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Finite Element Analysis of Fluid Flow through a Porous Scaffold in a Perfusion Bioreactor

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ABSTRACT: The dynamic physical environment and geometric architecture required for tissue engineering can be achieved by combining tissue engineering scaffold and biological reactors. These bioreactors are used to perform mechanical stimulation on cells to create tissue. These cells are planted on the surface of the scaffold. In this system, the amount and distribution of mechanical stimulation applied to cells depend on the scaffold's microstructure. The geometry of the designed scaffold depends on two independent parameters. By changing these independent parameters, three scaffolds with different porosity are created. A flow rate of 0.05 ml/min has been used to perfuse the bioreactor. Simulations performed under steady-state conditions using continuity and Navier-Stokes equations. Based on the results, there was an increase in flow within the scaffold with the lowest porosity up to 10 times. The maximum wall shear stress and flow velocity were observed in the scaffold with the lowest porosity. The maximum wall shear stress on the scaffold with the highest porosity was 4.95×10^{-7} kPa. According to the findings, in order to apply the appropriate shear stress on cells and maintain a uniform pressure gradient across the scaffold, porosity can be increased to some extent that does not damage the ideal surface area to volume ratio.

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1- INTRODUCTION

Tissue engineering is currently one of the most important fields focused on repairing damaged tissue or creating a new one [1]. Cartilage repair, as a subset of tissue engineering, aims to create adequate microenvironment and culturing strategies in order to cultivate cells in-vitro. According to the fact that three-dimensional scaffolds provide an excellent environment for cell culture, numerous geometrical designs for three-dimensional scaffolds have been introduced over the years. The combined use of three-dimensional porous structures with bioreactors has provided the needed conditions for the cultivation of cells. Due to the different biochemical factors, a specific mechanical simulation is necessary to attain the differentiation of cartilage tissue in-vitro [2]. Some of the most important factors to consider in order to design an ideal scaffold are the existence of porous structure, the size of the porosity, and sufficient specific surface for cellular binding, proliferation, and differentiation [3]. In order to reproduce and evaluate the results in different studies, it is essential to characterize scaffold using different parameters [4].

The scaffold is often placed inside the bioreactor. Oxygen and nutrients flow continuously within the bioreactor and nourish the cells that are planted on the scaffold. In this process, the culture medium passes through the pores of the scaffold, allowing the attached cells to grow and proliferate [5, 6]. This fluid can act as a biomechanical factor in stimulating cells and determining their fate. It has been shown that this effect is achieved by stimulating through shear stress and fluid hydrodynamic pressure [7, 8]. The described bioreactor is called a perfusion bioreactor, which is better than other models (e.g., the spinner flask bioreactor and the rotating wall vessel bioreactor), since the mass transfer is enhanced within the scaffold [9]. However, increased flow can increase the shear stress, and the latter is a factor in separating the cells from the scaffold surface [10]. It is noted in the literature that high shear stress is a factor that causes the cells to separate from the surface of the scaffold and leads to cell apoptosis, while proper shear stress restores tissue and helps cells to proliferate [11]. Shear stress has a stimulating effect on matrix synthesis and re-expression of chondrocyte phenotypes [12]. For this reason, it is essential to find a compromise between mass transfer and shear stress [11].

Due to the complexity of monitoring and controlling the growth and proliferation of cells, it is not possible to measure the local shear stress distribution within a scaffold by means of experiments [13]. For this reason, research on scaffolds and bioreactors is carried out through modeling. In particular, the use of a combination of biological reactors and 3D porous scaffolds has necessitated the survival and reproduction of cells in a wide range of simulations [11]. Some studies [14-16] investigate characteristics such as porosity and permeability

