A New Approach for Designing Biodegradable Bone Tissue Augmentation Devices by Using Degradation Topology Optimization

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ABSTRACT

The current study proposed a topology optimization method accounting for base material degradation and create a degradable device that retains sufficient stiffness through the degradation process to provide load bearings for tissue regeneration in orthopaedic applications. Degradable materials are less stiff than permanent materials and suffer further stiffness reduction through time when considering those as substitutes to replace permanent materials for many reconstruction applications. Merely replacing the permanent material with a degradable material in the same design may lead to early device failure. Since many degradable materials lose material through bulk erosion without shape change, the proposed optimization method creates a density distribution map for selected time points during degradation. These different density distributions are then linearly superposed using both time and degraded base stiffness weighting factors. In this paper, the method is applied to design a degradable spine interbody fusion cage device from poly(propylene fumarate)/beta-tricalcium phosphate (PPF/β-TCP). The weighted optimization study successfully produced designs that maintained device stiffness better than either non-weighted or conventional designs. Any bulk degrading material can be designed using this process for any skeletal reconstruction application.

Keywords: biodegradable polymer, topology optimization, bone tissue augmentation device, spine fusion cage, poly(propylene fumarate)/beta-tricalcium phosphate

1. INTRODUCTION

It has become increasing prevalent to use biodegradable materials for bone tissue augmentation/reconstructions devices to facilitate tissue regeneration and improve integration with host tissues [1-4]. However, simply replacing the base material from the original design with biodegradable polymers may not be appropriate, especially for the development of load bearing devices in joint reconstructions and spine arthrodeses, since degradable materials typically have less stiffness and strength than non-degradable materials. Furthermore, this stiffness and strength will degrade over time, further reducing the mechanical competency of the device.

A qualified biodegradable tissue augmentation/reconstructions device must retain adequate stiffness and strength until tissue regeneration is sufficient for the tissue to assume load bearing function. However, since polymer degradation behavior is stochastic, targeting specific locations to reinforce a priori within a previously developed scaffold design becomes difficult. Therefore, a more direct and generalized approach accounting for the stochastic nature of degradation should be developed to create scaffolds designed to retain desired stiffness after a specified degradation period.

Degradation at the physiological conditions is a chemical process of chain cleavage that occurs by hydrolysis of functional groups of biodegradable polymers in an aqueous environment. Hydrolysis begins when water intrudes into the polymer bulk. The rate of water intrusion determines the type of polymer erosion. If water is mainly consumed on the surface by hydrolysis due to fast degrading velocity, erosion occurs as a surface phenomenon and is thus categorized as surface or heterogeneous erosion. Polymers such as polyanhydrides and poly(ortho easters) have been reported belonging to surface eroding polymers [5]. Göpferich and Langer modeled the surface erosion of biodegradable polyanhydrides, and successfully matched experimental data [6]. They also predicted the erosion front position to investigate the movement of the erosion front that separates eroded from non-eroded polymers, indicating that scaffold features would become progressively thinner. This may suggest that a reasonable reinforcement for surface eroding biodegradable devices will come from thickening or dilating the size of struts or primary structure elements of the devices.

If hydrolysis is slower than diffusion, the bulk polymer matrix will be affected by erosion known as bulk erosion or homogeneous erosion. The progress of bulk erosion is complex and stochastic. However, the phenomenon indicates a more generalized approach should be incorporated in the reinforcement of bulk erosion polymers such as poly(α-hydroxy esters) to retain the mechanical demands through the degradation.

Before the rapid decline of the mass loss in bulk erosion, individual element of the polymer undergoes degradation depending upon the probability that an element degrades within the time interval 0 to infinite. According to Göpferich's model for bulk erosion [7], the lifetime until degradation of polymer element (pixel in the model) is based on the assumption that the degradation of individual pixels is a Poisson process and can then be described by a first order Erlang probability density function $e(t) = \lambda e^{-\lambda t}$. The degradation process is therefore considered as randomized distribution and reinforcing specific features in an existing design against degradation becomes unpredictable. Nonetheless, the general concept of bulk degradation is that the polymer matrix will lose molecular weight and stiffness in a predictable average sense over time. We propose a new material density weighting approach coupled with an integrated topology optimization technique to create scaffold designs for bulk degrading materials that retain stiffness for longer time periods. This approach creates scaffold designs de novo for specific anatomic regions and mechanical loading regimens. We apply this design approach to degradable spinal interbody fusion cages, and demonstrate that the new approach can create designs that retain greater stiffness for longer periods of time.

