Creation of a unit block library of architectures for use in assembled scaffold engineering

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Abstract

Guided tissue regeneration is gaining importance in the field of orthopaedic tissue engineering as need and technology permits the development of site-specific engineering approaches. Computer Aided Design (CAD) and Finite Element Analysis (FEA) hybridized with manufacturing techniques such as Solid Freeform Fabrication (SFF), is hypothesized to allow for virtual design, characterization, and production of scaffolds optimized for tissue replacement. However, a design scope this broad is not often realized due to limitations in preparing scaffolds both for biological functionality and mechanical longevity. To aid scientists in fabrication of a successful scaffold, we propose characterization and documentation of a library of micro-architectures, capable of being seamlessly merged according to the mechanical properties (stiffness, strength), flow perfusion characteristics, and porosity, determined by the scientist based on application and anatomic location. The methodology is discussed in the sphere of bone regeneration, and examples of catalogued shapes are presented. Similar principles may apply for other organs as well.

Keywords: Rapid prototyping; Tissue engineering; Computer-aided design; Scaffolds; Computer-aided tissue engineering (CATE); Cellular solids; Permeability

1. Introduction

Guided tissue regeneration focuses on the implantation of a scaffold architecture which acts as a conduit for stimulated tissue growth. Successful scaffolds must fulfill three basic requirements: provide architecture conducive to cell attachment, support adequate fluid perfusion, and provide mechanical stability during healing and degradation. The first two of these concerns have been addressed successfully with standard scaffold fabrication techniques. The use of solvent casting or gas leaching [1] and melt molding [2] has produced scaffolds that are globally porous with void architectures large enough to support cellular adhesion, migration, and differentiation. At high enough porosities (> 60\%), these scaffolds provide adequate fluid flow to deliver nutrients and remove degradation products [3–6]. In instances where load-bearing implants are required, such as in treatment of the spine and longbones, application of these normal design criteria is not always feasible. The scaffold may support tissue invasion and fluid perfusion but with insufficient mechanical stability, likely collapsing upon implantation and subsequent loading as a result of the contradictory nature of the design factors involved. It is believed that the random architecture due to the fabrication process contributes to low mechanical integrity. Also, a compensatory increase of porosity for fluid perfusion considerations innately results in reduced mechanical properties. Using solvent leaching with NaCl particulates, porosity must be at least 60\% by volume to provide an open-cell architecture for adequate fluid perfusion, a level which seriously compromises the mechanical stability of all but the strongest materials [4], none of which are resorbable [7].

Addressing mechanical stability of a resorbable implant requires specific control over the scaffold design. With design and manufacturing advancements, such as rapid
prototyping [8–10] and other fabrication methods, research has shifted towards the optimization of scaffolds with both global mechanical properties matching native tissue [11], and micro-structural dimensions tailored to a site-specific defect [12]. Recent work by Kelsey et al. [13], proposed a selection process for composite implants based on patient specific parameters coupled with a finite element code. The authors purport that a criterion-based selection system will improve the matching of patient defect to implant size and reduce the failure rate of the implant. While this study demonstrates the need to design patient-specific implants, it only highlights the ability to select the most adequate implant for entire prostheses. Hollister et al. [14] generated a scheme for regular, repeating architectures, which have the advantage of being described by constitutive equations relating microstructure to global structure based on homogenization theory. For example, a cube was generated with intersecting, hollow, orthogonal, embedded cylinders. Indices describing the architecture were related to modulus and stiffness and optimized in a way to maximize porosity whilst maintaining stiffness [14]. The advantage of these systems is that the architecture is designed to promote strength independently of material, thus maximizing material arrangement.

While these preliminary studies have demonstrated improved research into the role of material organization of bioengineered scaffolds, certain deficiencies still exist which make direct application of these improvements difficult [15]. The previous research has demonstrated the ability to create architectures of repetitious microstructures and characterize them. However, the ideal implant is one that would readily be assembled in series or parallel, each location corresponding to specific mechanical and perfusion properties. This implant would aid in load transfer as well as match the already existent geometry of the defect. Furthermore, current databases or libraries of architectural building blocks are incomplete in describing the load transfer environment, as determined strengths and stiffness are not necessarily representative of actual physiological load transfer from one unit block to the next. The lack of a common interface can result in stress lines and border fractures, but can be overcome with well planned Computer Aided Tissue Engineering (CATE) [16].

