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Bioresorbable scaffolds for bone tissue engineering: Optimal design, fabrication, mechanical testing and scale-size effects analysis

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ABSTRACT

Bone scaffolds for tissue regeneration require an optimal trade-off between biological and mechanical criteria. Optimal designs may be obtained using topology optimization (homogenization approach) and prototypes produced using additive manufacturing techniques. However, the process from design to manufacture remains a research challenge and will be a requirement of FDA design controls to engineering scaffolds. This work investigates how the design to manufacture chain affects the reproducibility of complex optimized design characteristics in the manufactured product. The design and prototypes are analyzed taking into account the computational assumptions and the final mechanical properties determined through mechanical tests. The scaffold is an assembly of unit-cells, and thus scale size effects on the mechanical response considering finite periodicity are investigated and compared with the predictions from the homogenization method which assumes in the limit infinitely repeated unit cells. Results show that a limited number of unit-cells (3–5 repeated on a side) introduce some scale-effects but the discrepancies are below 10%. Higher discrepancies are found when comparing the experimental data to numerical simulations due to differences between the manufactured and designed scaffold feature shapes and sizes as well as micro-porosities introduced by the manufacturing process. However good regression correlations ($R^2 > 0.85$) were found between numerical and experimental values, with slopes close to 1 for 2 out of 3 designs.

1. Introduction

Bone tissue engineering (BTE) has been an area of intense research for over 20 years. However the translation to clinical practice is extremely challenging due to existing technical, business and philosophical barriers [1]. Nevertheless, BTE is still seen as the alternative to traditional bone autografts and allografts, and thus further research is needed to face the challenges in this field [2].

A critical key for BTE success is to develop a bone scaffold that fulfills the requirements of form, function, formation, and fixation [1]. Form is related with the need of filling the bone defect site, function is the necessary temporary mechanical support that the scaffolds must provide, formation refers to the characteristics that permit bone tissue regeneration and fixation is the requirement to assure that the graft is attached to the defect boundaries [1,3]. An approach towards this objective is to use additive manufacturing to produce scaffolds embodied as periodic media through the repetition of a representative microstructure (or unit-cell) [4–6]. The design of the internal pore architecture of the scaffold microstructure is a critical issue that can be addressed using a variety of computational techniques. For instance, one way is using triply periodic minimal surfaces (TPMS) to obtain internal pore architectures [7–10]. Geometrically extremal microstructures can be obtained this way. However, the need to meet other performance measures (beyond pure geometrical issues) may call for alternative optimal design approaches [11–13]. For instance, topology optimization has been used to design the scaffold microstructure with optimal effective (homogenized) stiffness and diffusion properties that give structural integrity and allow cells to migrate, proliferate as well as to enhance nutrient supply. Integrated multiscale approaches that iteratively and concurrently optimize macroscopic constitutive properties and scaffold porous microstructure [14,15] are also very promising to design site specific bone substitutes. In addition, 3D printing and additive manufacturing techniques have shown the possibility of producing these complex, optimized microstructures in anatomic shapes despite some limitations in terms of feature size resolution.

Beyond technical requirements, translation requires that any design and manufacturing meet FDA quality system requirements (QSR), specifically the design control requirement that a finished device is

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verified to meet design inputs [12]. This issue is indeed an important research challenge regarding design for manufacture. Therefore, the objective of the present work is to investigate the accuracy of the final properties of polycaprolactone (PCL) scaffolds fabricated by selective laser sintering (SLS) and designed using a multiscale topology optimization model. Discrepancies between initial design and final product are investigated through the entire process from topology optimization, conversion of data from voxel based to .STL surface representation to final fabrication from the .STL representation using the PCL laser sintering process [5,17].

For this purpose, a multiscale model for the design of customized scaffolds is used to obtain a bioresorbable scaffold for spinal fusion [15,18]. The model assumes the scaffold is made through the repetition in 3D-space of a unit-cell (microstructure) obtained by the maximization of its stiffness with constraints on permeability, for a mechanical environment computed using a macro-model of the whole organ (the lumbar spine in this case). The relation between the macro-loads applied on the whole organ and the mechanical function of the scaffold at a given bone site defines the multi-scale character of the model. It should be noted that the unit-cell is a mathematical unit or, equivalently, a representative volume element. The focus of the paper is not on the multiscale model itself but instead on issues related to the design phase of the scaffolds, such as the numerical and geometrical perturbations introduced by filtering and lumping techniques to obtain a binary solid/void unit-cell, as well as the geometrical smoothing to obtain the STL files for fabrication. In addition, the mechanical properties are numerically analyzed, in particular the anisotropy of the obtained unit-cells. Furthermore, asymptotic homogenization [19] is used here in order to compute the equivalent macroscopic elastic properties of the scaffold. Homogenization assumes that the feature size of the unit-cell representative of the scaffold periodic microstructure is much smaller than the size of the scaffold itself, in the limit approaching infinitesimal. In practice this feature size ratio is finite (often in the range of 1/4 to 1/10) which gives rise to scale-size effects when evaluating the mechanical response of actual scaffolds. This also motivates here a comparative analysis between the actual mechanical properties of porous scaffolds with a limited number of unit-cells and those predicted by homogenization. Finally, the mechanical properties of the multiscale optimized PCL scaffolds fabricated by SLS are determined experimentally and compared to computational simulations. The results demonstrate that the multiscale design approach can predict the final functioning scaffold, a critical requirement for design verification and design to manufacture research.

