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Computer-aided characterization for effective mechanical properties of porous tissue scaffolds

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Abstract

Performance of various functions of the tissue structure depends on porous scaffold microstructures with specific porosity characteristics that influence the behavior of the incorporated or ingrown cells. Understanding the mechanical properties of porous tissue scaffold is important for its biological and biomechanical tissue engineering application. This paper presents a computer aided characterization approach to evaluate the effective mechanical properties of porous tissue scaffold. An outline of a computer-aided tissue engineering approach for design and fabrication of porous tissue scaffold, procedure of computer-aided characterization and its interface with design model, development of a computational algorithm for finite element implementation and numerical solution of asymptotic homogenization theory is presented. Application of the algorithm to characterize the effective mechanical properties of porous poly-ε-caprolactone scaffold manufactured by precision extruding freeform deposition will also be presented, along with a parametric study of the process and design parameter to the structural properties of tissue scaffold.
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Keywords: Computer-aided tissue engineering; Tissue engineering; Tissue scaffold; Freeform fabrication; Effective properties

1. Introduction

Three-dimensional (3D) tissue scaffolds plays an important role in cell attachment, proliferation, and guidance of new tissue formation. In theory, tissue scaffolds should be designed to have special characteristics in order to function as true tissue substitutes that satisfy the patient-specific biological, mechanical and geometrical requirements [1–3]. Such characteristics include: (1) biological requirements: the designed scaffold must facilitate cell attachment and distribution, growth of regenerative tissue and facilitate the transport of nutrients and signals; (2) biophysical requirement: the designed scaffold must provide structural support at the site of replacement and to guide tissue regeneration; and (3) anatomical requirement: it must be of an appropriate geometric size that provides an anatomical compatibility at the site of replacement. To address these considerations, the scaffold is often designed as a porous structure with appropriate porosity, pore size, shape and intricate interconnectivity so that the desirable biological network for cell migration, nutrient transportation, and the mechanical stiffness and strength can be obtained [4–6]. Research has shown that both mechanical and biological properties of porous scaffolds, as well as cell growth and migration processes are determined in part by the local microarchitecture of scaffold. For example, specific pore size and overall porosity of the scaffold are favorable to specific cells which affect their cellular adhesion, viability, ingrowth, distribution, and the formation of an extra cellular matrix [7,8]; the internal architectures of porous implants determine the mechanical properties of the implants [9] and control the degree of the tissue regeneration [10,11]. Ability to determine the mechanical properties and structural heterogeneity of the porous scaffold with designed micro-architecture is practically important for its intended tissue engineering application. This is particularly true for load bearing scaffolds to bone and cartilage tissue engineering application because this type of tissue requires its substitute to have highly intricate architecture to match the inherent tissue heterogeneity.

Available methods for characterization of mechanical properties of porous scaffolds and heterogeneous tissues were primarily based on using experimental approaches [12,13], finite element numerical calculation [14,15], or effective property modeling. For example, to characterize a heterogeneous bone tissue at different structural organization, an effective modeling approach was used to consider bone tissue as a composite material with

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complex microstructure and use a representative volume element (RVE) and standard mechanical approach to calculate the apparent moduli of the heterogeneous and/or porous tissue structure [16,17]. In the RVE-based approach, the prediction is based on the averaged field theory and is sensitive to the size and applied boundary conditions of the selected RVE. To overcome the size and boundary effects, an asymptotic expansion homogenization theory, based on the assumptions that the structure is varying on multiple spatial scales due to existence of a spatially periodic microstructure, was developed and applied to the characterization of various porous bone tissues [18–22]. However, although the asymptotic homogenization theory has been well developed [23–25], the application of the theory requires a finite element implementation and the associated computational algorithm for its numerical solution. Due to the complexity of the theory, the computational algorithm for the numerical implementation has not been well developed, for example, the authors have not been able to find a publicly available computational program for asymptotic theory-based homogenization.