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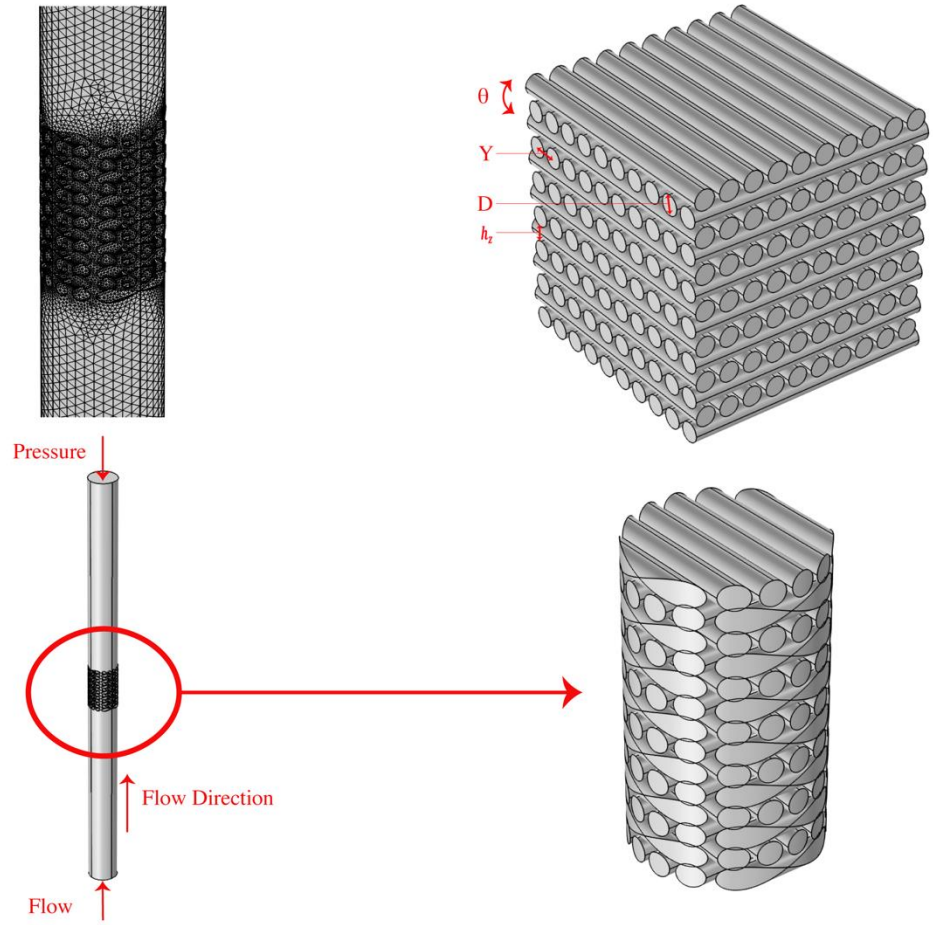

Fig. 1 . Geometry of the scaffold GT1 with controllable parameters and mesh details.

without considering mass transport phenomena. On the other hand, some studies included mass transportation in their work [17-19]. From previous studies, we can conclude that dynamic mechanical loading of articular cartilage significantly affects the regulatory pathways by which chondrocytes respond to their surroundings [20]. Because of the high computational cost, only a few recent studies have computed fluid perfusion dynamically combined with fluid-structure interaction (FSI) and mass transfer phenomena inside a scaffold [11]. Micro-computed tomography (μCT) method is used to obtain 3D geometry for scaffolds with an irregular geometric structure. In addition to μCT, another method for modeling irregular geometries is to consider the scaffold's internal structure as repeating units that can be designed with computer-aided-design (CAD) methods. CAD designed scaffold has been studied to investigate the effect of pore size and porosity on it, but this method will be accompanied by errors due to the simplification it requires. Currently, Rapid prototyping (RP) is being used to manufacture scaffolds with a regular structure. Besides being able to change their controllable microstructure, the geometry can be readily modeled by CAD methods [10].

In the present study as the first group of studies [14-16], investigation of mass transfer is neglected. For this study, a parametric scaffold for cartilage tissue engineering modeled with CAD methods. The effect of parameters such as the strands diameter and the scaffold porosity on the shear stress and pressure drop has been studied for the scaffold under perfusion. The approach used in this study requires less computational costs, but it is possible to modify and optimize the scaffold and bioreactor with an acceptable approximation.

2- MATERIALS AND METHODS

2-1- Scaffold and bioreactor configuration

Structure of the scaffold used in this study has been extensively explained in previous studies [10, 11]. For this reason, only a general overview is given. The geometry of ordinary parallel strands was considered to have a 90-degree offset in each layer compared to the previous one (Fig. 1). The scaffold architecture can be described by means of two parameters that can be controlled during the scaffold design [21, 22]. The first parameter is the diameter of the strands (D) forming each layer, which eventually builds the entire structure of the scaffold. The larger diameter results in a decrease in porosity and vice versa. The second factor is the horizontal spacing of the center of two adjacent strands in a layer. As the horizontal span (Y) increases, the porosity increases too, and vice versa. The third parameter, which is dependent on the two previous parameters, D and Y, is h_z defined as follows [22]:

Table 1. Geometrical dimensions and porosity of the scaffolds [11].

