Computational design of tissue engineering scaffolds

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Abstract

Tissue engineering utilizes porous biomaterial scaffolds to deliver biological factors that accelerate tissue healing. These two functions require scaffolds be designed for mechanical loading and mass transport. The purpose of this paper was to apply both ad hoc and topology optimization homogenization based design approaches to create scaffold architectures, and to determine how these architectures compare to theoretical bounds on effective stiffness. Open cell scaffold architectures demonstrated a wide range of permeability, but were all below isotropic effective stiffness bounds. Wavy fiber architectures provide a means to approach the lower bounds. Using image-based techniques, designed architectures may be incorporated in anatomic shapes.

Keywords: Tissue engineering; Scaffolds; Topology design; Effective property bounds; Homogenization theory

1. Introduction

Tissue engineering seeks to regenerate biological tissues by using porous, degradable biomaterials (hereafter termed “scaffolds”) to deliver cells, genes, and/or proteins (hereafter termed “biologics”) [1]. Theoretically, the scaffold will provide temporary mechanical support and define tissue shape while delivering biologics from internal pores and through release after degradation. Thus, three primary requirements for a scaffold are to: (1) define anatomic shape and volume, (2) provide temporary mechanical support, and (3) enhance tissue regeneration through biologic delivery.

Engineering scaffolds for optimal performance must begin by quantitatively defining scaffold requirements through specific target properties. The most straightforward definition is the anatomic shape which is defined geometrically by the tissue defect. Mechanical support can be defined through constitutive parameters of linear/nonlinear elasticity, viscoelasticity or poroelasticity, although in general the magnitude of these constitutive parameters necessary for adequate mechanical support has not been determined. Enhanced tissue regeneration is the most difficult to pin down. Enhanced tissue regeneration could be related to mass transport characteristics like permeability and/or diffusion, but will also depend on cell material interaction parameters like surface chemistry and roughness.

Defined target properties are attained by distributing specified base materials at length scales ranging over four orders of magnitude, from less than a micron to over several millimeters [2]. Material distribution at the tens to hundreds of micrometers (Note: this scale is typically termed microstructure or even mesostructure in the mechanics literature. However, in tissue engineering this level is called “scaffold architecture”). We therefore hereafter denote this scale as “architecture”) has in general not been designed, but instead controlled solely by fabrication processes including porogen leaching and gas foaming. Recent applications of solid free-form fabrication (SFF) have made design of scaffold architecture to a finite feature size realizable [2,3]. Regardless of fabrication method, it is desirable to calculate effective scaffold properties like elasticity, diffusion and permeability based on scaffold architecture, so

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that the effect of these properties on tissue regeneration may be better understood.

Design is further complicated by the fact that target properties for mechanical support typically conflict with those associated with enhanced tissue regeneration, essentially mass transport properties. Increasing mechanical properties, making a scaffold stiffer and stronger, comes at the expense of mass transport, and vice versa. Therefore, attaining the best possible combination of mechanical support and mass transport relies on optimizing material distribution within a porous structure. Attaining desired targets of both mechanical and mass transport properties will allow rigorous testing of design hypotheses concerning how these properties influence tissue regeneration.

Determining bounds on effective properties obtainable for specific architectures has been an area of intense study in applied mathematics, and applied and computational mechanics [4,5]. A significant goal of this research has been to determine bounds on single effective properties (elasticity, diffusion, conductivity, permeability) that can be attained at a specified porosity or ratio of base materials and how these materials should be arranged in three dimensional space to attain the bounds. Perhaps the most famous bounds are those of Hashin and Shritkman [8] for an effective isotropic composite composed of two isotropic phases. The most general structures that can attain all elastic bounds are finite rank laminates in which different scales of material are layered together [6,7]. Effective property bounds provide a foundation from which to begin tissue engineering scaffold design. These bounds define what properties may theoretically be attained for a given base scaffold material. In the case of the two phase composite materials used in tissue engineering where the second phase has zero stiffness, the lower bound is the trivial solution of zero effective stiffness. Nonetheless, these bounds give the complete range of effective properties that may be attained for a scaffold composite consisting of one base biomaterial and pores.

