Mathematical modeling of curvature-based cell/tissue growth on open porous scaffolds for bone tissue engineering

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Open porous scaffolds are widely used constructs in a wide range of tissue engineering disciplines as initial support for the subsequent cell growth and tissue development. A suitable construct should be able to promote cell growth with a homogeneous cell distribution. While physicochemical and biological properties of scaffolds are understood to affect the cell growth process, it has been proved by several studies that their architectural and geometrical characteristics, such as pore size and shape as well as curvature, play a significant role in the efficiency of the scaffolds in terms of cell attachment and growth during *in vitro* culture [1]. These parameters should be optimized to enhance cell growth and proliferation rate, requiring dedicated *in vitro* and *in vivo* investigations.

In addition to *in vitro* and *in vivo* models, a third class of models is getting momentum for aiding tissue engineering designs prior to conducting costly experimental efforts, namely *in silico* or computational models. This approach can be employed for various aspects of the scaffold design process such as material selection, mechanical properties, mass transfer, and structure (topology) optimization. However, this needs computational models of the neotissue (cell + extracellular matrix) growth process to evaluate the efficiency of different designs. These computational models should be able to take into account the effect of topological features of the scaffold, the most important of which is the curvature because it affects cell density and contraction or expansion of the local surface area [2].

In this study, a semi-quantitative computational model is developed to investigate the growth of neotissue and cell proliferation process on any arbitrary shape in 2D and 3D. From a mathematical point of view, this has been achieved by formulating the tissue growth phenomenon as a moving interface problem, an approach that has been successfully applied to other models in tissue engineering such as the bone-healing process [3] and scaffold biodegradation [4]. In this method, the boundary between the neotissue and the void space in the bioreactor is captured and tracked over time, utilizing mathematical equations correlating the effect of curvature to the rate of growth. By doing this, the cell/tissue growth behavior can be simulated for any desired shape *in silico*.

The equations describing the curvature-based growth are relatively simple and general from a mathematical point of view, but in practical implementations, developing an *in silico* model may become quickly complicated since treating the equations require special techniques. In this work, 2 separate mathematical models are derived using well-known interface tracking techniques, i.e. level-set and phase-field, which are similar from a tissue engineering perspective but with fundamental differences in their mathematical basis. The models are implemented using the finite element method for simulating the tissue growth process, for which the results show that both produce the same output for similar geometries. Currently, the models are getting validated using experimental observations from different scaffold shapes. Once validated, these models can be used for predicting the efficiency of the open porous scaffold design from the structural perspective.

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