The goal of this study was to design a library of implantable micro-structures (unit blocks) which may be combined piecewise, and seamlessly integrated, according to their mechanical function. Once a library of micro-structures is created, a material may be selected through interpolation to obtain the desired mechanical properties and porosity. This procedure will allow a tissue-engineering approach to focus solely on the role of architectural selection by combining symmetric scaffold micro-structures in an anti-symmetric or anisotropic manner as needed. Our study incorporated a linear, isotropic, finite element analysis on a series of various micro-structures to determine their material properties over a wide range of porosities [17]. Furthermore, an analysis of the stress profile throughout the unit blocks was conducted to investigate the effect of the spatial distribution of the building material.

2. Biomimetic design theory and implementation

Bone and other architectures contain complex geometry with mechanical properties that vary spatially and with anatomic site. In a region of interest (ROI), at least two continuous phases (bone matrix and interstitial fluid) are responsible for the global mechanical properties. Subdivisions of this ROI will contain smaller regions of discrete architecture and thus mechanical properties which when summed together result in the global properties. If for example, the defect site contained both cortical and trabecular bone, then homogenization theory would correctly assume the global properties but would fail in the determination of the properties of the subregions of the ROI. To complete and replicate load transfer upon implantation of an implant, especially in a region containing varied architecture and properties, an engineered scaffold must mimic the variants with respect to direction. In this regard, the interior properties of the bone under study can be obtained by a quantitative computed tomography based approach (QCT). The CT slices of the ROI can be queried to obtain the CT# for a discrete number of voxels within the ROI of volume $V_m$, given by

$$\varphi_k(x, y, CT#)N_k = V_m, \quad k = 1, 2, \ldots n$$

where $x, y, z$ represent the position of the voxel within the coordinate space; $N_k$ represents the number of voxels within the slice; $t$, the thickness of each slice; $n$ represents the total number of slice planes. Phi is a function that relates the outer contour of the slice to the contained voxels. This functions serves as a database of information containing the density of the voxel as well as a description of the contour of the region of interest of each slice. Mechanical property characterization can be achieved by correlating the CT# to density by a linear interpolation using relations available in published literature. This density can in turn be then related to $E$, the Young’s modulus of the tissue structure, allowing the heterogeneous elasticity of the bone to be defined [18,19]. The ROI is then subdivided into discrete units, with each unit associated with its own characteristic Young’s Modulus, $E$.

The intended 3D scaffold that replaces $V_m$ will be composed of discrete subunit architectures $V_i$

$$V_m = V_1(P_1, S_1) \cup V_2(P_2, S_2) \cup V_3(P_3, S_3) \cup \cdots \cup V_i(P_i, S_i)$$

(2)

where sub-volume $V_i$ denotes the unit block, $P_i$ denotes the spatial position of the unit block and $S_i$ denotes the characteristic unit block assembled in $V_m$. Each unit block has specific mechanical properties and will be matched
based on the initial mechanical property characterization using data set available in Eq. (1). Varying mechanical properties can be achieved by either altering the porosity of the unit block or changing the internal architecture of the unit block while keeping the porosity the same. Thus, subdivisions of the engineered scaffold must mimic the select architectural properties of these regions. We propose that the micro-architecture be designed to replicate the site-specific mechanical properties at a resolution that match the achievable feature size of current solid freeform fabrication methods.

Design of unit blocks with varying architectural properties may result in non-congruous borders when matched with adjacent neighboring blocks. These discontinuities will critically reduce the mechanical properties of the solid along the borders of the architectures and invalidate the model design. To prevent this, a common interface is required along the borders of each unit block. This common interface will need to be a shape that does not detract from the overall strength of the unit block itself but also enacts a complete load transfer between adjacent blocks as a result of the border. In addition, the design of unit blocks demands that the scaffold should contain architecture, which promotes both cell viability functions and fluid transfer throughout the scaffold. These demands would be satisfied by the generation of an architecture, which is at a porosity near those of the non-specific scaffold preparation methods. These properties may be improved by adding regularity to the design of the architectures.