	GT1	GT2	GT3
D (mm)	0.4	0.3	0.2
Y (mm)	0.5	0.7	0.9
h_z (mm)	0.358	0.225	0.16
Porosity	34%	64%	80.6%

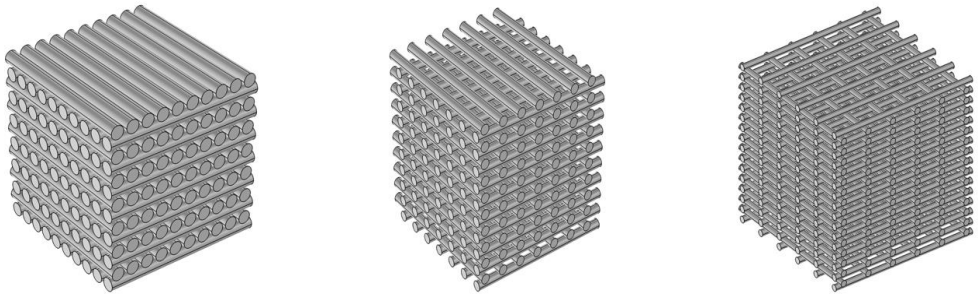

Fig. 2. Three scaffolds with different porosities. GT1 and GT3 have the least and most porosity, respectively.

Table 2. Fluid properties and boundary conditions at inlet and outlet [11].

Fluid density	Dynamic viscosity	Inlet velocity	Outlet pressure
1000 Kg/m^3	0.001 Pa.s	0.0000125 m/s	0 pa

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

In Eq. (1), h_z has been defined 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 ($\sigma_e = 11.0\,Pa$), the horizontal span (Y) and the angle between two consecutive layers (θ) [22]. Taking into account different values of the scaffold's parameters, we arrive at three different porosities with unique behaviors against the flow (see Table 1. and Fig. 2) [11].

2-2- Governing equations

The Navier-Stokes equations govern the motion of fluids, which are always solved together with the continuity equation [23]. Since simulations are performed under steady-state conditions, the time-dependent derivative is set to zero. Gravity is neglected, and for this reason, there are no external forces. Considering fluid to be laminar, incompressible with a constant density, the continuity and Navier-Stokes equations reduce to:

$$\nabla \cdot u = 0 \quad (2)$$

$$\rho(u \cdot \nabla u) = -\nabla p + \nabla \cdot \left(\mu\left(\nabla u + (\nabla u)^T\right)\right) \quad (3)$$

where u is the fluid velocity, p is the fluid pressure, ρ is the fluid density, and μ is the dynamic viscosity.

2-3- Boundary conditions

According to researches carried out in previous studies [10, 11], a flow rate of 0.05 ml/min has been proposed, which creates the balance between the advantages and disadvantages of low and high flow rate (Low flow rate increases the chances of cell proliferation, but on the other hand, it is possible that the flow of nutrients and oxygen does not reach all sections of the scaffold. A high flow rate causes the cell to separate from the surface of the scaffold and initiates cell apoptosis.) [24]. For the GT1 scaffold, three different velocities were considered at the input; the results reported in Table 4. The flow condition has been adapted according to the inlet diameter [25]. For the outlet boundary condition, the average pressure at the outlet was set to zero. Fluid properties and boundary conditions at inlet and outlet are reported in Table 2. The wall was considered as a rigid body, and a no-slip condition was also applied [10]. The simulations were performed for all three types of the geometry described in Table I. The volume of the scaffold was reduced from the volume of the biological reactor. All that remained was possible paths for fluid to flow through the scaffold in case the scaffold is inside the bioreactor. due to the described conditions, there is no interaction between the fluid and the scaffold. (see Fig. 1).

