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Modeling the flow and mass transport in a mechanically stimulated parametric porous scaffold under fluid-structure interaction approach

M. Malvè[a,b,c,*], D.J. Bergstrom[d], X.B. Chen[d,e]

[a] Aragón Institute of Engineering Research, Universidad de Zaragoza, C/María de Luna s/n, E-50018 Zaragoza, Spain
[b] CIBER-BBN. Centro de Investigación en Red en Bioingeniería, Biomateriales y Nanomedicina, C/Poeta Mariano Esquillor s/n, E-50018 Zaragoza, Spain
[c] Universidad Pública de Navarra, Departamento de Ingeniería, Edificio de los Pinos, Campus Arrosadía s/n, E-31006 Pamplona, Spain
[d] Department of Mechanical Engineering, University of Saskatchewan, College of Engineering, Engineering Building 57, Campus Drive, Saskatoon, SK S7N 5A9, Canada
[e] Division of Biomedical Engineering, University of Saskatchewan, College of Engineering, Engineering Building 57, Campus Drive, Saskatoon, SK S7N 5A9, Canada

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ABSTRACT

Tissue engineering scaffolds combined with bioreactors are used to cultivate cells with the aim of reproducing tissues and organs. The cultivating process is critical due to the delicate in-vitro environment in which the cells should reproduce. The distribution of nutrients within the engineered construct depend on the scaffold morphology and the analysis of the fluid flow and transport phenomena under mechanical loading when the scaffold is coupled with a bioreactor is crucial for this scope. Unfortunately, due to the complicated microstructure of the scaffold, it is not possible to perform this analysis with experiments and numerical simulation can help in this sense. In this study we have computed the fluid flow and the mass transport of a parametrized scaffold in perfusion bioreactors analyzing the influence of the microstructure of the scaffold using the fluid-structure interaction approach. The latter allows considering the porous construct as compliant yet determining important structural parameters such as stresses and strains that could be sensed by the cells. The presented model considered flow perfusion that provided nutrients and mechanical compression. In particular, we have studied the effect of controllable parameters such as the diameter of the scaffold strand and the porosity on the mechanical stresses and strains, shear stress and mass transport. The results of this work will help to shed light on the necessary microenvironment surrounding the cultivated cells improving culturing scaffold fabrication.

1. Introduction

Cartilage repair tissue engineering aims to cultivate cells by creating adequate microenvironment and culturing strategies in-vitro. In recent years, a variety of porous tridimensional scaffolds have been designed for this goal, considering that these structures provide a good architecture for cell culture. In particular, the combined use of bioreactors with three-dimensional (3D) porous structures has provided the necessary conditions for the cells to live and reproduce by means of a variety of stimuli. The latter is crucial for cartilage tissue, which needs a specific mechanical stimulation for maintaining its differentiation in-vitro under different biochemical factors [1]. The scaffold is commonly located in a bioreactor. In this device, oxygen and nutrients continuously flow within the culture medium through the pores of the scaffold, allowing the attached cells to grow and proliferate. In the literature of the field it is stated that the shear stresses on the scaffold due to this fluid motion can positively or adversely affect the culture. While a moderate shear stress could benefit the formation of glycosaminoglycan (GAG) and as a consequence the cartilage tissue repair and growth, on the other side a high shear stress may sweep off the attached cells or cause their apoptosis [2]. For this reason, for the cell culture is crucial to find a compromise between the mass transfer and the shear stress. Computational fluid dynamics (CFD) has been widely used for solving and determining the shear stress distribution of idealized [3, 4] and complex microCT-based scaffold structures [5, 6, 7, 8, 9, 10, 11, 12]. Recently, a validation of such models using particle image velocimetry (PIV) has been proposed with the aim of investigating how fluid flow conditions modulate cell motion and deposition during perfusion [13, 14, 15]. These models provided insight to the shear stress on the scaffold-attached cells and to investigated global characteristics such as porosity and permeability, but neglect the mass transport phenomena that, on the contrary, is included in other studies [16, 17, 18, 19, 20, 21, 22, 23]. Computational modeling has been applied also under pure structural finite element analysis to predict the mechanical stimulation experienced within tissue engineered scaffolds due to mechanical compression/stretching in vitro [24, 25,

