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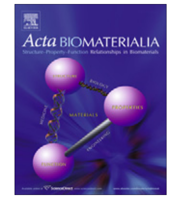

Shaping the micromechanical behavior of multi-phase composites for bone tissue engineering

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ABSTRACT

Mechanical stiffness is a fundamental parameter in the rational design of composites for bone tissue engineering in that it affects both the mechanical stability and the osteo-regeneration process at the fracture site. A mathematical model is presented for predicting the effective Young's modulus (E) and shear modulus (G) of a multi-phase biocomposite as a function of the geometry, material properties and volume concentration of each individual phase. It is demonstrated that the shape of the reinforcing particles may dramatically affect the mechanical stiffness: E and G can be maximized by employing particles with large geometrical anisotropy, such as thin platelet-like or long fibrillar-like particles. For a porous poly(propylene fumarate) (60% porosity) scaffold reinforced with silicon particles (10% volume concentration) the Young's (shear) modulus could be increased by more than 10 times by just using thin platelet-like as opposed to classical spherical particles, achieving an effective modulus $E \sim 8$ GPa ($G \sim 3.5$ GPa). The mathematical model proposed provides results in good agreement with several experimental test cases and could help in identifying the proper formulation of bone scaffolds, reducing the development time and guiding the experimental testing.

1. Introduction

Among the several approaches proposed and currently under investigation for bone tissue engineering the most promising strategy is based on the design, synthesis and application of three-dimensional (3D) polymeric matrices incorporating cells and bioactive molecules [1–4]. Such an assembly, generally referred to as a 3D scaffold, tends to bio-mimic the structure and biology of the original tissue. Differently from classical orthopedic implants, engineered bone scaffolds must be rationally designed to provide mechanical stability, post-traumatic osteo-regeneration and complete fracture healing with the deposition of normal, healthy bone in a timely fashion. For this, an optimal scaffold should have mechanical properties similar to those of the original bone, degrade in a predictable fashion with low toxicity, cause minimal foreign body response, favor the adhesion, integration, differentiation and proliferation of the harvested cells and support angiogenesis and the formation of new bone tissue tuned to time with the degradation dynamics [5,6]. In this respect, scaffolds for bone engineering can be considered as multifunctional and multi-phase biomedical devices operating over multiple length scales, from the molecular level, where bioactive molecules promote new bone formation, to the macroscopic scale, where the whole assembly is designed to support external mechanical loads.

The rational design of bone scaffolds is a complex multi-objective optimization problem with constraints of a different nature. For instance, the mechanical stiffness of a scaffold should be selected by considering both mechanical stability and osteo-regeneration at the site of the defect. In the absence of an external fixator system the first objective would ideally require scaffolds matching the biomechanical properties of healthy bone, which in the case of human cortical bone would lead to a compressive modulus $E \sim 18$–20 GPa [7]. On the other hand, if an external fixator system is employed, which is often the case to provide stabilization to the fracture site, scaffolds with lower compressive moduli can be employed. Conversely, the second objective would require scaffolds with high interconnected porosity, to support cell recruitment and migration to the fracture site, and sufficient mechanical compliance, in that locally the formation of healthy bone is favored by microstrain fields of the order of ~ 100–5000 [8,9]. Metal implants have succeeded in providing optimal

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mechanical stability but have failed in supporting extensive and effective bone tissue regeneration and implant integration [10]. On the other hand, biodegradable natural polymers (alginate, chitosan, collagen and silk) and synthetic polymers [poly(α-hydroxy esters), poly(propylene fumarate) (PPF) and poly(hydroxy-alkanoates)] have been shown in several biomedical applications to support effective tissue regeneration but are generally characterized by low mechanical properties compared with healthy bone [11].

In an attempt to find the right balance between mechanical stability and new bone deposition several biocomposite materials have been proposed and characterized over the last decade by combining natural and synthetic polymeric matrices reinforced with stiffer micro/nanoparticles [12]. Generally, in these applications the role played by the stiffer particles is twofold: enhancement of the mechanical properties of the polymer matrix (reinforcement) and controlled release of bioactive molecules for the recruitment of cells and the deposition of new bone crystals (drug delivery). Particles with different geometrical features and material properties have been reported, such as hydroxyapatite (HA) nanofibers with a characteristic length of 100–300 nm and an aspect ratio (longer by shorter axis) of 3–5 [13–17], bioactive glasses beads (BG) of spherical shape with a diameter ranging between 200 and 600 μm [18], calcium phosphate (CaP) composite microspheres with a diameter of 100–300 μm [19], single walled carbon nanotubes (SWNTs) with a diameter of ~1 nm and aspect ratios ranging from 5 up to several thousand [20,21], mesoporous silica spherical particles with diameters of a few hundred nanometers [22] and other man-made reinforcing micro/nanoparticles.

The list presented above, far from being comprehensive, has the merit of emphasizing the large variety of combinations so far proposed and potentially still available for bone substitute composites. The overall mechanical properties of the biocomposite can be tailored by selecting the mechanical properties, porosity and pore interconnectivity of the polymer matrix and the geometry (size and shape), physico-chemical properties and concentration of each individual reinforcing particle. Clearly, the number of possible combinations is enormous and predictive tools could help in identifying proper formulations of the bone scaffold limiting expensive experimental testing and reducing the development time.