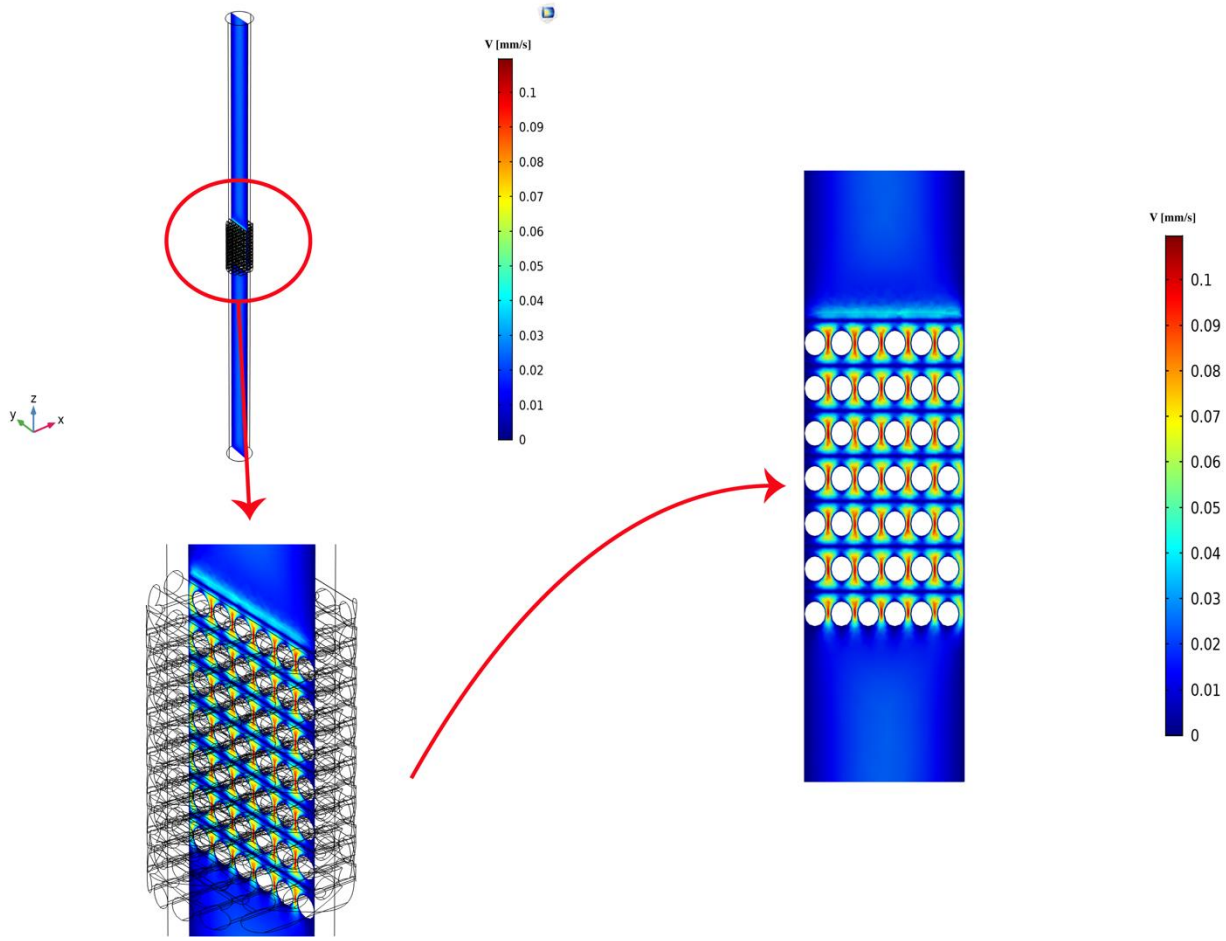

Fig. 3. Velocity magnitude contours within the GT1 scaffold architecture.

2-4- Numerical discretization

The meshing operation was performed automatically by the software, COMSOL Multiphysics® v. 5.5 [26], and its definable parameters such as curvature factor, resolution of narrow regions, and element size were redefined by the user according to the local geometrical situation. Non-uniform and non-structural elements were used. In order to limit the computational cost, only two boundary layers were used. In meshing, higher-order elements were also used, but due to the sharp increase in the cost of the calculations, they were ignored, and instead, first-order elements were used. In order to ensure the independence of the solution from the grid size, nine different grids were defined, with elements rising from 125,379 to 801,469. The percentage difference of the results between the finest mesh and the selected one (consisting of 557,892 elements) was 4.2% only, which is an acceptable difference considering analyses being performed under residual convergence criteria of 10^{-4}. Therefore, the grid consisting of 557,892 elements was assumed to be fine enough to accurately compute the fluid flow, and the wall shear stress within the scaffold. The mesh profile was kept approximatively constant for all of the simulated geometries. A Generalized Minimal Residual (GMRES) iterative solver was used to evaluate the fluid velocity and pressure. Also, a sensitivity analysis has been done to investigate the effect of varying fluid flow rates on the distribution of shear stress and pressure. We considered the flow rate as a parametric variable, reducing and increasing it by 50%. The purpose was to examine how other parameters change to this increase and decrease. The pressure and shear stress parameters were proportional to the fluctuations in the flow velocity at the input indicating the acceptability of the mesh profile obtained through mesh convergence. In this test, the GT1 scaffold was used.