The objective of this paper is to present our study on developing a computer-aided characterization approach for the evaluation of mechanical properties and structural heterogeneity of porous tissue scaffolds. The central of the computer-aided characterization is the development of computational algorithm for numerical implementation of asymptotic homogenization theory. This computational algorithm enables the integration of design, fabrication, and characterization of tissue scaffold within one computer aided tissue engineering paradigm, and provides quantitatively characterized mechanical and structural properties for tissue scaffold application. For example, the developed characterization approach is applicable to predict the effective mechanical properties of a designed cellular tissue scaffold, to study the effect of the process parameters on the scaffolds structural properties, and to understand the local deformation behavior of the scaffold under global loading.

2. Design and fabrication of tissue scaffold

A computer-aided tissue engineering (CATE) approach [6,26,27] for modeling, design and fabrication of tissue scaffolds has been utilized in this study. The CATE approach begins with the acquisition of noninvasive image and the image processing of appropriate tissue region of interest, followed by a 3D reconstruction of anatomical structure using enabling imaging reconstructive and reverse engineering techniques (MIMICS [28] and Geomagic [29]). The next step is to define tissue anatomic features and to characterize the tissue properties by quantitative computed tomography method. A computer-aided design (CAD) technique (Pro/Engineer [30]) is applied to design CAD-based cellular unit cell models according to the defined tissue features. These cellular unit cells will serve as building blocks to construct final scaffolds. Based on the designed CAD geometrical configuration and the selected scaffolding materials, the computer-aided characterization approach introduced in this paper is applied to determine the scaffold effective mechanical properties. The designed scaffold mechanical properties are compared to the to-be-replaced tissue mechanical properties, and the unit cells with matching properties will be selected as candidate unit cells (building blacks) to construct the tissue scaffold. These candidate unit cells will be further evaluated according to their internal architectures and the intended biological purpose. With the help of CAD solid modeling technique and Boolean operation algebra, a set of such selected unit cells will be integrated with the shape of the tissue to form the final tissue scaffold with specified internal architecture, structural properties, and the external geometry to match that of the actual replaced tissue [26].

Once the cellular tissue scaffold is designed, a process planning algorithm will convert the designed scaffold architectures to layered deposition patterns for the freeform fabrication of cellular scaffold. In this study, a precision extruding deposition (PED) system was used to freeform fabricate poly-ε-caprolactone (PCL, Sigma Aldrich, Inc., Milwaukee, Wisconsin) cellular tissue scaffolds [31]. The PED system consists of an XYZ position system, a material extruder system, a temperature control system, a data processing and system control software. Before the fabrication process, the designed CAD-based scaffold unit cell model was first converted into a stl format, and then sliced by the data processing software to generate the process toolpath. The system control software monitors the deposition of material through the material extruder system according to the process toolpath layer-by-layer to construct 3D cellular scaffold. The major difference between our PED process and the conventional fused deposition modeling

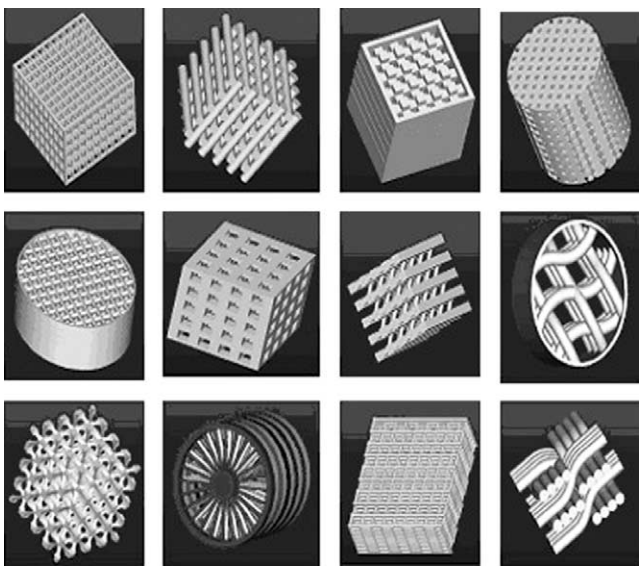

Fig. 1. Library of designed cellular 3D scaffolds.

