure 1a shows a squared unit cell). A preliminary qualitative assessment was carried out using in vitro experimental data [2,3]. The model was able to capture the global cell/matrix growth patterns in all the different unit cells with a same time scale factor for all geometries and pore sizes.

Simulations of cell/matrix growth under dynamics conditions (with fluid flow) showed that the coupled model was able to predict changes in the flow profile in time due the increase of the cell/matrix domain (porous media) (Figure 1b).

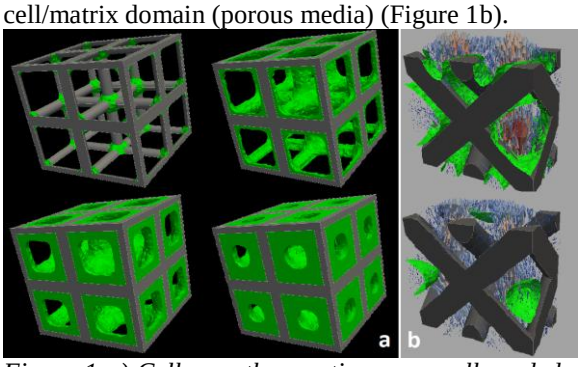

Figure 1:a) Cell growth over time on a cell-seeded squared unit scaffold. b) Velocity profile in a pore at two different time steps (red/blue arrows) and the cell/matrix interface (green).

Discussion

The proposed model is an interesting computational tool to investigate the behaviour of 3D cell growth in regular scaffolds with different unit cell geometries under static and dynamic conditions. In a next step, the growth velocity will be made dependent on specific culture conditions (e.g. fluid flow, medium), and the computational tool can then be used to design optimal combinations of in silico scaffold geometry and culture conditions to, e.g., maximize in vitro cell growth.

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References

[1] Rumpler M. *et al* J. Roy Soc Interface, 2008; [2] Papantoniou I. *et al*, in preparation, 2012 ; [3] Van Bael S. *et al* Acta Biom, 2012.