3- RESULTS AND DISCUSSION

Fig. 3 shows the simulation results for the GT1 scaffold corresponding to Y = 0.5 mm, D = 0.4 mm, and porosity of 34 percent. The flow comes from the frontal surface of the scaffold and leaves from the back surface. However, given the fact that porosity inside the scaffold creates different pathways, we expect an increase in the perfusion inside the scaffold [11, 27], which is confirmed by the results. This increase can be up to 10 times or higher, depending on the porosity and geometrical characteristics of the scaffold. The increased perfusion inside scaffold GT1 can be seen in Fig. 4. As shown in Fig. 5, by increasing the porosity, the rate of increased perfusion has been reduced. In order to prevent cell apoptosis, it is essential to have adequate perfusion inside the

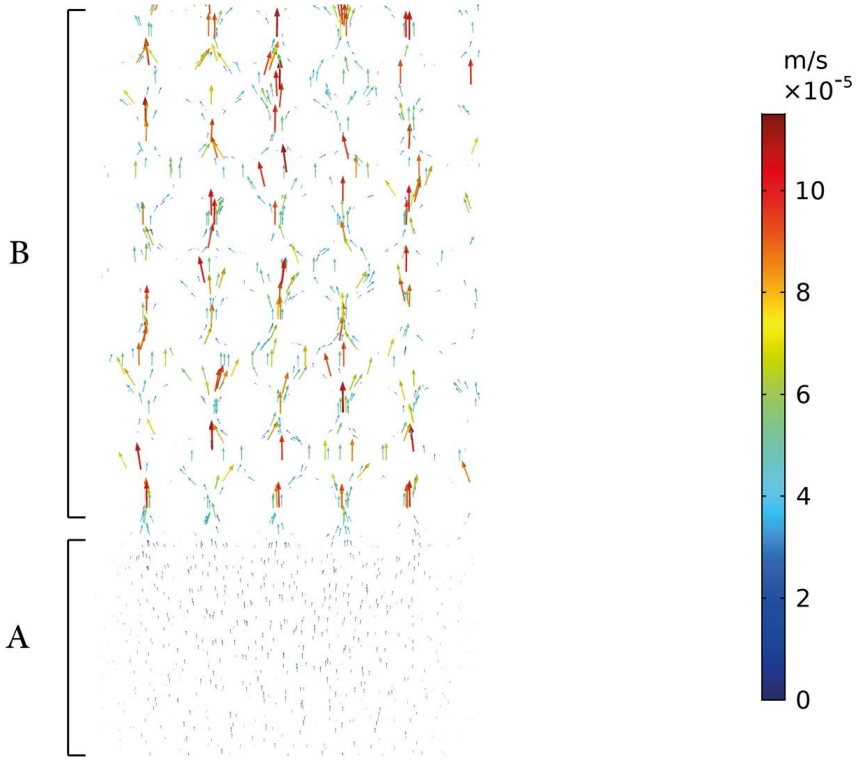

Fig. 4. Velocity field within bioreactor before entering porous domain (A) and inside GT1 scaffold (B) is shown in which an increase in the magnitude of velocity inside the scaffold can be observed.

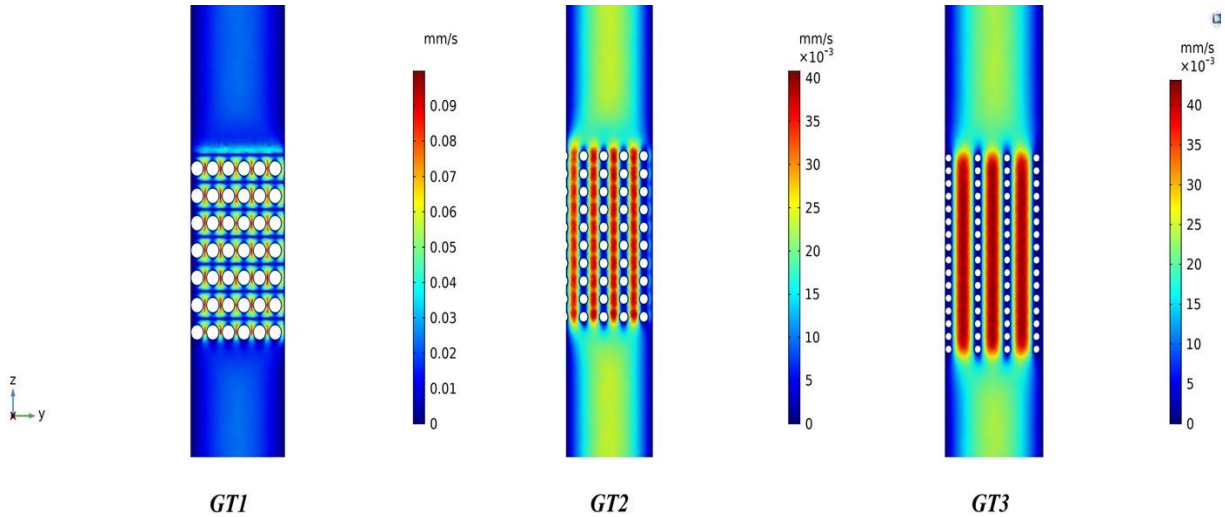

Fig. 5. Velocity magnitude contours within all scaffold architectures. With increasing the porosity, the rate of increased perfusion has been reduced.

scaffold, which can be controlled by porosity [3, 11].