Of course, the real issue for creating tissue engineering scaffolds is to derive an architecture design that will give the desired effective properties. This may be done in two ways. First, in an ad hoc approach, an architecture may be designed first and its effective properties then computed. In the second approach, described by Sigmund [9], a topology optimization method is used to iteratively design the architecture that gives rise to the desired properties. Each approach creates a volumetric 3D design by replicating unit cells periodically in 3D space, an approach that has been used previously to design tissue engineering scaffold architecture [10,11].

Whichever method is used, homogenization theory [12] is the basis for deriving the architecture. For the ad hoc design, an architecture is designed and its effective properties are computed by solving finite element or finite difference implementations of local homogenization problems for elasticity or fluid flow. For the second approach, dubbed an inverse homogenization problem by Sigmund, the objective function is to minimize in a least squares sense the difference between the computed and target effective properties, with constraints on architecture porosity. Homogenization theory is used within an iterative optimization scheme to compute effective problems as part of the objective function.

The added difficulty with tissue engineering scaffold design is that the designed architectures must ultimately be built and tested, which introduces further fabrication constraints such as a minimum feature size into the problem. Although SFF does allow fabrication of complex architectures, it has practical restrictions of finite minimum feature size, necessity for interconnected pores to allow removal of support material, and in general a limitation to building with a single material. This makes theoretical limits achievable with finite rank laminates difficult to achieve in physical scaffolds, which are one phase with finite size scale.

The goal of this paper is to examine what effective elastic and permeability constants can be achieved using both the direct and inverse homogenization approach for one phase materials. Specifically, we seek to determine what range of elastic and permeability properties can be spanned using these approaches. These architectures can then be tested both in vitro to determine how well fabricated scaffold architectures can match the computational design and in vivo to determine if these designs will affect tissue regeneration.

2. Methods

The fundamental components to computing effective elastic and permeability constants are (1) developing a computational model of the architecture, and (2) a numerical implementation appropriate to the computational model. We choose to represent architecture using image based techniques [13,14]. In this approach, density distributions within a structured voxel dataset define topology.

For elastic homogenization, we assume that the displacement field may be asymptotically expanded as

\[ u'_i \approx u'^0_i + \epsilon u'^1_i + \cdots, \]  

where \( \epsilon \) represents the size ratio between the architecture and global scales, \( u'_i \) is the total displacement, \( u'^0_i \) is the average displacement at the global level, \( u'^1_i \) is the perturbation in displacement due to the presence of a architecture and \( \epsilon \) is the ratio of the microscopic length scale to the macroscopic length scale. The total displacement gradient with respect to both scale levels may be written as

\[ \frac{\partial}{\partial x^i} = \frac{\partial}{\partial x'^0_i} + \frac{1}{\epsilon} \frac{\partial}{\partial x'^1_i}, \]  

where the coordinates \( x'^0_i \) are the global coordinates and \( x'^1_i \) are the architecture coordinates. Using Eqs. (1) and (2) in the elastic equilibrium equations leads to two scale equilibrium equations, for which the local elastic unit cell problem is stated as...
where $C_{ijkl}$ is the elasticity tensor for the base scaffold material and $z_{ij}^{PNI}$ are characteristic displacements that result from six unit strains applied separately to the architecture with periodic constraints. Once Eq. (1) is discretized it may readily be solved using element-by-element conjugate gradient techniques specially developed for voxel datasets with periodic node numbering [13]. An 8-node isoparametric element was used in the finite element formulation. The resulting solutions for $z_{ij}^{PNI}$ are used to compute the effective scaffold elasticity tensor as

$$C_{ijkl}^{\text{scaffold}} = \frac{1}{V_{\text{micro}}} \int_{V_{\text{micro}}} \left( C_{ijkl} - C_{ijpq} \frac{\partial z_{ij}^{PNI}}{\partial x_p} \right) dV_{\text{micro}},$$

(4)

where $C_{ijkl}^{\text{scaffold}}$ is the effective or homogenized elasticity tensor for the scaffold architecture, $V_{\text{micro}}$ is the volume of the architecture analyzed, and $\delta_{pk}$ is the Kronecker delta.

