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3D MODELING OF SHEAR STRESS DEVELOPMENT DURING NEOTISSUE GROWTH IN A PERFUSION BIOREACTOR

Y. Guyot*(1,4), I. Papantoniou(2,4), J. Schrooten(3,4), L. Geris(1,4)

1.Biomechanics Research Unit, University of Liège, Belgium, 2.Skeletal Biology and Engineering Research Center, KU Leuven, Belgium, 3.Department of Metallurgy and Materials Engineering, KU Leuven, Belgium, 4.Prometheus, Division of Skeletal Tissue Engineering, KU Leuven, Belgium.

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Introduction

The kinetics of in vitro cell growth has been shown to depend partially on the local surface curvature of the culture substrate, an observation that led to the description of curvature-driven cell growth models [1,2]. Furthermore cells seeded on a 3D scaffold have been shown to grow not only on the scaffold surface but gradually within the void resulting in total scaffold filling, by cells and secreted extracellular matrix (henceforth called neotissue). This process has been seen to be positively influenced by fluid flow in perfusion bioreactor systems [3]. Neotissue growth however will result in a time-dependent change of the flow patterns developed within the scaffold over the culture period. Current CFD modeling approaches, have a severe limitation due to the fact that the geometries modeled are based on empty scaffold geometries not incorporating the neotissue. This result in insufficient characterization of the condition that the cells will experience. Quantifying the stress magnitude that cells experience within the neotissue but also at the free flow interface (between neotissue and empty space), will be crucial since shear stress has been shown to affect growth kinetics, extracellular matrix secretion and also stem cell commitment.
In order to tackle this challenge, this study addresses for the first time a coupling of the proposed 3D curvature dependent growth model [2] with a Level-Set approach to a specific fluid flow model.

Methods

To account for the curvature dependent nature of the mathematical growth model, a Level-Set method was used because of its ability to deal with moving interfaces and its convenient way to compute local curvatures.
The fluid component of the model is represented by the Brinkman equation which is a composed of the Darcy equation, characterising the flow profile through porous media (neotissue domain), coupled to the Stokes equation for the free flow domain.
In order to take into account the changes in permeability within the neotissue, the simulations have been performed with different values of the neotissue's pore size. The resulting changes in shear stress distribution were investigated.
The model was implemented in FreeFem++ (http://www.freefem.org/), a dedicated language for Finite Element Analyses based on C++.

Results

In a first step, this model was applied to simulate neotissue growth in cell-seeded regular scaffolds with different unit cells. A preliminary qualitative assessment was carried out using in vitro experimental data [2]. The model was able to capture the global growth patterns. Simulations of neotissue growth under dynamic conditions (exposed to fluid flow) showed that the coupled model was able to predict changes in the flow profile in time and space due to the gradual increase of the porous media domain (figure 1). As a result, the model was able to estimate the mechanical environment that cell experience at the neotissue-free flow interface as well as inside the neotissue with a simple approximation mainly based on the pore size. This study demonstrated that the inside shear stress could be 10 to 50 higher than at the neotissue interface for a same flow rate.

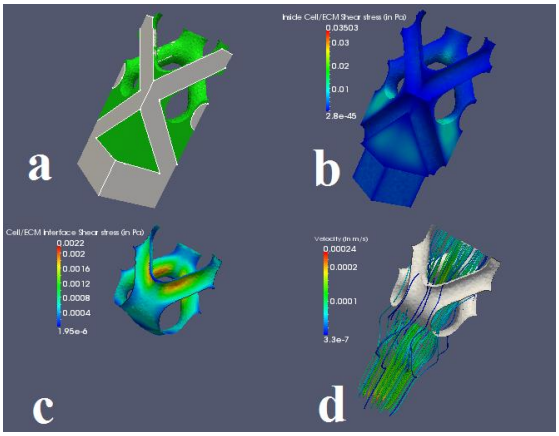

Figure 1:a) Neotissue growth at 50% of filling in the "diamond" unit cell. b) Shear stress distribution within the neotissue with a pore size equal to 50µm. c) Shear stress distribution on the interface. d) Fluid velocity stream lines within the unit cell

Discussion

The proposed model is an interesting computational tool to investigate the time dependent environment that cells will be exposed to during 3D neotissue growth in regular scaffolds under dynamic flow conditions. This will allow to understand the actual impact of shear stress on the experimentally determined biological read outs (ie cell phenotype post culture). In a next step, the growth rate will be linked to specific culture conditions (e.g. fluid flow, oxygen concentration). This modeling platform could be then used as a selection tool to optimize scaffold and bioreactor design specifications..

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References

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