* Corresponding author at: Universidad Pública de Navarra, Departamento de Ingeniería, Edificio de los Pinos, Campus Arrosadía, E-31006 Pamplona, Spain.
E-mail address: mauro.malve@unavarra.es (M. Malvè).

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26]. The finite elements method (FEM) offers the possibility of handling complex geometry such homogeneous or non-homogeneous microstructures and analyzing the scaffold architectures [7, 24, 5, 27, 28]. It is known that cartilage reconfigures both in vivo and in vitro in response to mechanical loads [6, 29]. For this reason, mechanical stimulation is believed to be a potential tool for modulating extra-cellular matrix synthesis in tissue-engineered cartilage [30]. Thus, apart from the fluid motion, another important parameter to take into account for cell culturing is the mechanical load applied to the scaffold. In vitro studies on cartilage cultures have demonstrated that static loading generally inhibits glycosaminoglycan (GAG) synthesis [31], while cyclic loading can increase or suppress GAG synthesis, depending on the load frequency [31, 32, 33], amplitude [34] and duration of load application [33]. In cartilage tissue engineering studies for cell-seeded scaffolds, the effects of the frequency of dynamic loading have been studied over a wide range of frequencies in conjunction with factors such as cell seeding density [35] and loading configuration [36] with the aim of measuring the regeneration of the extra cellular matrix over the culture time period [29]. From these studies we can conclude that a dynamic mechanical loading of articular cartilage massively affects the regulatory pathways by which chondrocytes respond to their surroundings [37]. Only a few recent studies have attempted to compute fluid perfusion through the scaffold labyrinth and mass transfer phenomena considering the effective micro-architecture of the scaffold because of the computational time required for such analyses, especially when further combined with fluid-structure interaction (FSI) [23, 27, 38, 39, 40]. Although mass transfer in porous medium such as a tissue engineering scaffold has attracted much attention for providing the correct environment for cells to reproduce, its analysis is incomplete and further knowledge is necessary. A few works oriented to oxygen consumption have proposed mass transport models for this kind of application [23, 41, 42, 43]. Other studies characterized the porosity and mass transport properties of polyurethane non-regular scaffolds [44, 45]. For reproducing in silico the microenvironment within cartilage tissues by means of in vitro models, the evaluation of the conditions surrounding a cell at a given flow rate in a certain location of the scaffold represents essential information. As discussed, mechanical stimuli depend on both fluid motion and scaffold structural loading. For this reason, the presented work analyzes in detail the flow within a scaffold under mechanical stimulation as a function of the structural parameters of the scaffold. In addition, the analysis of the mass transport in each architecture is provided. The scaffold considered in this work is a manufactured structure that has been fabricated by means of rapid prototyping (RP) techniques and has the advantage that its microstructure is regular and controllable so that the geometry can be modeled by CAD methods. For this device, a study of the effect of parameters such as the diameter of the scaffold strand and the scaffold porosity on the shear stress in the fluid, on the structural stresses and strains, and mass transport within the scaffold is proposed. Such knowledge will help to improve scaffold design, fabrication and culturing strategies.