Effective permeability is determined by solving Stokes flow through the architecture to find the average fluid velocity for three unit pressure gradients. Integrating the three average fluid velocity vectors gives the permeability tensor. For this case, we expand both the fluid pressure and velocity as

$$p \approx p^0 + \epsilon p^1 + \cdots,$$
$$v_i \approx v_i^0 + \epsilon v_i^1 + \cdots,$$

(5)

where $p$ is the total pressure, $p^0$ is the global pressure, $p^1$ is the perturbation in pressure due to the architecture, $v_i$ is the total velocity, $v_i^0$ is the average velocity, and $v_i^1$ is the perturbation in the velocity due to the architecture. When the expansions from Eq. (5) are substituted into the governing Stokes flow equations, we obtain the governing local flow equation:

$$\frac{\partial \epsilon p^1}{\partial t} + \frac{\partial}{\partial x_j} \left( \epsilon p^1 v_j \right) = 0,$$

(6)

where $\epsilon$ represents three unit pressure gradients applied to the architecture. Due to the voxel model representation, Eq. (6) is solved using a finite difference approach known as a Marker and Cell approach. Note that unlike the elasticity case, the average field variable of fluid velocity is dependent on the local coordinate $x^i$. This is due to the fact the viscosity in low Reynolds number cases the local viscosity is actually multiplied by $\epsilon^{-2}$ based on dimensional arguments [14].

The permeability tensor is then calculated as

$$K_{ik} = \frac{1}{\mu V_{\text{micro}}} \int_{V_{\text{micro}}} \epsilon v_{ik}^{PNI} dV_{\text{micro}},$$

(7)

where $K_{ik}$ is the permeability tensor, $\mu$ is the fluid viscosity, and $v_{ik}^{PNI}$ is a second order tensor containing the three global velocity vectors that correspond to three unit pressure gradients. Thus, effective elasticity and permeability can be computed using Eqs. (4) and (7) for any architecture design based on a periodic repeating unit cell.

The second approach to designing architecture is to utilize Eqs. (3), (4), (6) and (7) in a topology optimization approach [9,15]. We [15,16] have developed two such approaches, one in which the architecture is designed for effective elasticity with a constraint on porosity, and a second in which permeability is maximized with a constraint that desired effective elasticity constants are met within a specified tolerance and a porosity constraint. We applied the second case to design architectures for this study, with the formal optimization statement:

$$\max \rho \left( K_{ii}^{\text{scaffold}} + K_{ii}^{\text{scaffold}} + K_{ii}^{\text{scaffold}} \right),$$

subject to:

$$\left[ C_{ijkl} - C_{ijkl}^{\text{target}} \right] \leq \alpha \left[ C_{ijkl}^{\text{target}} \right],$$

$$1 - V_{\text{total}} \leq \text{porosity},$$

where $K_{ii}^{\text{scaffold}}$ denotes the diagonal term of the effective permeability tensor calculated using Eq. (7), $C_{ijkl}^{\text{scaffold}}$ is the effective elasticity tensor for the scaffold calculated using Eq. (4), $C_{ijkl}^{\text{target}}$ is the target value of the effective elasticity tensor, $V_{\text{micro}}$ denotes the volume of the unit cell architecture, $V$ denotes the volume of the solid material, and $\alpha$ is a tolerance term that is gradually reduced during the course of iteration until convergence is achieved. Eq. (8) is a multiphysics optimization problem and is solved using a combination of a Method of Moving Asymptotes (MMA, [17]) to update elasticity [15,16,18] and an evolutionary structural optimization (ESO, [18,19]) scheme to update the density distribution for permeability (Fig. 1).

The MMA scheme originally developed by Svanberg [17] was applied to solve the elasticity sub-optimization problem. The MMA solves a sub-problem defined as

$$\min \rho \sum_{N_{\text{elm}}} \left( P_{\text{obj}} \frac{U - \rho}{U - \rho_L} + Q_{\text{obj}} \frac{\rho - L}{\rho - L} \right) + R_{\text{obj}},$$

subject to:

$$\sum_{N_{\text{elm}}} \left( P_{\text{g}} \frac{U - \rho}{U - \rho_L} + Q_{\text{g}} \frac{\rho - L}{\rho - L} \right) + R_{\text{g}} \leq 0,$$

$$L \leq \rho \leq U,$$

where $\rho$ is the element density ranging between 0 and 1, $N_{\text{elm}}$ denotes summation over all the elements in the model, and the other parameters are defined as

$$P_{\text{obj}} = (U - \rho)^2 \max \left\{ 0, -\frac{\partial \text{OBJ}}{\partial \rho} \right\},$$
$$Q_{\text{obj}} = (\rho - L)^2 \max \left\{ 0, -\frac{\partial \text{OBJ}}{\partial \rho} \right\},$$
$$R_{\text{obj}} = \text{OBJ} - \sum_{N_{\text{elm}}} \left( P_{\text{obj}} \frac{U - \rho}{U - \rho_L} + Q_{\text{obj}} \frac{\rho - L}{\rho - L} \right),$$