3. Example—generation of unit block library

3.1. CAD generation of architectures

Unit block polyhedral models were generated using Rhinoceros 3D (McNeel Associates, Seattle, WA). All polyhedra were generated within the same bounding box of 3 mm × 3 mm × 3 mm which placed constraints upon the possible size of each structural element [15]. All generated architectures exhibit symmetry along the three orthogonal axes and were thus considered orthotropic with respect to geometry, with isotropic behavior with respect to the built material. Two types of models were generated, the first based on solid geometry with the inclusion of void spaces to create porosity and the second based on geometric regular polyhedra.

The first type of architecture was a space filling solid structure, such as a sphere or cube. A void structure was superimposed onto a solid structure using standard Boolean processes [20], resulting in hollow or shelled structure exhibiting the desired geometry. Void structures were applied in such a manner as to result in an architecture which was symmetric in three directions. Porosity of these solid architectures was determined from the ratio of solid volume to the global bounding box volume. The porosity of the solid architectures was adjusted to predetermined values by modifying the volume of the void elements until the porosities matched.

The second type of architecture generated were wire-frame approximations of the basic set of geometric polyhedra, the Archimedean and Platonic solids [21]. The advantage of using these polyhedra as models is that they are regular, that is both equiangular and equilateral, and thus exhibit the desired symmetry. These models were initially employed as volumetric representations, as illustrated in Fig. 1A for the case of the rhombicuboctahedron (RCO). Each edge was converted to a beam of the corresponding length. As shown in Fig. 1B, the resulting shape contains the same number of beams as the original shape had edges. Each beam was equilateral and had the same diameter. The porosity of the architectures was determined from the ratio of the summation of the beam volumes to the volume of the bounding box. Porosity adjustment was accomplished by globally modifying the beam diameters until the desired value was obtained, while compensating for shrinkage of the bounding box.

The final porosity of each architecture was resized to 80% volumetric porosity, a value corresponding to the porosity of trabecular bone. The 12 architectures generated including their common interface are displayed in Fig. 2. Briefly, the square holes architecture is a solid cube with square void placed in orthogonal directions. The plumber’s nightmare was taken from a common structural organization of lipid bilayers and is composed of hollow orthogonal pillars with a shelled sphere central to the architecture. The hollow sphere is the superposition of a solid sphere with a void sphere applied to the center of the shape, while the hollow corners architecture has four void spheres applied to the corners. The fire hydrant is composed of three orthogonally arranged beams. The eight spheres architecture is composed of eight-shelled spheres arranged adjacent to each other. The cross beams scaffold consists of four beams equi-spaced around the center of the volume copied orthogonally to each other. The truncated octahedron and the rhombicuboctahedron are exact representation of platonic solids. The curved connector is composed of three quarter-tori at each corner connecting the common

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**Fig. 1.** (A) Rhombicuboctahedron, space filling solid model. (B) Wireframe approximation of rhombicuboctahedron. Each beam has the same length and diameter as the edges of the space filling equivalent.
interface. The previously listed three shapes were also modified to include cross beams in the center of the architecture. The cross beam architecture was generated at additional porosities of 50, 60 and 70% porosity to illustrate the effect of volume on material properties.

3.2. Inclusion of common interface

Previous studies that have discussed the use of a unit library for the creation of scaffold architectures utilizing continuum modeling such as homogenization theory [13]. These theories account for the determination of the mechanical properties of a single architecture with the constraint that the micro-architecture be used throughout the global architecture or within the modeled continuum [14]. When matching two continuums of differing micro-architectures, stress discontinuities will occur. No studies have yet addressed the manner in which objects such as these may be joined together to create a global scaffold with mechanical properties dependent upon location. In this study, we have applied a common interface in the form of a torus. This shape was added to each side of the polyhedra to add regularity to each architecture and aid with load transfer when connected in series and in parallel. The torus was sliced axially so that each side had one half torus, thus when two shapes were combined, a whole torus was produced. An illustration of the torus concept of matching sides is depicted in Fig. 3. The dimensions of each torus were kept constant for complete load transfer during joining. Following the addition of the torus, all architectures were checked and resized to the appropriate porosity if required and subsequently exported as .igs files in preparation for finite element analysis (FEA).