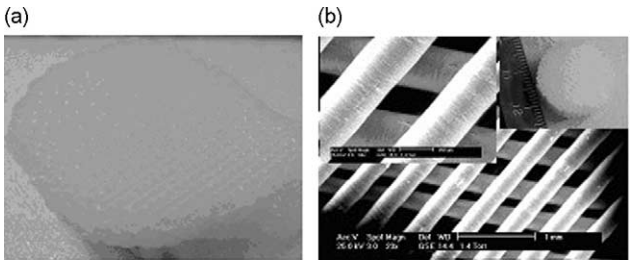

Fig. 2. Sample of fabricated scaffold. (a) Fabricated PCL scaffold (pore size: ~250 μm). (b) SEM image of internal pore connectivity.

(FDM) process lies in that the PED process can directly deposit scaffolding material without the need of filament preparation, for example, while the FDM process requires the pre-preparation of material in a filament form before deposition, our study directly deposits a pellet-formed PCL to build cellular scaffold. Samples of the designed scaffold unit cells and the fabricated PCL scaffolds with micro-architectures of about 250 μm scale level are shown in Figs. 1 and 2, respectively.

The following PED processing parameters were used for the scaffold fabrication: the processing liquefier temperature 90 °C, the orifice diameter of the tip 0.25 mm, deposition velocity at 20 mm/s, and the layer thickness at 0.254 mm. Two specific scaffold patterns were analyzed: 0°/90° and 0°/60°/120°. Schematic of the scaffold layout patterns is shown in Fig. 3.

3. Computer-aided characterization of tissue scaffold

We consider a heterogeneous tissue scaffold as a linearly elastic heterogeneous body Ω^ε with periodic micro-structure repeated by a porous unit cell as shown in Fig. 4. In a general case, Ω^ε is subjected to a body force f, a traction t at the traction boundary Γ_t, a displacement d at the displacement boundary Γ_d, and also consists of multiple network channels (or voids) and a pressure p applied on the void internal surfaces.

The stress–strain and strain–displacement relation in the heterogeneous body can be expressed as

$$\sigma_{ij}^\varepsilon = E_{ijkl}^\varepsilon e_{kl}^\varepsilon, \qquad e_{kl}^\varepsilon = \frac{1}{2}\left(\frac{\partial u_k^\varepsilon}{\partial x_l} + \frac{\partial u_l^\varepsilon}{\partial x_k}\right) \tag{1}$$

where σ_{ij}^ε, e_{ij}^ε, E_{ijkl}^ε and u_i are the stress, strain, stiffness matrix, and displacement within Ω^ε.

Applying the principle of virtual work, we obtain

$$\int_{\Omega^\varepsilon} E_{ijkl}\frac{\partial u_k^\varepsilon}{\partial x_l}\frac{\partial v_i}{\partial x_j}\mathrm{d}\Omega = \int_{\Omega^\varepsilon} f_i^\varepsilon v_i \,\mathrm{d}\Omega + \int_{\Gamma_t} t_i v_i \,\mathrm{d}\Omega + \int_{S^\varepsilon} p_i^\varepsilon v_i \,\mathrm{d}S \tag{2}$$

where v_i denotes the virtual displacement, S^ε denotes the boundary of all void domains.

3.1. Asymptotic homogenization and finite element implementation

Introducing an asymptotic expansion of $u_i^\varepsilon : u_i^\varepsilon(x) = u_i^0(x,y) + \varepsilon u_i^1(x,y) + \varepsilon^2 u_i^2(x,y) + \cdots$ into Eq. (2) yields

$$\begin{aligned}\int_{\Omega^\varepsilon} E_{ijkl}\Bigg\{&\varepsilon^{-2}\frac{\partial u_k^0}{\partial y_l}\frac{\partial v_i}{\partial y_j} + \varepsilon^{-1}\Bigg[\left(\frac{\partial u_k^0}{\partial x_l} + \frac{\partial u_k^1}{\partial y_l}\right)\frac{\partial v_i}{\partial y_j} + \frac{\partial u_k^0}{\partial y_l}\frac{\partial v_i}{\partial y_j}\Bigg] + \Bigg[\left(\frac{\partial u_k^0}{\partial x_l} + \frac{\partial u_k^1}{\partial y_l}\right)\frac{\partial v_i}{\partial x_j} \\ &+ \left(\frac{\partial u_k^1}{\partial x_l} + \frac{\partial u_k^{21}}{\partial y_l}\right)\frac{\partial v_i}{\partial y_j}\Bigg] + \varepsilon(\ldots)\Bigg\}\mathrm{d}\Omega \\ &= \int_{\Omega^\varepsilon} f_i^\varepsilon v_i \,\mathrm{d}\Omega + \int_{\Gamma_t} t_i v_i \,\mathrm{d}\Omega + \int_{S^\varepsilon} p_i^\varepsilon v_i \,\mathrm{d}S\end{aligned} \tag{3}$$