$$P_{\text{g}} = (U - \rho)^2 \max \left\{ 0, -\frac{\partial \text{Porosity}}{\partial \rho} \right\},$$
$$Q_{\text{g}} = (\rho - L)^2 \max \left\{ 0, -\frac{\partial \text{Porosity}}{\partial \rho} \right\},$$
$$R_{\text{g}} = \text{Porosity} - \sum_{N_{\text{elm}}} \left( P_{\text{g}} \frac{U - \rho}{U - \rho_L} + Q_{\text{g}} \frac{\rho - L}{\rho - L} \right),$$

(10)
where $L$ and $U$ are lower and upper bounds on the density design variables, being 0 and 1, respectively. The sensitivity derivative for the above parameters is defined as

$$\frac{\partial \text{OBJ}}{\partial \rho} = 2 \cdot (C_{\text{ijkl}}^{\text{scaffold}} - C_{\text{ijkl}}^{\text{target}}) \cdot \frac{\partial C_{\text{ijkl}}^{\text{scaffold}}}{\partial \rho},$$

$$\frac{\partial C_{\text{ijkl}}^{\text{scaffold}}}{\partial \rho} = \frac{1}{|Y|} \int_Y \left( \delta_{im} \delta_{jn} - \frac{\partial y_i}{\partial y_n} \frac{\partial y_j}{\partial y_m} \right) dY,$$

$$\frac{\partial C_{\text{ijkl}}^{\text{mnpq}}}{\partial \rho} = pp^{-1} C_{\text{ijkl}}^{\text{base}},$$

where $Y$ is the characteristic deformation from Eq. (3), $C_{\text{ijkl}}^{\text{scaffold}}$ is the effective elasticity tensor for the scaffold architecture, $C_{\text{ijkl}}$ is the elasticity tensor for a local finite element in the architecture, and $C_{\text{ijkl}}^{\text{base}}$ is the elasticity tensor for the base scaffold material. Note that in this formulation, each element base material elasticity tensor will change depending on the density of the element. Thus, to account for this change in base scaffold material elasticity tensor, we have utilized the SIMP model [20], where the local element stiffness $C_{ijkl}$ depends on the base material stiffness as

$$C_{ijkl} = \rho^p C_{ijkl}^{\text{base}},$$

where $p$ is a constant chosen between 2 and 3.

In the ESO, the fluid velocity in each element is calculated by solving Eq. (6), and a fluid sensitivity parameter is calculated as

$$J'(y) = \frac{1}{|V_e|} \int_{V_e} \|v(y)\|_2 dV_e,$$

$$s(y) = \frac{J'(y)}{J^{\text{max}}},$$

where $J^{\text{max}}$ is the maximum value of the fluid velocity norm and $s$ is the fluid sensitivity parameter. A low $s$ indicates that there is little flow through the element and it can be converted to a solid element. The algorithm is considered to be converged when the density change reaches a steady state. The algorithm typically takes from between 800 and 1000 iterations to converge. The algorithm runs 30 iterations of the elasticity optimization and then switches to the permeability evolutionary optimization scheme and runs 4–5 iterations.

As a reference, we will compare designed architectures to bounds on the effective elastic modulus for both isotropic and cube symmetry [7]. For the case of isotropic symmetry we have:

$$E_{\text{upper}}^{\text{isotropic}} = \frac{2E\rho(7 - 5v)}{\rho(15v^2 + 2v - 13) - 15v^2 - 12v + 27},$$

where $E$ is the Young’s modulus of the base material, $\rho$ is the volume fraction of the solid material ($0 < \rho < 1$), and $v$ is the Poisson’s ratio of the base material. Note that the base material is assumed to be isotropic. For the case of cubic symmetry, we have:

$$E_{\text{upper}}^{\text{cubic}} = \frac{2E\rho(2 - v)}{\rho(3v^2 + v - 2) - 3v^2 - 3v + 6},$$

where again the base material is assumed to be isotropic.

