Fracture safety of double-porous hydroxyapatite biomaterials

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Biological requirements call for substantial porosities in clinical biomaterials – challenging the mechanical integrity and strength of the latter. In this study, the authors resort to quantitative engineering principles to assess the fracture safety of double-porous hydroxyapatite ceramics: micro-computed tomography scans give access to the morphology of macropores at the submillimeter scale, as well as to voxel-specific microporosities. Advanced micromechanics of porous ceramics with needle-shaped elementary units then allows for translating voxel-specific microporosities to corresponding elasticity and strength properties, as well as to macro-to-micro scale transition ('concentration') tensors. These mechanical properties and tensors are fed into a large-scale finite-element model of a biomaterial granule as used for mandibular tissue regeneration. Loading the granule in splitting mode, up to physiological strain, evidences stress concentrations at the loaded poles and close to internal macropores and cracks. A parallel computing-supported subvoxel analysis of needle orientations evidences that in highly loaded regions, the intravoxel 'single crystals' oriented perpendicular to the loading direction undergo the most unfavorable loading. Still, only 0.6% of the finite-elements show stresses indicating failure, and the mean safety factor against fracture is as high as 7. This analysis confirms, from an engineering science viewpoint, the successful use of the investigated biomaterials in clinical practice.

Notation

a_{ij}	matrix element at position i, j	GV_{thr}	threshold gray value between air-related voxels and voxels containing ceramics
$B_{HA}(\varphi, \vartheta)$	fourth-order stress concentration tensor of needle-shaped hydroxyapatite phase oriented in the (φ, ϑ) direction	I	fourth-order identity tensor
C_{poly}	fourth-order stiffness tensor of porous hydroxyapatite polycrystal	i	index
C_{HA}	fourth-order stiffness tensor of pure hydroxyapatite	j	index
E	(voxel-specific) micromechanics-derived Young's modulus	k	total number of finite elements in the finite-element model
e_x, e_y, e_z	unit base vectors of orthonormal reference base frame	M	matrix dimension
e_θ, e_φ, e_r	unit base vectors of orthonormal local base frame of a single hydroxyapatite needle	N	orientation vector aligned with the longitudinal axis of hydroxyapatite needle
GV	(voxel-specific) X-ray attenuation-related 8-bit gray value	N_{cn}	total number of computing nodes
GV_{air}	most frequently occurring gray value of air-related voxels	N_{cr}	number of central processing unit (CPU) cores per computing node
GV_{HA}	gray value corresponding to a voxel of pure hydroxyapatite	N_{cpu}	total number of CPU cores
		N_{eval}	number of evaluation steps
		n	matrix dimension
		$\mathbf{n}$	orientation vector perpendicular to N
		$O(\cdot)$	big O notation of computational complexity of quantity $(\cdot)$
		$p(\cdot)$	probability density function of quantity $(\cdot)$
		p_{father}	father process