where ε is a small scaling parameter between two length scales. In general, it is equal to the ratio between the unit cell size and the size of the macroscopic region in which it exists.

The detailed theoretical derivation of asymptotic homogenization theory and the formulation for its finite element implementation were reported in authors' recent publication [32]. For the sake of simplicity, we only include a few key equations in the following description in order to continue the presentation. For example, after a series of variable substitutions and derivations, Eq. (3) can be rewritten as

$$\begin{aligned}\int_\Omega [E_{ijkl}^H]\frac{\partial u_k^0(x)}{\partial x_l}\frac{\partial v_i(x)}{\partial x_j}\mathrm{d}\Omega &= \int_\Omega [\tau_{ij}(x)]\frac{\partial v_i(x)}{\partial x_j}\mathrm{d}\Omega \\ &+ \int_\Omega (b_i(x)v_i(x))\mathrm{d}Y\mathrm{d}\Omega + \int_{\Gamma_t} t_i v_i \,\mathrm{d}\Gamma\end{aligned} \tag{4}$$

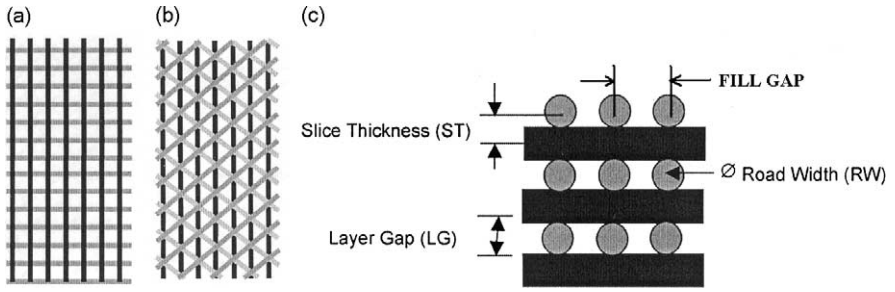

Fig. 3. (a) 0°/90° layout pattern; (b) 0°/60°/120° layout pattern; (c) layout pattern definition.

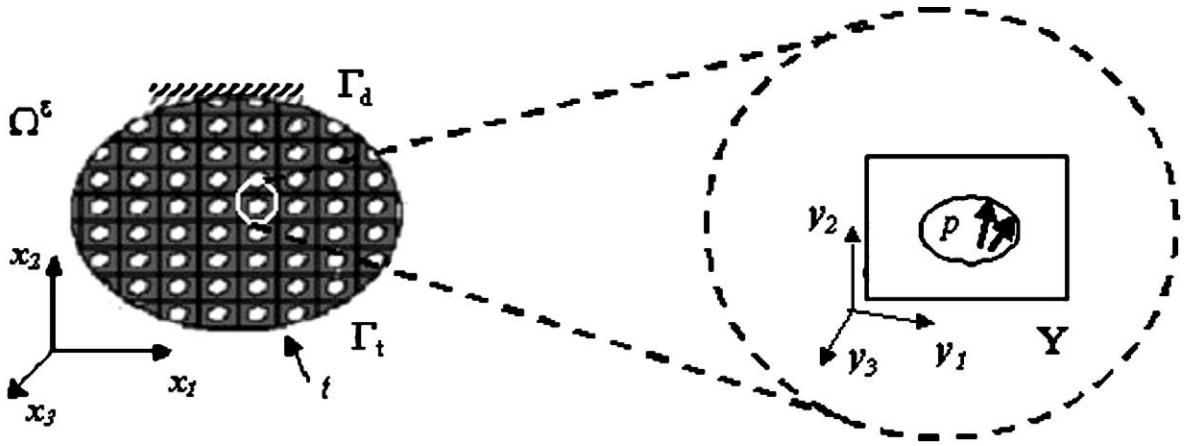

Fig. 4. Heterogeneous body and its periodic unit cell. (a) Heterogeneous body, (b) periodic unit cell.