3.3. Finite element analysis

Finite element analysis was completed on the architectures of the building blocks to determine their apparent material properties due to specific material arrangement. Each polyhedra was imported into ABAQUS CAE (ABAQUS Inc., Pawtucket, RI) from the prepared .igs file and subjected to a linear, prescribed displacement test. An illustration of the finite element procedure is provided in Fig. 4. Isotropic material properties for each polyhedra were assigned with an elastic modulus of \( E = 2 \) GPa and a Poisson’s ratio of 0.3, approximating currently available biomaterials [22]. Each polyhedra was displaced the equivalent of 1% and the reaction force (RF) was calculated from the top nodes of that polyhedra. Young’s Modulus (\( E \)) was calculated by dividing RF over the bounding box area divided by the strain. First, a convergence study was completed with the cross beam architecture to determine the required mesh density for the subsequent analysis. The architecture was meshed at varying seed densities with tetrahedral elements and subjected to a linear perturbation test. Results of this study are illustrated in Fig. 5. Convergence was achieved when the model contained...
more than 50,000 elements (RF error less than 1% compared to highest mesh density). Consequently, we chose a seeding density of 0.075 (ABAQUS CAE option) for all polyhedra at 80% porosity which resulted in meshes with roughly 75,000 elements.

Linear displacement of the polyhedra was completed for two cases, confined and unconfined compression. Confined compression included roller boundary conditions on the vertical faces, which restricted a bulging effect during displacement. The confined case illustrates the properties of the polyhedra as it may act when placed within a continuum in a global scaffold. The unconfined case represents the deformation characteristics of the polyhedra without the influence of adjacent cells. The loading scenario subjected to a unit block in a large scaffold will most likely be in between the investigated cases. Fig. 6 displays the results of the displacement test for the Cross Beam polyhedra at the varying porosities. At the highest material volume, the elastic modulus of the architecture was 652 and 600 MPa for confined and unconfined, respectively. As material volume decreased, so did the modulus in both cases according to a squared polynomial equation. At 80% volumetric porosity, the elastic modulus between confined and unconfined compression differed by less than 3%.

Fig. 7 illustrates the calculated elastic moduli for all architectures evaluated. These values represent the average of the confined and unconfined case for each unit block. Despite the fact all shapes, for a given porosity, contain the same amount of material and material properties, there was a large range of modulus values obtained, with the weakest architecture (curved connectors) having a modulus of 0.96 MPa, while the strongest architecture (square holes) had an elastic modulus of 174 MPa.

Elemental principle stress distribution was evaluated for each polyhedra as a method to characterize the loading on each architecture as a result of the spatial arrangement of the building material. For each prescribed displacement, the maximum principle stress was calculated and outputted as a histogram normalized to the number of elements per architecture. Selected results of this analysis are displayed in Fig. 8. As can be seen from Fig. 8A, the material volume plays a direct role in the resulting stress profile for each architecture. The majority of the elements in the 80% porous cross beams architecture experienced little to no stress. This is the first trend that was illustrated from the analysis of the stress profiles. As the material volume increases, the stiffness of each architecture also increases peak stress that is experienced on the cross beams architecture increases and also the stress profile spreads
out to encompass more values as a result of increased elements contained in the architecture. All of the shapes exhibit a distinct final peak that occurs at approximately $25.0 \text{ MPa}$. This outer peak is a trend that was observed in other architectures as seen in Fig. 8C such as the fire hydrant architecture. Also to be observed from this figure is the similarities in stress profile at and around zero stress for the two dissimilar architectures of the fire hydrant and the hollow corners. In Fig. 8B, it can be seen that the cross beams 80 architecture has twice as many elements that are near zero stress as the other four architectures. The cross beams architecture also exhibits two distinct peaks while the remaining shapes may be more widely dispersed or have more peaks.

4. Conclusions

In this study we have demonstrated the creation of a unit library of architectures that can be used to assemble a complex scaffold of individual, well characterized microstructures. This strategy allows the scientist to tailor the mechanical properties of localized regions while maintaining the integration between adjacent microstructures. The mechanical properties of microstructures of a different porosity or even shape from those outlines may be intelligently interpolated through Figs. 6 and 7. Additionally, design characteristics such as strength instead of modulus can be also be deduced, as linear finite element analyses were conducted. As was illustrated with the cross beam polyhedra, the mechanical properties vary with material volume. Due to demands imposed by the need for tissue ingrowth, solid materials will not allow adequate tissue ingrowth or fluid perfusion. For these reasons, a porous material is required which may support such demands.