The wall shear stress results are very similar due to its relation with velocity, and it is possible to increase porosity in order to reduce the amount of shear stress, which is responsible for the separation of cells from the scaffold. With increasing porosity, the flow rate decreases, and the shear stress level decreases with increasing porosity (see Fig. 6 and Table 3) [24]. For the GT1 scaffold, three different velocities

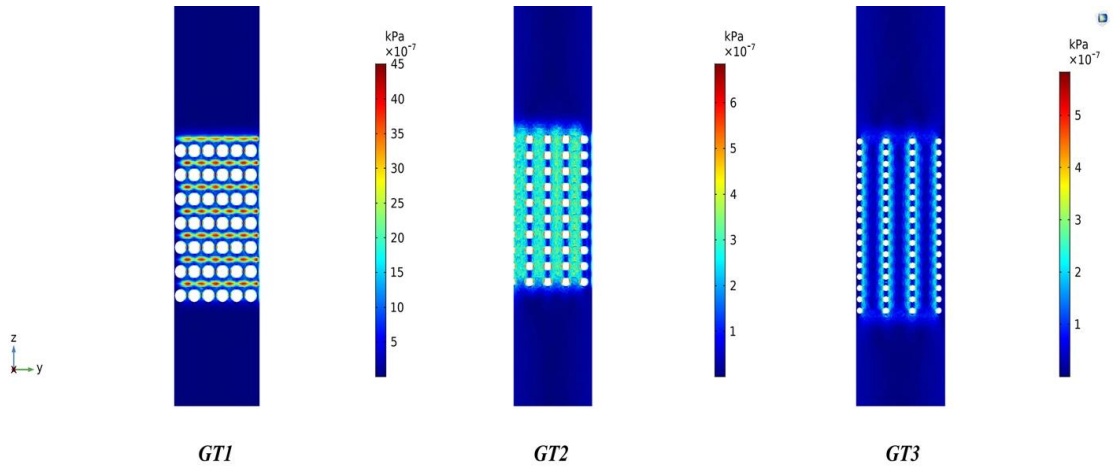

Fig. 6. Wall shear stress distribution contours within all scaffold architectures. With increasing the porosity, the wall shear stress has been reduced.

Table 3. Maximum shear stress and maximum velocity within the different scaffolds.

	Maximum shear stress (kPa)	Maximum velocity (mm/s)
GT1	45.5×10^{-7}	0.11
GT2	7.22×10^{-7}	0.4
GT3	4.95×10^{-7}	0.4

Table 4. Average and maximum interstitial velocity for different inlet velocities in GT1 scaffold.

Inlet velocity (mm/s)	Average interstitial velocity (mm/s)	Maximum interstitial velocity (mm/s)
0.0125	0.034504	0.11328
0.0150	0.041405	0.13593
0.0170	0.046926	0.15404

were considered at the input; the results reported in Table 4 indicate that the average and maximum interstitial velocities increase in higher inlet velocities.

In general, the flow that passes through the scaffold suffers from a pressure drop over the scaffold compared with the beginning of the scaffold. This pressure drop in all three geometries was observed expectedly (see Fig. 7). However, with increasing porosity, i.e., increasing span size Y and decreasing strand diameter D, the pressure drop decreased. Figs. 8-10 shows the pressure drop diagram of the central section along the bioreactor. As expected, the pressure drop decreases with increasing porosity. Resistance in the path of fluid decreased due to the decreased scaffold porosity, which manifested in proportionally decreased pressure drop at a tested flow rate [28]. The tendencies shown suggest that architectures with a smaller strand diameter D can be used for limiting the wall shear stress and the pressure drop within the scaffold [11]; however, horizontal span Y can also be used to regulate shear stress inside the scaffold.

In this study, we investigated the biological reactor in combination with 3D porous scaffolds without considering their mechanical interaction. The results of the analyses reported the flow behavior, shear stress distribution, and pressure drop, which were consistent with previous studies, relatively [11]. In the case of a comparison with the results of a FSI study, the maximum shear stress in a scaffold is produced in the outer parts, and due to the absence of interaction between the fluid and deformable scaffolds, it is not possible to observe this phenomenon in the results presented in Fig. 6. In order to protect cells from this increased shear stress, they are planted in the central part of the scaffold [10, 14].