The architectures considered in this paper included basic geometric architectures (orthogonal struts, enclosed spherical voids with communicating pores, total enclosed box and sphere pores), wavy fibered architectures to increase compliance, and a topology optimized design created by solving Eq. (8). Solid volume fractions of 25% and 35% were designed. We also demonstrate that these architectures can be designed within global geometric shapes for testing purposes and within more complex anatomic shapes for use as in vivo tissue engineering scaffolds.
3. Results

Fig. 2 illustrates both the ad hoc designed scaffold architectures, as well as an architecture created using the topology design method of Lin [16]. Normalized modulus versus permeability for all designs shown in Fig. 3, illustrating a loose trend towards decreased modulus with increasing permeability. However, the relationship between modulus and permeability is extremely architecture dependent, in that architectures with the same modulus can have significantly different permeability and vice versa. All designs were created with a unit cell size of 2.5 mm, so that feature sizes could be fabricated on SFF machines. As expected, the closed cell design previously proposed by Sigmund [7] came closest to matching the upper cubic modulus bound, but had zero permeability. The wavy fiber design produced a much more compliant architecture than other designs for the same volume fraction. Overall, the designed single phase architectures spanned a significant portion of the bound range (Fig. 4). Note that spherical void structures were stiffer but less permeable than the cylindrical void structures. The optimization results did not improve significantly upon results that could be obtained using the spherical void structure, as seen in Fig. 4.

Each designed architecture was then created within a cylindrical mechanical specimen testing shape (Fig. 5). This demonstrated that designed architectures can be created in desired configurations for experimental evaluation. Finally, the designed architectures were also created in specific anatomic defect shapes, in this case a minipig mandibular condyle (Fig. 6). This capability will allow testing of scaffold architecture and material effects on tissue reconstruction in vivo.

An issue of importance for any optimization algorithm is the solution uniqueness. To examine this issue, different material layouts were used as an initial condition for the design iteration. These included a spherical void structure with 33% porosity, a closed cubic cell structure with 75% porosity, and a random structure with 75% porosity generated digitally using a random number generator which set random voxels to full density (Fig. 7a). Target normalized modulus was 0.142, equal to the isotropic bound at 75% porosity, which was also set as the porosity constraint. Results showed that the different initial densities led to different final designs (Fig. 7b). Although the average moduli were similar, the resulting permeability varied widely between the designs (Fig. 8). Furthermore, the achievable permeability was less for designs with less initial permeability. This indicates that the algorithm does not produce unique solutions, and that the final design depends on the initial guess for density distribution.

Fig. 2. Architecture topologies: (a) 35% volume fraction (VF) spherical void; (b) 35% VF orthogonal cylindrical pore; (c) 35% VF wavy fiber; (d) 26% VF topology optimized; (e) 25% VF spherical void; (f) 25% VF orthogonal cylindrical pore; (g) 25% VF wavy fiber.

Fig. 3. Plot of normalized modulus versus permeability for designs illustrated in Fig. 2. Relationships between permeability and normalized modulus are architecture dependent, with some architectures having similar modulus but very different permeability and vice versa.

Fig. 4. Optimized Design: Modulus vs. Permeability

Optimized Design: Modulus vs. Permeability
4. Discussion

The results in this study demonstrate that it is possible with designed architectures to cover a significant portion of theoretical bounds for effective stiffness. However, the requirement of preserving mass transport, characterized by permeability, restricts designed architectures from reaching theoretical upper stiffness bounds. The result was also noted by Sigmund [7] who found that architectures optimized for stiffness alone produced closed unit cell architectures that achieved theoretical upper bounds, but found that architectures optimized with a fluid conductance constraint did not achieve the upper bounds. A further limitation on achieving bounds is the lower bound restriction due to a limited fabrication feature scale size. It is known that finite rank laminates having multiple scales can achieve theoretical stiffness bounds, but it is much more difficult to achieve bounds with single scale architecture.

Fig. 4. Relationship of various designed unit cells to both isotropic (dashed line) and cubic (solid line) theoretical bounds on normalized modulus (normalized modulus is effective modulus/base scaffold modulus). The closed cubic cell proposed by Sigmund [9] is the only single phase architecture that meets the cubic bounds. Other open cells do not meet theoretical bounds. Wavy fiber unit cells produce effective stiffness in the lower range of theoretical bounds, which are zero for all porous materials.

Fig. 5. Example of two of the designed architectures: (a) spherical void 25% volume fraction, (b) topology optimized 25% volume fraction and (c) wavy fiber 35% volume fraction created in the shape of cylindrical test specimens.