There are gross differences in the global properties of several of the unit blocks which are directly related to the architecture. The curved connectors shape contains material only in the corners of the shape thus offering only limited structural support to any mechanical deformation. Even with a 90% increase in modulus from the unconfined to the confined case, the shape is still the weakest by two orders of magnitude. As seen in Fig. 6, there is little difference in the elastic moduli between a confined and unconfined case for the cross beams. This may be due to the uniform material arrangement, which positions the majority of the load to be transferred directly through the architecture. As a result, as seen from the histogram in Fig. 8, the majority of the elements for the 80% porosity were completely unloaded. This supports the previous claim that the arrangement of the material supports the stress in all three principle directions. The stress profile serves to demonstrate the contribution of architecture to the global loading. Counter-intuitively, the cross beams architecture at 80% porosity has more elements that are not loaded than the other three similar architectures with lower porosity values (Fig. 6). This means that the higher the porosity of an architecture, the greater dependence is placed upon elements that truly add to the strength of the architecture whereas in the lower porosity architectures, less dependence is placed upon the material organization and thus more elements are able to carry higher stress values overall. The contribution to specific stress profiles can be seen in Fig. 8B in comparison of the RCO, RCO w/cross beams and the cross beams architecture. The RCO exhibits a two-peak stress profile but the RCO w/xbeams includes a third peak, which is reminiscent of the cross beams architecture. We posit that this peak is due...
to the cross beams which are present in the center region of these architectures but which are missing from the original RCO architecture. Additionally in Fig. 8C, we see that hollow corners exhibits a related, yet optimized stress profile to the fire hydrant, despite their very distinguishable material organization.

Studies have shown that mineral deposition and cell dependent growth is correlated to the mechanical environment of cells [23]. We hypothesize that stress profiles with uniform distributions may do better at promoting cell adhesion. A comparison of a cutaway profile for the fire hydrant and plumber’s nightmare can be seen in Fig. 9. Stress distributions in the dominant loading direction for the plumber’s nightmare reveal an axial transfer of stress to the non-loading direction as evidenced through elements in tension on the periphery due to buckling. Additionally, there are no stress-free elements in the plumber’s nightmare which possibly provides a biologically favored architecture, as evidenced through the Von Mises stress distribution. The solid framed fire hydrant exhibits a more predictable stress profile with minimal off axis stress distribution.

Previous studies have demonstrated the need to document a library of scaffolds which may be assembled, but did not provide an adequate means in which to join parts of varied architecture [14,24]. With the addition of a common border in the form of a torus between the shapes, even grossly dissimilar architectures can be joined together to obtain a stress free border, which is important in the design and fabrication of a complex implantable vertebral body replacement. In the case of cortical bone, which exhibits porosities much lower than trabecular bone, there would be a mismatch between the borders of the shapes due to material volume. Furthermore, steps to actually develop a library of different shapes and summarize the mechanical property trends, had not previously been undertaken for a number of shapes. Here we have

Fig. 8. Histogram of finite element results. Top, stress distribution of the cross beam architecture at four porosities. Middle, stress distribution of four additional architectures evaluated against the cross beams 80% porosity architecture. The majority of the elements in these four architectures are loaded with few elements if any experiencing null levels of stress. Bottom, stress distribution of the fire hydrant architecture displayed against the hollow corners architecture. The stresses of both architectures near zero are identical. Several of the architectures exhibited a second peak near 2 MPa.

Fig. 9. Display of the stress profiles in two architectures for both the Von Mises stress and the principal stress in the loading direction. (A) the fire hydrant architecture experiences most of its loading along the dominant axis and elsewhere stress is near zero. (B) The plumber’s nightmare distributes more stress in non-loading directions as a result of the spherical, hollow, center chamber.
documented 12 shapes as the beginning of sizeable library. Future steps include improvement of this library by increasing the availability of shapes, surface optimization schemes to reduce stress concentrations, and introduction of anisotropic architectures and material properties. Experimental studies need to be designed to create the compromise between the engineering aspect of the scaffold micro-architecture as presented here and the biological component responsible for tissue ingrowth.

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References


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