Given that the increase in porosity appeared to be a positive phenomenon in flow, shear stress, and pressure analysis, the possibility of increasing porosity to resolve issues such as high shear stress must be considered. One of the issues associated with increasing porosity is the surface area to volume ratio. The higher the porosity, the lower the surface area to volume ratio is. As a result, the area required for cell culture is reduced. That is why we need to balance the porosity and the surface area to volume ratio with regard to analyses of flow,

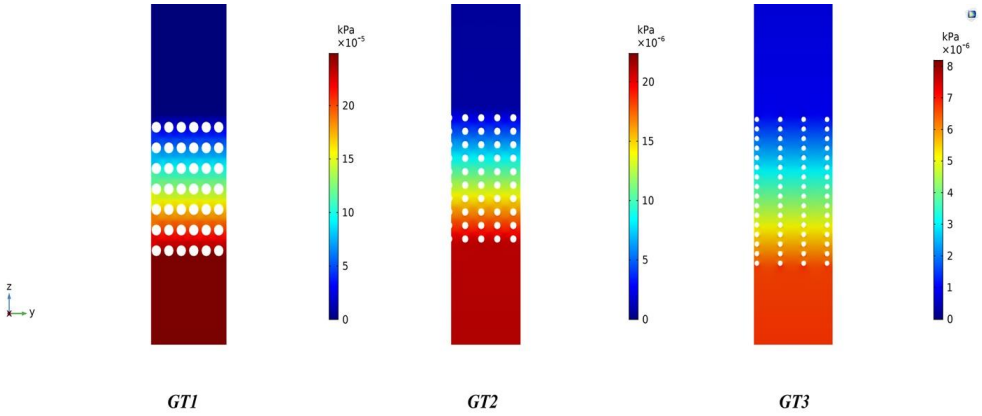

Fig. 7. Pressure distribution contours within all scaffold architectures.

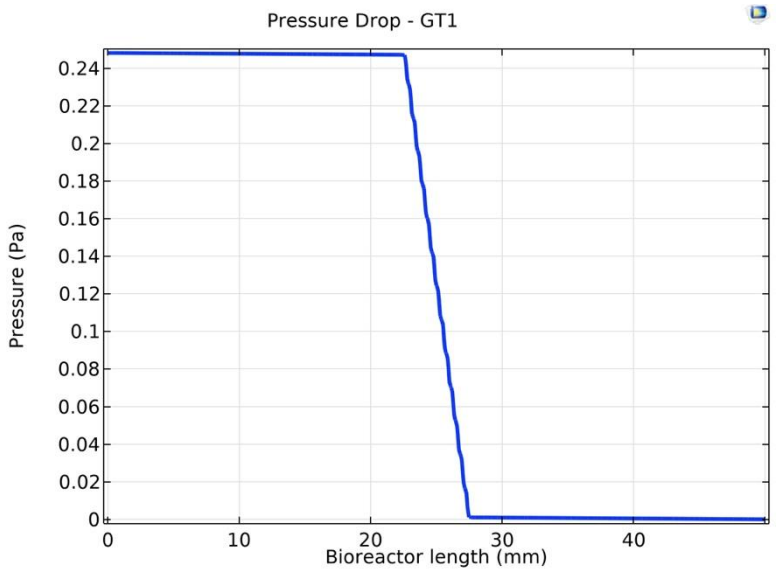

Fig. 8. This diagram depicts the pressure drop of the central section along the bioreactor with the GT1 scaffold. The GT1 scaffold has the highest pressure drop among the designed scaffolds.