in which, E^H_{ijkl} is defined as the homogenized effective stiffness constants calculated from the local unit cell. Express E_{ijkl} by a compact matrix form D_{ij},

$$[E_{ijpq}] = [\,d_1 \quad d_2 \quad d_3 \quad d_4 \quad d_5 \quad d_6\,] = \begin{bmatrix} D_{11} & \cdots & D_{16} \\ \vdots & \ddots & \vdots \\ D_{61} & \cdots & D_{66} \end{bmatrix} \tag{5}$$

It has been shown that Eq. (4) can be represented by

$$\int_Y \varepsilon^{\mathrm{T}}(v)[D_{ij}]\varepsilon(u^j)\mathrm{d}Y = \int_Y \varepsilon^{\mathrm{T}}(v)d_i\,\mathrm{d}Y, \quad i = 1,\ldots,6 \tag{6}$$

It can be seen that the expression of Eq. (6) is similar to a generalized displacement based finite element formulation, if we consider D_{ij} in Eq. (6) as a stiffness matrix, $\varepsilon(u^j)$ and $\varepsilon(v)$ as strains. Therefore, the homogenized effective stiffness constants E^H_{ijkl} can be determined through a finite

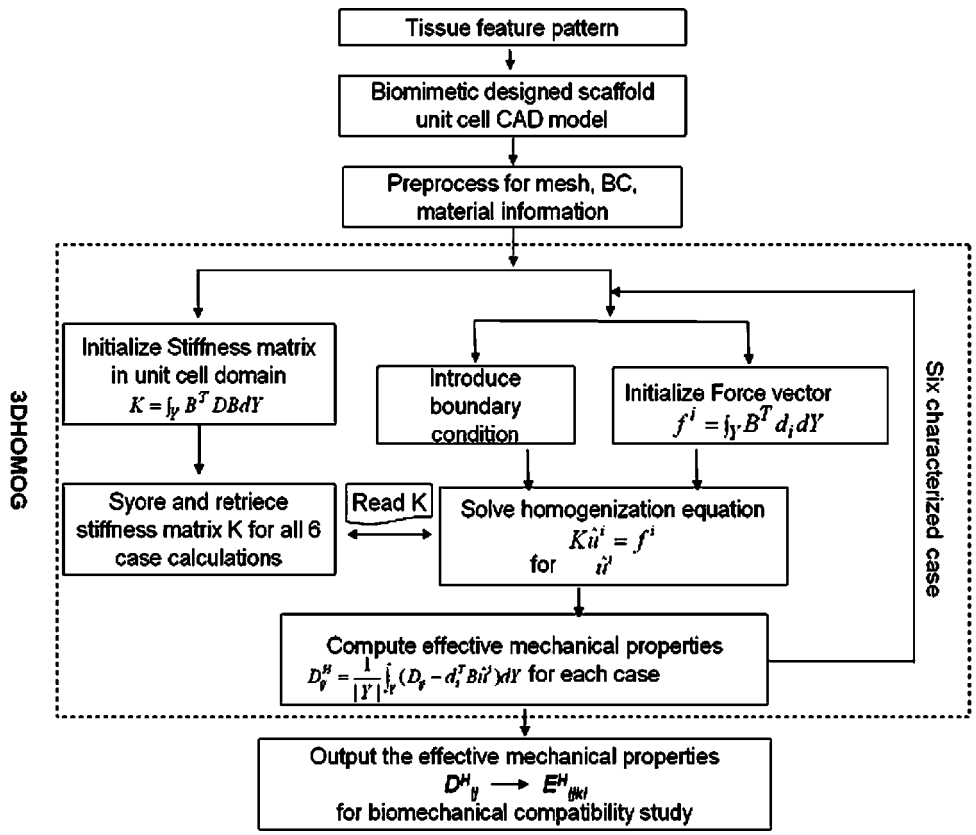

Fig. 5. Functional flowchart of 3DHOMOG.