Fig. 6. Two views of an anatomically shape scaffold for mandibular condyle reconstruction with heterogeneous designed architecture combining a spherical void section for the cartilage (top unit cell) and a strut architecture for bone regeneration (bottom unit cell).
features [7]. Increasing scale resolution will increase the capability to achieve stiffness bounds, however this will require advances in fabrication technology to realize.

It is generally accepted that there are a number of factors that prevent numerical inverse homogenization techniques from producing architectures that reach theoretical bounds [7,21,22]. Design length scale is one significant factor restricting the ability of designed architectures to reach prescribed bounds. It is known that such bounds can only rigorously be reproduced using materials with multiple length scales, known as rank \( N \) laminates [21]. For single phase materials, only closed cell materials [7] are known to reach upper bounds on modulus for cubically symmetric materials. Furthermore, even the assumption of basic unit cell shape will limit the possibility of achieving theoretical bounds. Diaz and Benard [22] noted that restriction of unit cells to square or rectangular shapes may restrict possible solutions. Finally, finite element mesh resolution will also restrict achievable properties, with coarser meshes producing results farther from theoretical bounds. Guedes et al. [21] noted significantly different architectures for different mesh resolutions, even though the spread in final effective properties for these architectures was only 3.5%.

This last fact, that a large range of optimized architectures give rise to nearly identical effective moduli, points to the non-uniqueness inherent for architecture optimization. Again, Guedes et al. [21] note that single length scale architecture optimization is a non-convex problem that contains several local optimal solutions. They noted that different initial starting densities lead to strikingly different architecture designs, although the resulting effective energy was nearly identical. This result is similar to the present results, where the final architecture configuration depended on the initial starting density distribution. In this sense, material design algorithms for single scale designs are not unique. This is due to the fact that multiple architectures can give rise to the same average or effective properties.

The ability to design scaffold architectures that achieve desired stiffness and permeability levels could have significant impact on tissue engineering. Although numerous

Fig. 7. Effect of initial starting density on final optimized design: (a) 33% porous spherical void (left) as the initial starting density with final optimized architecture (right); (b) 75% porous enclosed cubic void (left) as the initial starting density with final optimized architecture (right); (c) 75% porous random structure (left) as initial starting density with final optimized architecture (right).

Fig. 8. Effect of initial starting configuration on (a) final average effective modulus and (b) final effective average permeability for the three initial starting configurations shown in Fig. 6. Average modulus was defined as the average of the three orthogonal moduli. Average permeability was defined as the average of the three diagonal permeability coefficients. Error bars indicate standard deviation for modulus and permeability. Higher standard deviation indications larger variation from cubic symmetry.
hypotheses concerning the influence of scaffold stiffness, diffusion, and permeability on tissue regeneration [23] have been put forth, there has been little testing of these hypotheses. This is largely due to the lack of fabricated scaffolds with controlled stiffness and permeability. Theoretical bounds are a critical first step since they define what effective properties can be achieved for a given scaffold material. These bounds coupled with homogenization based computational architecture design techniques will allow creation of scaffolds that have rigorously controlled stiffness and mass transport properties. These scaffolds can then be tested in \textit{in vivo} systems to determine the influence of architecture on tissue regeneration.

Finally, there are two crucial points of research in the area of effective property bounds and computational material/architecture design. First, it will be important to establish theoretical bounds for multi-functional material/architecture. As shown here and by Sigmund, materials designed to achieve both mass transport and stiffness cannot achieve bounds derived for either characteristic singly. Thus, it is necessary to determine if these multi-functional materials achieve bounds for combined effective properties. Second, for computational material/architecture design, it is important to pursue systematic optimization techniques that can design for the entire range of porous material bounds. Typical optimization techniques have been applied to maximize effective stiffness. However, for soft tissue engineering, it is important to achieve a low stiffness that differs from the trivial lower bound solution of 0 for porous materials.

In conclusion, we have presented both direct and topology optimization techniques for designing tissue engineering scaffold architecture that can achieve significant ranges within the bounds on effective stiffness. These techniques provide the capability to rigorously test how scaffold architecture affects tissue regeneration, since scaffolds can be fabricated that have different stiffness and permeability for the same porosity. Furthermore, it will allow tailoring of scaffold properties to match those of normal tissue, if this requirement turns out to be important for enhancing tissue regeneration.

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\textbf{References}


