COMPUTATIONAL FLUID DYNAMICS ON MICROCARRIER DESIGN IN TISSUE ENGINEERING. PART I

Eric T. Crumpler (1), Ronald A. Gutierrez (2),

(1) Biomedical Engineering Institute
Florida International University
Miami, Florida

(2) Mechanical Engineering Department
Florida International University
Miami, Florida

INTRODUCTION

The loss or failure of an organ or tissue is one of the most frequent, expensive and severe problems in human health care. The world demand for organ and tissue transplant surpasses the existing supply [1]. In the Unites States almost 25% of the patients die waiting for a suitable donor, and the projection for the future indicates that this amount will increase [2]. Current therapy includes transplantation of living organs, limited by the scarcity and compatibility of the donor, and implantation of artificial devices, which never completely restore the organ and tissue's previous functionality [2]. Despite all organ and tissue organizations that expend exorbitant amounts of money and time to get an appropriate donor for a particular patient, the clinical requirements have not been fulfilled. Therefore, new technologies and procedures have to be developed.

A new field, Tissue Engineering (T.E), which is an interdisciplinary field, can solve several of the problems related with organ transplantation [1]. The promise is that biological function lost in host tissues will be able to be restored and maintained by harvesting a small number of living cells from the recipient's own tissue. With the selection of the cells, the next step is to develop a matrix in which these cells are organized in a three-dimensional architecture and grown *in vitro* with functional characteristics such that a specific tissue is mimicked. The benefits of this novel procedure allow the surgeon to implant only the cells or tissue of interest, and since they are autologous, there would be less chance of compatibility problems. These cells have the potential to multiply *in vitro,* hence subsequent tissue supply will lessen the cost of treatment, thereby making an early intervention during the patient's illness entirely possible [3].

For many tissue types, such as bone marrow, liver or lung tissue, it is essential to conduct long-term tissue cultures. Therefore the mechanical properties expected around the tissue culture will be important. One of these mechanical properties is the wall shear stress exerted on the surface, that directly influence the cell culture, mainly in the production of Glycoaminoglycans (GAG) and collagen II [4]. These cellular secretion products predetermine the cell matrix stiffness and the fibrillar framework, respectively. Despite many investigations that have been conducted on the modification and redesign of the currently used matrices or scaffolds, few have related the cell growth with the poor hydrodynamic geometry of the microstructures. Thus, the aim of this study is to obtain direct qualitative and quantitative correlations of the hydrodynamics parameters with scaffold morphology by comparing wall shear stress effects on scaffold design. Novel matrices generated would allow the design and manufacture of constructs for future GAG and collagen II enhancement experiments. The development of computational models representing the different shapes and simulating the different flow parameters within an *in vitro* cell culture system will be presented.

MATERIALS AND METHODS

Bioreactor and Initials Conditions

The final step in forming an organ or tissue *de novo* is placing the seeded culture into a bioreactor and allowing cells to differentiate and begin developing the desired tissue. In this study, flow conditions within a rotating bioreactor around suspended microcarriers were simulated by applying Computational Fluid Dynamics for computing three-dimensional velocity profile and shear stress interactions. The model rotating bioreactor for tissue engineering is composed of the annular space between two concentric cylinders with endwalls, which rotate about their common axis at average steady angular velocity of 15-28 rpm for speeds of 2-4 cm/s [5]. Fluid-flow simulation was performed in a 1:1 scale model of Synthecon Reusable Slow Turning Lateral Vessel (STLV®). The flow field is confined to the annular region of the vessel with inner radius of 0.95 cm, outer radius of 2.75 cm and a length of 2.6 cm. The annular space was charged with 55 ml of cell culture medium with kinematic viscosity ν =1E-6 m^2/s, a density ρ_f= 1030kg/m^3 and a constant temperature of 37.5º C.

Models Geometries

Two bioreactor/scaffold models placed separately within the rotating bioreactor were constructed with varying shapes. Between the rotating concentric cylinders, the constructs were subjected to Couette

shear flow conditions generating well-defined flow fields. After real exposure, the scaffold remained in a continuously free-falling state near 14-16 rpm and maintained a non-wall contact environment. In both models, the construct material consisted of polyglycolic acid and polylactic acid where PGA: PLA was 50:50 wt% and density was set at 1528 kg/m^3. The first model had a disc shape with a radius of 5 mm and height of 2 mm (Figure 1). The second had a rugby-ball shape and was used to minimize wakes and/or turbulence by attempting the streamlines follow the geometry's contour. It was drawn with the same dimensional relationship of an ordinary rugby-ball such that its total height in diameter was 60% of actual measurements. Thus, the dimensions predetermined for the rugby-ball model were 6 mm in diameter and 10 mm in height (Figure 2).

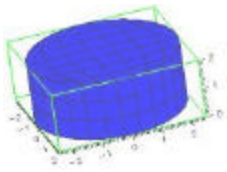

Figure 1. Disc shape scaffold

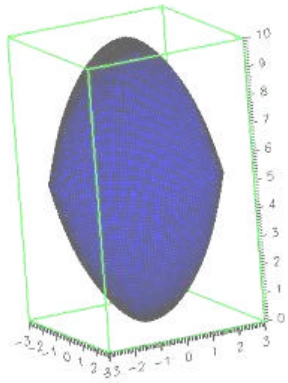

Figure 2. Rugby-ball shape scaffold

Computational Fluid Dynamics and Mesh Convergence

The computational fluid dynamics commercial software used to model the constructs was CFDRC[7]. First we carried out flow computations using a sequence of two finite element meshes of increasing mesh density for the bioreactor flow conditions, assuming a no z-direction flow due to the solid-body rotation of the fluid. This option considerably reduces the size of the model and as well as the running time, thus lessening memory consumption and resulting in a better computer's performance.

The grid density was consecutively doubled and compared until the estimated global relative error dropped below a preselected value (a 5% was used for this study), showing that the mesh independence has been attained.

RESULTS

Preliminary results of the iteration cycle are shown in Figure 3. The y-axis represents error magnitude converging in the vicinity of 280 points per line with a standard error of 3 %. This error is within the preselected value.

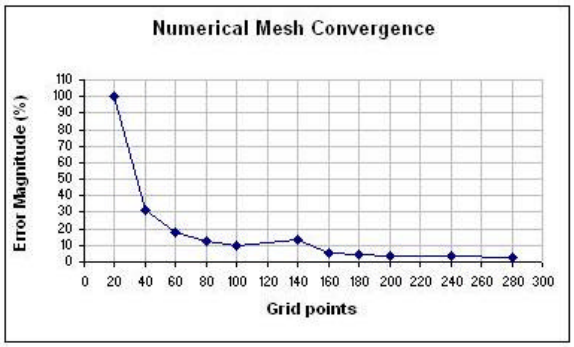

Figure 3. Numerical Mesh Convergence

CONCLUSION

The grid value obtained in this setup gives an idea of the mesh generation to be applied on the 3D bioreactor model. These results have important implications for the accuracy of existing and future compartmental models. The results suggest that the numerical instability associated with a coarse mesh, rather than the particular choice of membrane parameters, is partially responsible for driving some of the simulations to spike threshold. The prior absence of automatic mesh-generation software required the creation of compartmental models for every grid point's increment.

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