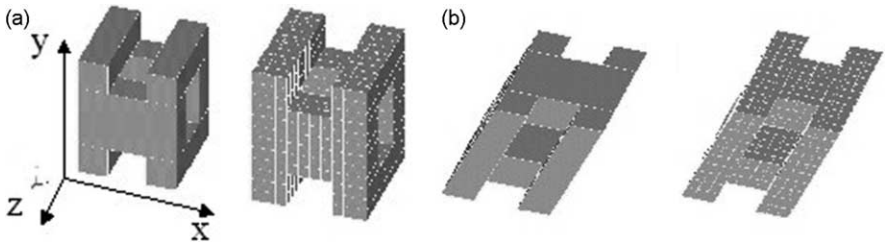

Fig. 6. Unit cell and meshing: (a) with 0°/90° layout pattern, (b) with 0°/60° layout pattern.

element implementation and numerical solution algorithm by solving Eq. (6) for overall mechanical properties D_{ij}^{H}.

3.2. Computational algorithm for numerical solution

A computational algorithm was developed to conduct the numerical implementation of asymptotic theory based homogenization. An outline of the computational algorithm for the solution procedure is described in Fig. 5. For a designed cellular unit cell, the solution process starts from the modeling tissue feature patterns, the designing CAD based scaffold unit cells, the discreterization of unit cell model into a finite element model with appropriate meshing, boundary conditions and assigned material properties. Then, a computational algorithm, 3DHOMOG, developed within our research group will be applied to perform the numerical calculation of the asymptotic theory-based homogenization. The 3DHOMOG is 3D in nature and is capable for unit cells with either isotropic or anisotropic material properties. According to the functional flowchart shown in Fig. 5, the 3DHOMOG begins with to input the modeling information, such as the elements, nodes, material and boundary conditions, to compute local stiffness matrices, and to reassemble the global stiffness matrix for effective property calculation. In 3DHOMOG, the global stiffness matrix only needs to be assembled once for all the six cases in 3D model. The local and global force vectors are calculated and assembled for each case. After the boundary conditions are applied and the global stiffness matrix is input, the local-level displacements for each given cases can be calculated using the Gaussian elimination method. The overall effective mechanical properties can then be determined.

4. Application for characterization of the effect mechanical properties of PCL scaffold

The 8-node hexagon elements with a total node numbers of about 1500 were used in the finite element implementation algorithm for the numerical calculation. The cellular unit cell models and the corresponding meshing for both 0°/90° layout pattern and 60° layout pattern are shown in Fig. 6. Results of the prediction of the effective constants of the PCL scaffolds with the two different layout patterns are presented in Figs. 7 and 8, respectively.

For PCL scaffold unit cell with 0°/90° layout pattern, there are six independent elastic constants $E_x(E_y = E_x)$, E_z, G_{xy}, $G_{xz}(G_{yz} = G_{xz})$, μ_{xy}, and $\mu_{xz}(\mu_{yz} = \mu_{xz})$ due to its symmetry to x and y axis. It can be seen from Fig. 7 that an increase of the fill gap (the distance between the centers of two adjacent struts), will in general result in a decrease of the modulus and Poisson ratio, particularly for the fill gap between 0.42 and 0.69 mm. This can be explained that the increase in the fill gap will result in a increase in scaffold porosity, thus a decrease in the effective constants. However, the change of the out-of-plane Poisson ratios seems to be not as sensitive as the other constants. The effect of the fill gap on the effective properties of the 0°/90° layout pattern PCL scaffold is presented in Fig. 7.

The PCL scaffold unit cell with 0°/60° layout pattern behaves as a typical anisotropic material with 13 independent elastic constants shown in Fig. 8. The same trend can be observed that a increase of the fill gap in general will result in a decrease of the stiffness constants, particularly for D_{33}. This is because the increase in the fill gap will result in a larger scaffold porosity, thus a decrease in the effective constants, as shown in Fig. 8.