2. MATERIALS AND METHODS

Purpose: Designed architectures are required for degradable devices such that the stiffness satisfies load bearing requirements at time 0. Sufficient stiffness must also be maintained through degradation until devices are fully integrated with or replaced by new tissue.

Optimization Process for Degradation Reinforcement-General Description: Topology Optimization [8-11] is a design technique that provides optimal distribution of material under applied force to satisfy the objective of maximal stiffness with desired porosity, under constraints of the three design criteria. The design domain for any biodegradable/bioresorbable tissue augmentation/reconstruction device can be defined with arbitrary shapes according to the implant size, anatomic geometry, and/or disease/injury requirement. The optimized topology design with the design domain is then discretized into finite elements, and each element will contain a predicted material density between 0 and 1. 0 indicates void space and 1 indicates complete material; values in between indicate partial material with the corresponding volume fraction. The effective modulus is theb interpreted by the density method as $E_{ijkl} = X_p E_{ijkl}^0$ to indicate the solid, porous and void regions, where E_{ijkl} represents the effective modulus of each finite element, X_p is the fraction of the material and the base material property is E_{ijkl}^0. The macroscopic or 1st scale topology optimization solution provides the general density and location of material within the implant site to limit the displacement under applied load for desired stability with a constraint to enforce the desired porosity.

In the degradation design, the density in each element is weighted by the degradation profile. The weighted material density in each element within the global optimized topology will compensate the loss of the degraded material from the original design and retain sufficient stiffness through the degradation process. A set of densities for each element is first predicted using global topology optimization at specific points in the degradation profile, utilizing a reduced base modulus. A final global density is created by weighting all the densities from each degradation time point with two weighting factors. The two weighting factors are 1) time lasting factor: defined as (total degradation period - time of selective point)/total degradation period. This factor accounts for the influence of the time past implantation on reinforcement of the scaffold architecture. 2) degrading modulus factor: defined as reduced modulus at the selected time divided by the original modulus.

The factor indicates the weight percentage of the original material equivalent to the superposed material densities based on the degrading modulus at selected time points. Therefore, the optimal density distribution for the degradable device material is created by superposing the multiple time optimal densities weighted by a time lasting factor $T_{wt} = (T_{total} - T_{current})/T_{total}$ and degrading modulus factor $E_{wt} = E^0_{ijkl}(T_{current})/E^0_{ijkl}(T_{initial})$ as $X_{pw} = \Sigma X_{pt} T_{wt} E_{wt}$, where T_{total} is total degradation duration, $T_{current}$ is the time at a selected point, X_{pw} is the final fraction of the base material, X_{pt} is the temporary fraction of the reduced/degraded modulus corresponding to a selected time point, and , T_{wt}, E_{wt} are time lasting factor and degrading modulus factor for selected time points as mentioned and defined previously.) These two factors together can utilize the superposed material for the reinforcement in a more efficient manner since they take both the degree of modulus reduction and the time past implantation into account. As time proceeds further past implantation, tissue ingrowth will begin to carry load, reducing the need for scaffold structure. The weighted material distribution can reinforce the stiffness at the regions that require denser material to provide sufficient load bearing especially when the base material stiffness is reduced due to the bulk erosion. Thus, the weighting process produces designs where high load bearing regions are reinforced to compensate for subsequent stiffness degradation due to bulk erosion

Microstructure Design: The global design gives a density flag with an associated volume fraction. However, since the resolution is too coarse, it does not give the specific microstructure that will be located within that point of the scaffold. Furthermore, since we would like the microstructure to have specific elastic properties at a fixed porosity, homogenization based topology optimization is used to design the microstructure [12, 13]. The microscopic or 2nd scale topology optimization approach gives the specific microstructure design that achieves a desired compliance while matching the predicted volume fraction of the macroscopic or 1st level topology optimization.

Design material microstructure using Topology Optimization can be considered as an optimal material distribution problem within the periodic design domain. Homogenization method provides an analytical solution to find the effective material properties by identifying the periodic microstructure. From the material design perspective, we are interested in discovering the topology of the microstructure, which can achieve the prescribed effective material properties. This design process is considered as an inverse homogenization design (Figure 1).