2. Materials and methods

2.1. Scaffold and bioreactor configuration

The scaffold structure used in this work has been already described in details in a previous study [9] so that here only a general overview is given. Its design consists of a regular distribution of cylindric strands with variable diameter and spacing between elements (Fig. 1). The diameter and height of the scaffold are 3 mm and 5 mm, respectively. Each layer of elements is organized by an offset of $\theta = 90^{\circ}$ in their orientation from layer to layer. The scaffold architecture can be described by means of two parameters that can be controlled during the scaffold fabrication [46, 47]: the strand diameter (D) and the horizontal span (Y). These parameters with the distance between two adjacent horizontal (h_{xy}) and vertical (h_z) strands, represent the pore sizes sketched in the Fig. 1. In previous research [46], the vertical pore size (h_z) has been described as a function of geometrical and material properties of the scaffold i.e. the diameter of the strand (D), the density of the scaffold material (ρ), the material elastic limit stress (σ_e), the horizontal span (Y) and the angle between two consecutive layers (θ) (see Fig. 1). On the contrary, the horizontal distance (h_{xy}) is exclusively associated with the strand diameter (D) and the horizontal span (Y). The approximate relationship can be described as follows:

$$h_z = D \cdot \sqrt{1 - \frac{\rho g Y}{2\sigma_e} \cdot sin\theta} \tag{1}$$

As in previous studies [46, 9] the scaffold is fabricated using a chitosan solution with 40% hydroxylapatite (HA) gel with an elastic limit stress of $\sigma_e = 11.0$ Pa. In the present study, the strand diameter D was varied from 0.2 to 0.4 mm, while the horizontal span Y was varied from 0.5 to 0.9 mm. As a function of the parameters Y and D we considered 9 different scaffolds that are classified in the Table 1. The vertical pore sizes corresponding to each scaffold are given in Table 2. With this information, the geometrical model was carried out by means of the software Rhineceros (Robert McNeel & Associates, Seattle, WA, USA). From the geometrical model, the porosity, which is defined as the ratio of the void volume to the total volume, was calculated for each scaffold (see Table 2). As mentioned, for reason of computational costs, unlike the study in [9], only a cylindrical sample of the entire scaffold was considered. The bioreactor consists of a cylindrical tube of 50 mm length and with the same diameter as the scaffold. The computational model was implemented using the software package Adina R&D (Adina Inc., Watertown, MA, USA) with the aim of evaluating the the wall shear stress, the stresses and strains and the mass transport within the porous scaffold structure considering the fluid-structure interaction. The cell culture media consisted of water and dissolved nutrients so that it was considered as incompressible, homogeneous and Newtonian with a density of 1000 kg/m^3 and a viscosity of 0.001 Pa s [10]. For the FSI model we considered the structure of the scaffold to be made of a homogeneous, isotropic and elastic material [7, 23, 48]. The FSI simulations were performed assuming quasi-steady condition for the flow model and static condition for the solid model under a residual convergence criteria of 10^{-4}.

2.2. Boundary conditions

The scaffold structure was considered as deformable. Its elastic modulus was set to 0.4 MPa [49, 50]. As mechanical stimulation, a uniaxial compression with a maximum strain of 5% was applied. This compressive strain is similar to that encountered inside the human body (which is less than 6% [51]). The latter was mimicked by means of a uniform displacement equivalent to a uniaxial strain of 5% applied on the nodes of the upper side of the meshes while fixing the nodes of the lower side [7]. Regarding the necessary fluid flow to be provided, low velocity may increase cell proliferation while peaks of high velocity are associated with cell apoptosis. However, high levels of fluid velocity are necessary for cell seeding within the scaffolds [7]. In this context, it is clear that a compromise is required [2]. Considering that an increase of flow promotes an increase of wall shear stress (WSS) within the scaffold elements as evaluated in [9], we considered only one flow condition of 0.05 ml/min. The latter was adapted to the inlet diameter of the present study that is smaller than that designed in [9]. For the outlet boundary condition, as usual for fluid-structure interaction models, pressure conditions should be prescribed. Generally speaking, for correctly computing the stresses and strains, flow/velocity-pressure conditions are required. Since we imposed the flow at the inlet and the pressure at the outlet was unknown, we performed a CFD analysis of the fluid domain imposing the flow at both inflow and outflow. Once the pressure was determined, we used its value as outlet condition for the FSI