2. Materials and methods

The scaffold is assumed here to be periodic porous medium generated by the repetition of a unit-cell throughout the entire scaffold domain in order to attain structural uniformity and manufacturability. The unit-cell is thus representative of the smallest periodic heterogeneity of the domain whose elastic properties are computed by homogenization [19]. The scaffold design problem is heterogeneous on the macroscale with the global mechanical environment being propagated down to the microstructure level of the unit-cell domain. The unit-cell domain is subjected to periodic boundary conditions where a material microstructure has to be designed to meet mechanical and biological criteria. Since these criteria are usually conflicting (i.e. denser material favoring the mechanical criteria of load bearing and more porous material favoring the biological criteria of cell infiltration and nutrient diffusion) one may take advantage of optimization techniques to achieve efficient, balanced as well as feasible designs [11,20,21]. Furthermore, the external mechanical environment to which the scaffold is subjected is site-dependent at the organ level. Therefore, a multiscale design model addressing simultaneously the organ/tissue scale and the pore scaffold scale as interconnected length scales is a must to accurately simulate the boundary conditions acting on the scaffold [22–24].

A high stress mechanical environment is especially prevalent in the intervertebral disc space requiring scaffold solutions to work as load bearing devices (increased mechanical stiffness) and displaying at the same time a network of interconnected pores for biological success (permeability of the porous medium must be controlled). Taking into account all these design requirements, a multiscale topology optimization model developed by Coelho and co-authors [14,15,25] was applied to the interbody fusion problem [11,18,26]. The focus of the present work is not on the multiscale model itself but instead on design to manufacture issues as illustrated in Fig. 1 for the three optimal unit-cell designs obtained from the previous work [18]. These issues, as discussed in the next sections, have to do with scale-size effects and perturbations on mechanical properties due to the assumptions of homogenization, the needed post-processing tasks to pass from the optimized design to the .STL file and the manufacturing process itself.

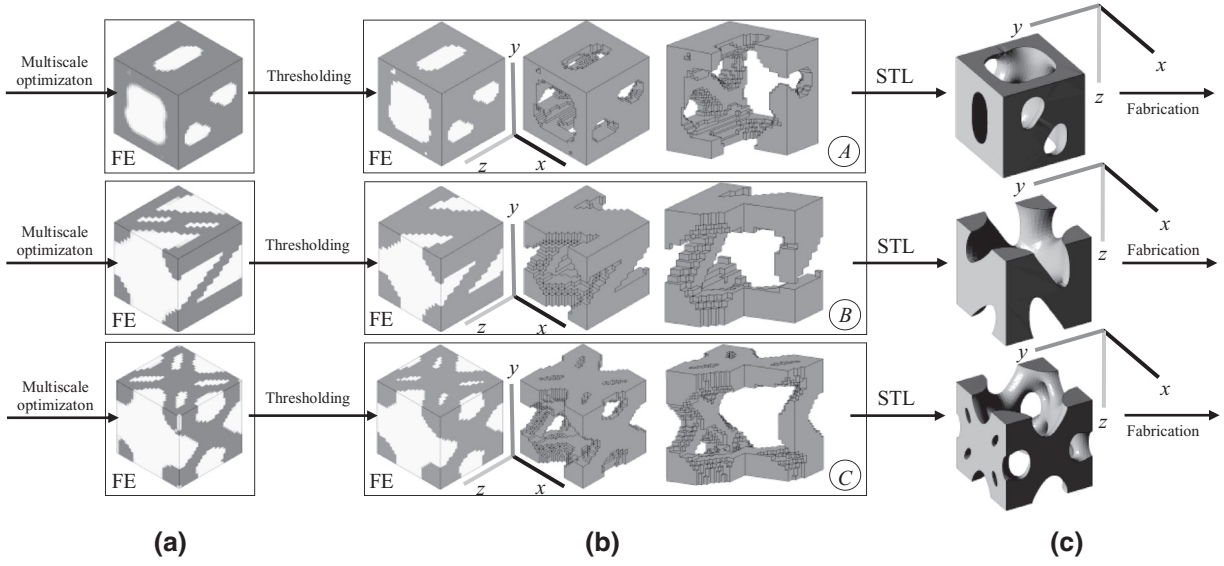

Fig. 1. Unit-cell topologies *A*, *B* and *C* from design to fabrication: (a) solutions as they were obtained via topology optimization on the top of the finite element mesh (20 × 20 × 20 or 30 × 30 × 30 of 8-node hexahedral isoparametric elements); (b) microstructures after thresholding, 0-1 design, solid phase and cut views; (c) conversion into STL format.

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