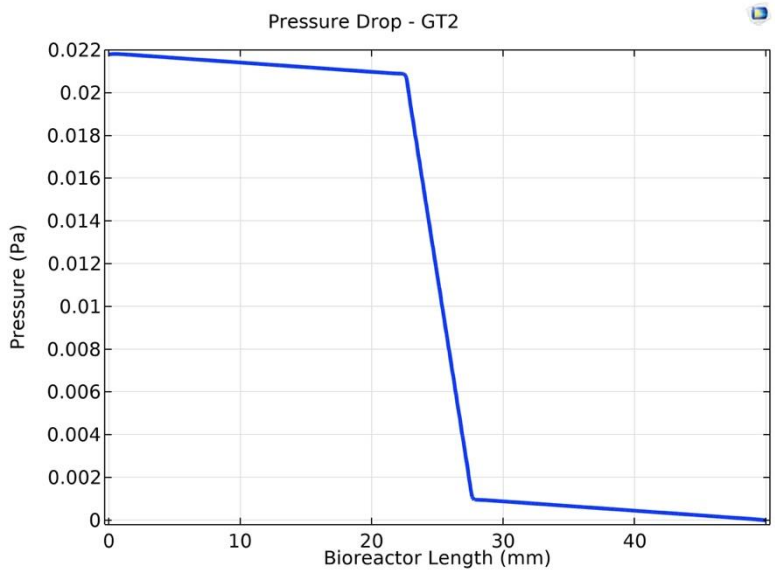

Fig. 9. This diagram depicts the pressure drop of the central section along the bioreactor with the GT2 scaffold.

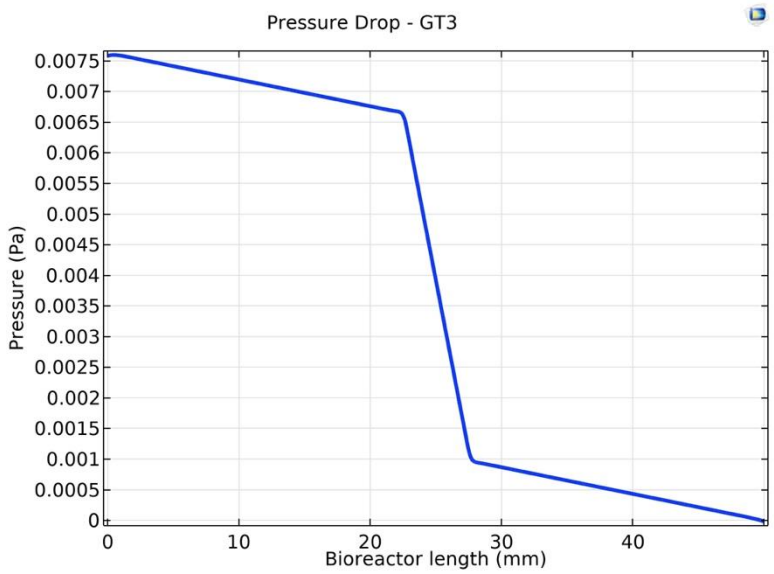

Fig. 10. This diagram depicts the pressure drop of the central section along the bioreactor with the GT3 scaffold.

shear stress, and pressure [29]. One of the suggested solutions is creating scaffold with porosity gradients that serve specific functions during the regeneration process [4].

Mass transfer in the scaffold was not considered in this study. Mass transportation and implanted cells should be considered in order to study oxygen transportation, distribution, and proliferation of cells. Solving the problem for mass transportation and fluid flow simultaneously will surrender a more accurate result on adjusting bioreactor and scaffold's biomechanical characteristics. Also, it has been shown that using oscillatory flow at the inlet could help the proliferation of cells [30, 31]. A computational model that considers the effects of fluid-structure interactions (considering deformability and viscoelasticity of cell/scaffold) and oscillatory flow of culture medium may be of great significance for functional tissue engineering of cartilage. Moreover, multiscale modeling relating macroscopic scale (bioreactor and scaffold scale) to microscopic scale (subcellular scale including cell membrane, cytoplasm, nucleus and cilia) may be of great significance in ongoing studies.

4- CONCLUSION

In this study, three geometries with different porosities were considered. These three parametric geometries were studied, and results were reported on flow velocity, shear stress, and pressure. Control factors and the effect of porosity on them were compared. Generally, with an increase in the diameter, the maximum wall shear stress increased; with an increase in the horizontal span, the wall shear stress decreased. Also, the relationship between the surface area to volume ratio, the amount of porosity, and the need to have a compromise between them were discussed. The effect of shear stress on cell apoptosis and nutrient availability was discussed. Due to ignoring fluid-structure interaction between deformable scaffold and fluid, scaffold's strain and deformation were the control factors that had no place in this analysis. The effects of the controllable factors, such as those of the scaffold microstructure, may be useful in the future for optimizing the scaffold design for different applications.

5- NOMENCLATURE

D Diameter of the strands, mm
g Gravitational acceleration, m/s^2
h Function of geometrical and material properties, mm
P pressure, Pa
u Fluid velocity, m/s
Y Horizontal span, mm

Greek symbols

θ Angle between two consecutive layers, degree
μ Dynamic viscosity, Pa.s
ρ Density, kg/m^3
σ Stress, Pa

Subscript

$_e$ Elastic
$_Z$ Z axis

Superscript

T Transpose

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