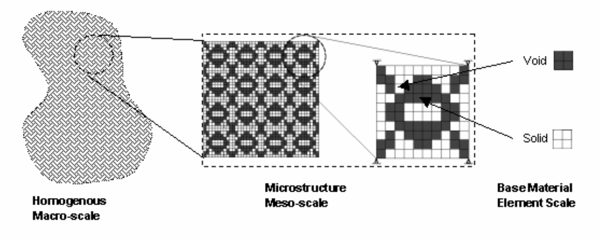


Figure 1. Schematic processes show the homogenization method to design the topology optimized microstructure that achieved the desired effective material properties.

Problem Formulation:
The material microstructure design is based on optimization update scheme. The problem is formulated to minimize the L_2 norm of the difference between the specified and homogenized material properties. The generalized optimization problem can be stated as follows:

$$\min_X \; w_1 \left\| C^H - C^* \right\|_{L_2} + w_2 \left\| \lambda^H - \lambda^* \right\|_{L_2} + ... \qquad (1)$$
$$s.t.$$

Volume fraction constraints on the constituent phases
Bounds on design variables
Geometry symmetry preference on the material distribution

Where the design variable, x, is the density and mixture coefficient within the element. w_1, w_2 are weighting factors to normalize the objective functions in the same scale. The material property tensor with a superscript,*, is the specified value, while the tensor with a superscript, H, is the homogenized value.

Optimization Procedure:
In order to solve the optimization problem as Equation (1) stated above, the sequential linear programming (SLP) method was numerically implemented to solve the sub-optimization problem, which linearizes the objective and constraint around the current design point, and obtains the optimized value (ΔX) for updating design variables. The sensitivity functions with respect to design variables are required to linearize the objective and constraint within the SLP procedure at each design point. The sensitivity functions can be derived along with homogenization process:

$$\frac{\partial C^H_{ijkl}}{\partial X^e} = \frac{1}{|Y|}\int_Y (\delta_{im}\delta_{jn} - \frac{\partial \chi^{ij}_m}{\partial y_n}) \cdot \frac{\partial C^e_{mnpq}}{\partial X^e} \cdot (\delta_{kp}\delta_{lq} - \frac{\partial \chi^{kl}_p}{\partial y_q}) dY$$
$$\frac{\partial \lambda^H_{ij}}{\partial X^e} = \frac{1}{|Y|}\int_Y (\delta_{ip} - \frac{\partial \psi^i}{\partial y_p}) \cdot \frac{\partial \lambda^e_{pq}}{\partial X^e} \cdot (\delta_{jq} - \frac{\partial \psi^j}{\partial y_q}) dY \qquad (2)$$

Once the sensitivity functions are obtained, the SLP sub-optimization problem can be formulated as follows:

$$\begin{aligned} &\min_{\Delta X} \left[\frac{\partial obj}{\partial X}\right]_{X=X_k} \cdot \Delta X \\ &s.t. \quad g_{\min} - g_k \le \left[\frac{\partial g}{\partial X}\right]_{X=X_k} \cdot \Delta X \le g_{\max} - g_k \\ &\qquad \Delta X_{\min} \le \Delta X \le \Delta X_{\max} \end{aligned} \qquad (3)$$

The g is the constraint function within [$g_{min,}$ g_{max}]. And ΔX are the design variables for the sub-problem. After solving the SLP problem, the design variables can be updated and closer to optimum point.

$$X_{k+1} = X_k + \Delta X \qquad (4)$$

Objective for Spinal Fusion (Exemplar Application): A suitable design for spinal fusion cages needs to limit displacements for stability, allow sufficient strain energy density transfer to ingrown bone to reduce stress shielding, and achieve desired porosity for tissue ingrowth. These objectives must be met at each time during the degradation process.

Spinal fusion cages are a prime example of a device that needs to meet multiple requirements for load bearing and tissue regeneration. A suitable design for spine interbody fusion cages needs to limit displacements for stability, allow sufficient strain energy density transfer to ingrown bone to reduce stress shielding, and achieve desired porosity for tissue ingrowth. We reported previously a similar approach by utilizing the integrated global layout and local microstructure topology optimization method for titanium interbody fusion cage design [14]. These objectives must even be met at each time during the degradation process when adopting degradable materials. The replacement of current permanent materials such as metals or carbon fibers with the degradable polymer reduces the stress shielding environment, but the higher compliance of degradable materials coupled with the continual stiffness reduction due to degradation will lead to insufficient load bearing capabilities if no compensation mechanism is incorporated in the initial design. Therefore, the design for a biodegradable spine interbody fusion cage should also take into account the maintenance of sufficient load bearings through the degradation.