In this spirit, a mathematical model for predicting the Young's and shear moduli of multi-phase composites to be used as bone substitutes is presented here. The model takes into account the contribution of the shape, material properties and volume concentration of each individual phase. The theoretical predictions are shown to be in good agreement with the experimental results already available in the literature for poly(lactic–co-glycolic acid)–hydroxyapatite (PLGA–HA) composites [13,14]. Additional experimental validation is provided by comparing the theoretical predictions with the compressive modulus of porous PPF alone and PPF mixed with silica microbeads.

2. Materials and methods

2.1. Mathematical formulation and geometrical anisotropy

Within the realm of effective medium (EM) theories, the equivalent poly-inclusion (EPI) approach [23] is employed to predict the elastic properties of a multi-phase biocomposite material. The EPI approach represents a unique development in homogenization theory, in that its predictions remain admissible and valid for any material symmetry groups of the phases, any orientation distribution and any fiber shape and volume fraction. As sketched in Fig. 1, the system is made up of a continuous polymer matrix (phase I) with pores (phase II) and reinforcing particles (phase III). The pores and particles have arbitrary shapes and are randomly oriented, in which case the EPI approach coincides with the Mori–Tanaka theory [24]. Within the model proposed pores are treated as particles having zero stiffness.

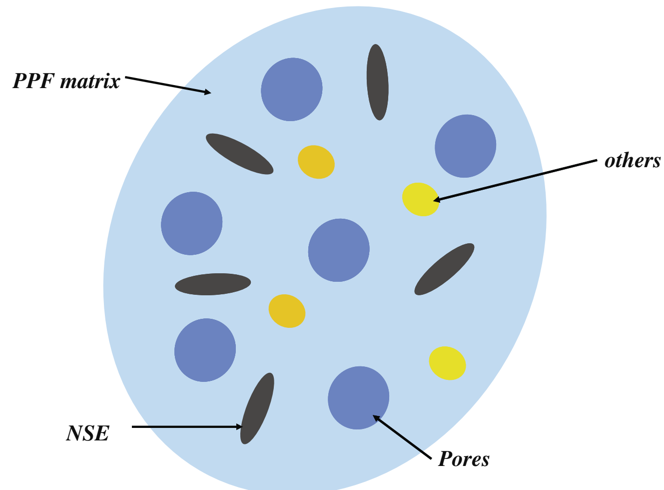

Fig. 1. Schematic presenting silicon particles (NSE) and pores embedded in a polymer matrix (PPF).

In the case of a bi-phasic composite, comprising a matrix with stiffness tensor $\mathbf{C}^{\mathrm{m}}$ and particles with stiffness tensor $\mathbf{C}^{\mathrm{f}}$ and volume concentration α, the resulting effective stiffness tensor $\mathbf{C}$ of the material can be expressed as [23]:

$$\mathbf{C} = \mathbf{C}^{\mathrm{m}} + \alpha\langle(\mathbf{C}^{\mathrm{f}} - \mathbf{C}^{\mathrm{m}})\hat{\mathbf{T}}\rangle \tag{1}$$

where the operator $\langle\bullet\rangle$ indicates the orientational averaging defined as follows on any fourth rank tensor $\mathfrak{I}$:

$$\langle\mathfrak{I}\rangle = \frac{1}{8\pi^2}\int_0^{\pi}\int_0^{2\pi}\int_0^{2\pi}\prod(\mathfrak{I})f(\psi_1,\phi,\psi_2)\sin\varphi d\psi_1 d\psi_2 d\varphi \tag{2}$$

where (ψ_1,ϕ,ψ_2) represent the triad of Euler angles, $f(\psi_1,\varphi,\psi_2)$ represents an appropriate orientation probability density function $[f(\psi_1,\varphi,\psi_2) = 1$ for uniformly distributed fibers] and $\prod(\bullet)$ indicates the frame change operator as defined in [25]. The tensor $\hat{\mathbf{T}}$ is defined as

$$\hat{\mathbf{T}} = [\mathbf{I} + \hat{\mathbf{E}}(\mathbf{C}^{\mathrm{m}})^{-1}(\mathbf{C}^{\mathrm{f}} - \mathbf{C}^{\mathrm{m}})]^{-1} \tag{3}$$

with $\mathbf{I}$ being the fourth rank identity tensor and $\hat{\mathbf{E}}$ a strain concentrator tensor defined as:

$$\hat{\mathbf{E}} = (1-\alpha)\mathbf{E} \tag{4}$$

within EPI theory. The tensor $\mathbf{E}$ represents the celebrated Eshelby's tensor [26,27] accounting for the shape of the particle. In the case of an isolated ellipsoidal particle embedded in an infinite matrix Eq. (3) becomes the well-known Eshelby relation:

$$\mathbf{T} = [\mathbf{I} + \mathbf{E}(\mathbf{C}^{\mathrm{m}})^{-1}(\mathbf{C}^{\mathrm{f}} - \mathbf{C}^{\mathrm{m}})]^{-1} \tag{5}$$

Eqs. (1)–(4) provide the mathematical framework for predicting the effective elastic properties of a bi-phasic composite as a function of the shape of the particle (captured by the tensor $\mathbf{E}$), the material properties of the particle ($\mathbf{C}^{\mathrm{f}}$), the volume concentration of the particle (α) and the material properties of the matrix ($\mathbf{C}^{\mathrm{m}}$).

In the case of a three-phase composite, as for a porous (non-dense) polymeric matrix with reinforcing particles, the resulting effective stiffness tensor $\mathbf{C}$ of the material can be derived by applying the set of Eqs. (1)–(4) twice. That is to say, first, Eqs. (1)–(4) are applied to the bi-phasic composite comprising the dense polymeric matrix (phase I) and the pores (particles with zero stiffness, phase