Scaffold Design for Functional Tissue Engineering and Cell-Based Gene Therapy Applications

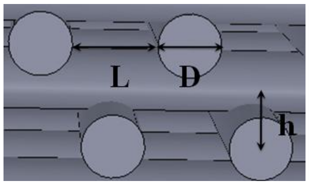
A.M. Yousefi
[1]Bioengineering, School of Engineering and Applied Science, Miami University, Oxford, OH, USA

Statement of Purpose: Maintaining adequate nutrient and oxygen diffusion to cells is an essential requirement for the success of tissue engineering.[1] It is hypothesized that 3D scaffolds should provide optimal porosity, pore interconnectivity, and a high effective surface for cell attachment while mimicking the stiffness of target biological tissues.[2,3] This work presents the effect of scaffold topology and micro- and macroporosity on the performance of 3D scaffolds produced by solid freeform fabrication techniques (3D-plotting and 3D-printing). Previously, blends of poly(L-lactic-co-glycolic acid) and hydroxyapatite (PLGA/HA) were used to produce scaffolds by a combination of 3D-plotting and porogen-leaching techniques for cell-based gene therapy applications. These micro/macroporous scaffolds demonstrated a desired level of protein release and cell viability for treating hemophilia B.[4,5] The implanted constructs were able to cure hemophilic mice for over 12 weeks, which is a considerable improvement over previous attempts using similar strategies. For treating anemia, the designed micro/macroporous poly(L-lactic acid)(PLLA) scaffolds were seeded with murine bone marrow-derived mesenchymal stromal cells (MSCs), genetically engineered to secrete erythropoietin (EPO)[3]. In another study, the 3D-plotted constructs were used for functional tissue engineering applications. The micro/macroporous PLLA scaffolds, designed to mimic cartilage and seeded with chondrocytes, improved the cell viability under dynamic loading conditions inside a bioreactor[6]. The present work gives an overview of the 3D-plotted scaffold topologies used in these studies and presents the results of an ongoing research on scaffold design (3D-printing), with a focus on prediction of mechanical response and mass transport performance at macro- and microscale.

Methods: 3D-printed scaffolds were fabricated using the fused deposition modeling (FDM) and stereo lithography (SLA) printing techniques. Three different polymers were used in this work. Figure 1 shows the topological parameters for the 3D-printed scaffolds and summarizes the scaffold topologies used in this study. The scaffolds were tested under successive unconfined ramp compression at different strain rates, and the maximum peak stress and the compressive stiffness were estimated for each ramp. The Comsol® modeling software was used to predict the mechanical response and mass transport performance of the scaffolds.

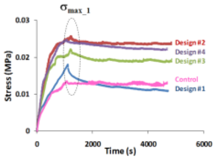
Results: Figure 2 compares the mechanical response of the scaffolds for the first compressive ramp (3% strain) and summarizes the effect of topological parameters on the peak stress (σ_{max_1}). It was found that normalizing the compressive peak stress by its respective value for the control sample (no pore) is a good indication of the role of scaffold topology on its mechanical performance (results not shown). In an effort to investigate the effect of pore interconnectivity on mass transport efficiency, the mass diffusion was compared for two scaffolds with different pore interconnectivity (design #1 and design #5). An imposed pore concentration (c=1 mol/m^3) and mass diffusion coefficient for the strand (D=3e^{-11} m^2/s) were used for comparison purposes. Figure 3 shows the simulation results, demonstrating a poor mass transport for a scaffold without interconnected pores (Design #5) and indicating the key role of pore interconnectivity on improved mass transport.

Conclusions: In future studies, the Comsol® software will be combined with multiscale modeling capability to predict the mass transport and mechanical response of the 3D-plotted and 3D-printed scaffolds. In parallel, further studies based on a higher number of scaffold topologies will be performed to build a model for predicting the effect of topological parameters and material stiffness on scaffold mechanical performance.



Design #	Diameter D (µm)	Pore Size L (µm)	Thickness h (µm)
1	1000	800	760
2	1400	800	1040
3	1400	1200	1040
4	1400	800	850
5	1000	800	N/A

Fig 1. Summary of the topological parameters for the 3D-printed scaffolds used in this study.



	Change in σ_{max_1} (MPa) – Ramp 1			
	Increase Factor	Mat I	Mat II	Mat III
Change D	40%	42.3%	46.8%	21.3%
Change L	50%	-13.8%	-2.5%	-
Change h	22%	4.0%	8.4%	-

Fig. 2. (left) Comparative stress relaxation curves (1st ramp) for the scaffolds and the control (no pore); (right) Comparison between the effect of each topological parameter on σ_{max_1} (1st ramp).

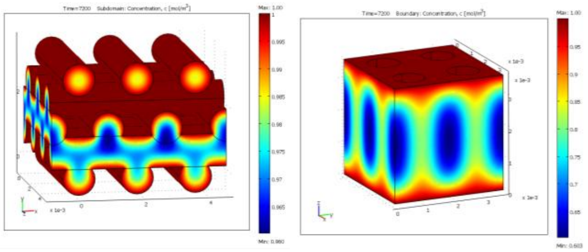


Fig. 3. Effect of pore interconnectivity on mass transport efficiency; (left) Design #1, (right) Design #5.

References:

1. Mooney DJ. J Biomed Mater Res. 1997; 37:413-420.
2. Yousefi AM, Polym Eng Sci. 2007; 47:608-618.
3. El-Ayoubi R. Tissue Eng. 2008; 14:1037-1048.
4. Coutu DL. J Biomat. 2010; doi:10.1016.
5. Coutu DL. J Cell Biochem. 2009; 108:537-546.
6. El-Ayoubi R. J Biomater Appl. 2009; doi:10.1177.