The example of a biodegradable spine interbody fusion cage design using poly(propylene fumarate)/beta tricalcium phosphate (PPF/β-TCP) demonstrates how the present approach can create designs that meet critical requirements and objectives concurrently through the degradation. A global topology optimization algorithm (Optistruct, Altair Computing, Inc.) was used to predict a global layout density under the constraint that strain at the vertebral surface were less than 8%. Two rectangular block design domains were used to represent the location of the implanted cages and the multi-directional loads of the physiological range including compression, lateral bending, torsion, and flexion-extension were applied to these domains implanted between vertebrae. A finite element model was then created to simulate the mechanical environment of the design domain within the disc space. In this paper, we created one design that did not account for degradation and called this the Optimal-Structure (OS) cage. By applying the proposed density weighting approach, we developed the new cage design for Optimal-Structure for Degradation (OSDeg) and compared it with one conventional design of threaded cylindrical cage (INTERFIX; Medtronic Sofamor Danek, Memphis, TN) (CON).

Micro-Computed Tomograpy (Micro-CT) Scanning: At the beginning (T=0) and each selected degradation time period degradation period, specimens were scanned and characterized by a MS-130 high resolution Micro-CT Scanner (GE Medical Systems, Toronto, CAN) at 40 μm resolution using 2x2 binning (75 kVp, 75mA). Average relative material density values and solid volume fractions were measured and compared before and after degradation.

Image-based Homogenization Analysis to Compute Effective Moduli: Instead of traditional finite element methods to mesh components and define the element types, an image-based approach was used to deal with the enormously large-scale problem generated by m complex 3D geometries of the designed cages. Image-based approaches allow very accurate replication of design detail, a characteristic not possible with the coarser traditional meshes. The homogenization algorithm is also used to precisely give the macroscopic properties of the composite. All aspects of the voxel finite element modeling process and homogenization method were performed using the commercial voxel finite element package Voxelcon HG (Quint, Inc., Tokyo, Japan).

3. RESULTS

The varied base material properties at each defined stage were approximated from previous studies of the degraded bulk material properties of poly(propylene fumarate)/beta tricalcium phosphate (Table 1) [15, 16]. The global density distributions at each selected time points were shown in Figure 2. Note that along with the degradation process, the base material properties keep decreasing so that more material will be then recruited to resist the external long. Therefore, it will be theoretically true that at the end of the degradation, the design domain should be almost filled with solid material with the weakest base property.

Select Time Points (T*)	**0**	**0.5**	**0.55**	**0.85**
Base Modulus (MPa)**	1000	875	780	250
Design/Effective Modulus				
OSDeg	319	279	249	80
OS	231	203	181	58
CON	111	97	87	28

* The total degradation duration
** Approximated base material properties of poly(propylene fumarate)/beta tricalcium phosphate (PPF/β-TCP) from previous study [16]

Table 1. Base material properties and designed cage effective modulus through the degradation proess of poly(propylene fumarate)/beta-tricalcium phosphate (PPF/β-TCP).

The layout density threshold was then processed to segment the entire interconnected architecture to three separate material phases of 65% solid, 45% solid, and completely void (0% material) regions to match the target porosities of the microstructure design while maintaining sufficient stiffness and acceptable connectivity as shown in Figure 3a. From the segmentation, it is clear that the density weighting method possesses reinforcement on specific regions that in particular support the cage integrity and provide the strength and the resistance to external loads. Figure 3b shows the reproduction of the final cage fabrication after the global density layout integrated with the designed microstructure from targeted PPF/β-TCP properties and desired porosities.