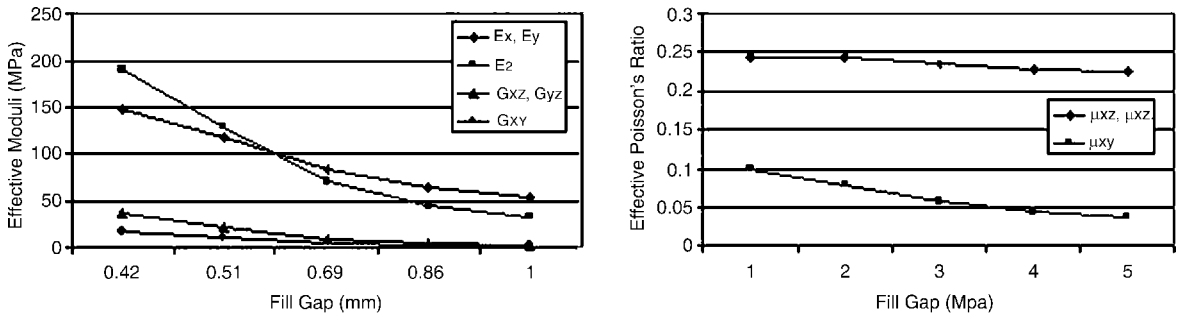

Fig. 7. Effect of the fill gap on the effective elastic constants (0°/90°).

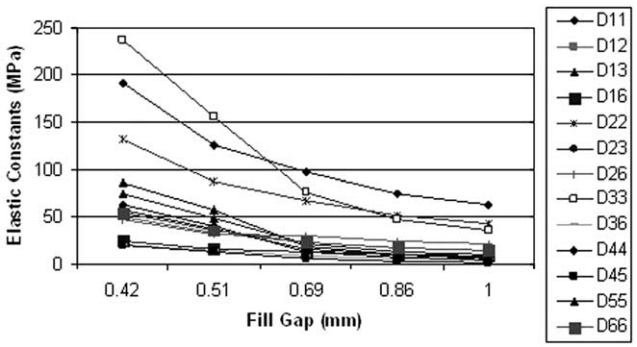

Fig. 8. Effect of the fill gap on the effective elastic constants (0°/60°).

The homogenization theory and the developed computational algorithm are also applied for a parametric study on the effect of porosity and scaffolding materials on the effective mechanical properties of the unit cells as shown in Fig. 9. A centered square channel which openly interconnected along X, Y and Z directions, and three different biomaterials: Hydroxyapatite (HA, $E = 14{,}000$ MPa, $\upsilon = 0.25$), Polycaprolactone (PCL, $E = 400$ MPa, $\upsilon = 0.33$), and copolymer of polylactic acid and polyglycolic acid (PLGA, $E = 1200$ MPa, $\upsilon = 0.33$) are considered in this study. If the edge length of the unit cell and the edge length of the square channel are L and A, respectively, the porosity of the scaffold can be determined by:

$$p = \frac{(3LA^2 - 2A^3)}{L^3}, \qquad A < L, \text{ for square channel} \qquad (7)$$

Due to its square symmetry, there are only three independent effective constants for the scaffold: the Young's modulus E^*, shear modulus G^*, and the Poisson's ratio υ^*. Results of these predictions are presented in Fig. 10a–c, respectively.

It can be observed that with the increase in porosity, these three elastic constants tends to decrease. At a special case that the unit cell becomes a fully porous structure, i.e. the porosity approaches to unity, the effective elastic constants tends to be zero. This trend agrees with the results reported in Refs. [33,34].

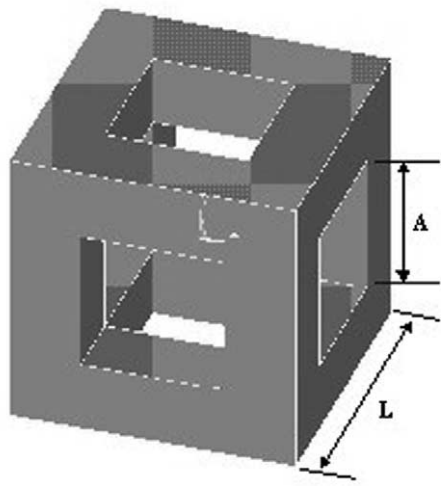

Fig. 9. Unit cell scaffold with open square pore.