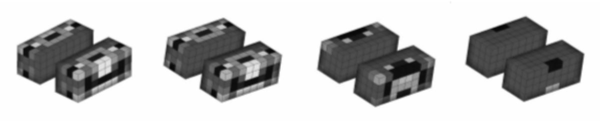
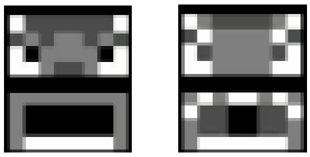
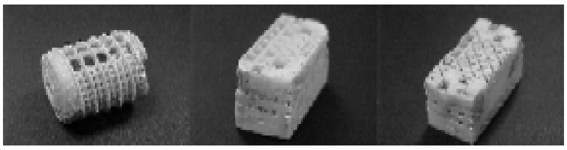


Figure 2: Density distributions at desired time points during degradation (based on poly(propylene fumarate)/beta tricalcium phosphate).



a.



b. CON OS OSDeg

*Figure 3: (a) Material density comparison of the segmented global layout from topology optimization before and after coupled with density weighting method (first two layers from the top). (b) The fabricated*PPF/β-TCP *cages of CON, OS, and OSDeg designs.*

The micro-CT scan at select time points revealed the bulk erosion phenomenon during the degradation. The shape and the geometry remained fairly intact through the degradation despite of the design approaches. Material density of the grayscale decayed during the degradation as indicated as percolation phenomena in Göpferich's model and our investigation also illustrated a matched scene with his simulation (Figure 4). Effective Young's moduli of the three designs (CON, OS, and OSDeg) calculated by the homogenization method at each stage during degradation are shown in Figure 5. The OSDeg cage design derived from proposed approach by Topology Optimization coupled with density weighting method showed superior mechanical stiffness over the other two designs. The OS design from the original topology optimization also showed higher stiffness than the conventional design of CON cage. The design from the present new method sustained a higher stiffness level than average vertebral trabecular bone (110 MPa). The long term degraded effective modulus remains close to 100 MPa, which implies the degraded cage and new bone regenerate composites can still provide sufficient load bearing capability for a stable fusion.

4. DISCUSSION

Recent efforts investigated poly(L-lactic acid) (PLLA) as the base material to fabricate reduced stiffness conventional designs. PLLA cages significantly enhanced lumbar interbody fusion, a result which was attributed to reduced stiffness [17, 18]. Nevertheless, the mere replacement of base material from original designs might lead to cages that cannot provide adequate stability.

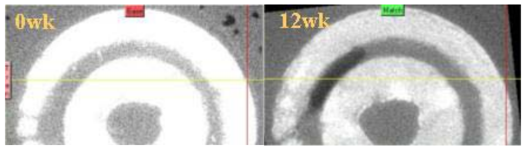


Figure 4: The comparison of the image density of the PPF/β-TCP *CON cage design taken from micro-CT scan. The images showed a decayed intensity of the grade scale density level without geometrical change, indicating an undergoing bulk erosion mechanism from 0 week to 12 weeks.*

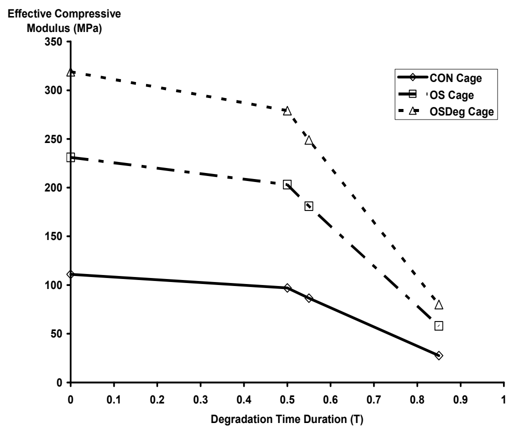


Figure 5: The comparison of effective compressive moduli of PPF/β-TCP *cages of CON, OS, and OSDeg designs through the degradation.*

We have developed the current design approach for biodegradable bone tissue augmentation devices and specifically applied to load bearing purposes as for lumbar spine interbody fusion cages, by using degradation topology optimization algorithms to define the structural layout and inner microstructures. The new design presents a superior reinforcement over the cage design domain by incorporating with our proposed density weighting method. The conventional and the optimal-structure designs for permanent materials perform well mechanical strength for providing segmental integrity. However, once replaced with degradable materials, these designs show comprised strength and reduced stiffness with slight feature detachment deteriorate the decrease of the resistance to the external loads.

The density weighted topology optimization method as a degradation topology optimization successfully produced designs that maintained device stiffness better than either non-weighted or conventional designs. The retained stiffness at the late stage through the degradation of the new design by the degradation topology optimization can even achieve required modulus close to cancellous bone. This suggests that the designed device can fulfill a suitable composite with new bone regenerates, which is capable to form a mechanically functional construct. Therefore, any bulk degrading material can be designed using this process for any skeletal reconstruction applications. The proposed designs have actually been fabricated (Figure 3b) and will be tested in a degradation process to verify the computational approach.

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