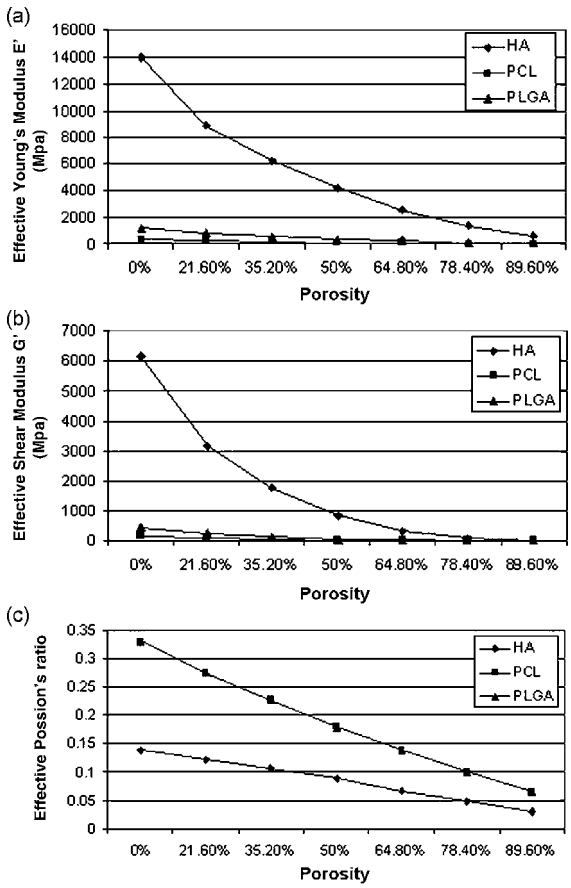

Fig. 10. Effect of the scaffolding materials and porosity (square shape pore). (a) Effect of scaffolding materials and porosity on Young's modulus. (b) Effect of scaffolding materials and porosity on shear modulus. (c) Effect of scaffolding materials and porosity on Poisson's ratio.

5. Conclusions and discussions

A computer-aided characterization approach for evaluation of mechanical properties and structural heterogeneity of porous tissue scaffolds was presented in this paper. The central idea of the characterization approach is the computational algorithm that was developed for the finite element implementation of the asymptotic homogenization theory. This algorithm enables the integration of design, fabrication, and characterization of tissue scaffolds within computer aided tissue engineering paradigm, which in doing so layout the foundation for computerization of tissue scaffold design and manufacturing.

The characterization approach was applied to predict the effective mechanical properties of PCL tissue scaffolds manufactured through precision extruding process and to

study the effect of the design and process parameters on the structural properties of the scaffolds. Results of the characterization show that the effective mechanical properties of the PCL scaffold are functions of the scaffolding materials, the orientation of deposition layout pattern, and the overall porosity of the scaffold structure. In general, the scaffold structures behave with anisotropic mechanical properties and the degree of the anisotropy is depending on the deposition layout pattern as shown in Figs. 7 and 8. The effective mechanical properties decrease with the increase of the porosity for all three scaffolding biomaterials, as shown in Fig. 10.

As indicated earlier, conventional mechanics modeling and the finite element model have inherent limitations in their application, for example, the boundary and size effect resulted from the applied boundary conditions in the calculation of the effective properties of the representation volume element. Asymptotic expansion theory based homogenization can reduce the error in the calculation of the effective properties. In addition, since the asymptotic homogenization applies an asymptotic expansion and double scale techniques to establish stress and strain relations at both micro- and macro-structural level in the prediction of the effective mechanical properties, this makes the theory potentially applicable to investigate the biological and biomechanical properties of the scaffold at both the tissue-scaffold level (global) and at the cell-scaffold level (local). The developed characterization approach and the computational algorithm overcome the difficulty in the implementation of the asymptotic homogenization theory, thus providing an effective computer-aided characterization tool for the scaffold application to tissue engineering.

Acknowledgements

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