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$\mathbf{P}_{\text{cyl}}^{\text{poly}}$	fourth-order morphology (or Hill) tensor for cylindrical inclusion in polycrystalline matrix
$\mathbf{C}_{\text{poly}}$	fourth-order morphology (or Hill) tensor for spherical inclusion in polycrystalline matrix
$\mathbf{P}_{\text{sph}}^{\text{poly}}$	fourth-order morphology (or Hill) tensor for spherical inclusion in polycrystalline matrix
S	safety factor: the ratio between uniaxial tensile strength of pure hydroxyapatite and critical needle stress
w	work chunk for computing nodes
β	the ratio between uniaxial tensile strength and shear strength of pure hydroxyapatite
ϑ	latitudinal coordinate of spherical coordinate system
ν	(voxel-specific) micromechanics-derived Poisson's ratio
Σ	second-order macroscopic stress tensor
$\sigma_{\text{HA}}(\varphi, \vartheta)$	second-order microscopic stress tensor of a needle-shaped hydroxyapatite phase orientated in the (φ, ϑ) direction
$\sigma_{\text{HA},\text{NN}}(\varphi, \vartheta)$	normal component of stress tensor $\sigma_{\text{HA}}(\varphi, \vartheta)$ in needle direction (φ, ϑ)
$\sigma_{\text{HA},\text{Nn}}(\varphi, \vartheta, \psi)$	shear component of stress tensor $\sigma_{\text{HA}}(\varphi, \vartheta)$ on planes orthogonal to the needle direction (φ, ϑ)
$\sigma_{\text{HA}}^{\text{crit}}$	critical stress at the most unfavorable oriented hydroxyapatite needle defined by the direction $(\varphi, \vartheta, \psi)$
$\sigma_{\text{HA}}^{\text{ult},\text{s}}$	shear strength of pure hydroxyapatite
$\sigma_{\text{HA}}^{\text{ult},\text{t}}$	uniaxial tensile strength of pure hydroxyapatite
Φ_{macro}	macroporosity
Φ_{total}	total porosity
φ	longitudinal coordinate of spherical coordinate system
ϕ	microporosity
$\varphi_{\text{step}}, \vartheta_{\text{step}}, \psi_{\text{step}}$	incrementation steps of the angles φ, ϑ , and ψ
χ mapping	matrix storage scheme described by Nadeau and Ferrari
ψ	rotation angle of vector $\mathbf{n}$
$\cdot$	first-order tensor contraction
$:$	second-order tensor contraction
$\langle(\cdot)\rangle$	averaging function of quantity $(\cdot)$
$(\cdot)^{-1}$	inversion of tensorial quantity $(\cdot)$

1. Introduction

Large bone defects that do not heal autonomously can be regenerated by means of tissue engineering strategies. A corresponding, particularly successful clinical example concerns filling of mandibular defects with double-porous hydroxyapatite granules that promote cell migration and tissue growth within the defect, eventually filling the latter.^{1–3} The aforementioned scaffolds provide not only sufficient pore space for cell migration and angiogenesis (both anticipating bone tissue production) but also remarkable stiffness and strength, since they undergo repeated mechanical loading in the course of normal physiological

use of the mandible. Hence, understanding of their mechanical function is of great interest, and their elasticity properties have been investigated in recent theoretical-computational campaigns,^{4,5} revealing that ‘macrocracks’ of the order of tens of micrometers are essential for tuning the scaffolds’ overall stiffness properties close to those of natural bone tissue and suggesting biomaterial resorption and bone apposition rates needed for maintaining the stiffness of the constructs consisting of tissue engineering scaffolds and bone tissue. As a complement to the aforementioned studies, the present study focuses on the strength properties of the aforementioned hydroxyapatite granules used for mandibular bone tissue regeneration: This study is based on a recently reported general theory for the poro-micromechanics of quasi-brittle porous polycrystals^{6–8} across many ceramic systems built up by randomly oriented needle- or disk-type single crystals. Being in mutual mechanical interaction and partially separated by pores, the aforementioned single crystals are predominantly loaded in compression, tension, or shear – while their largely random arrangement precludes bending modes. The corresponding poro-micromechanics theory allows for upscaling the intrinsic elasticity and strength properties of single crystals to the porosity-dependent mechanical properties of the overall polycrystal. For a given stress state acting at the length scale of the overall polycrystal, not only the stress magnification factor up to failure can be given but also the spatial orientation of the crystal phase that triggers failure at the microscopic scale. In the present context, these theoretical developments will be applied to the lower of the two pore scales making up the double-porous granules – that is, to porous polycrystalline material volumes with several micrometers of characteristic length. Their location-dependent – that is, inhomogeneously distributed – porosity will be determined from the X-ray attenuation-related gray values, characterizing voxels that make up micro-computed tomography (micro-CT) scans of the granular objects, according to a protocol,⁴ which also involves weighing experiments. These voxels are then converted to finite elements (FEs), so as to come up with a fully detailed structural model of the larger pore structure comprising cracks, with an inhomogeneous, microporous solid matrix in between. Loading the finite-element model (FEM) of the granule up to physiologically relevant strain levels and downscaling the voxel-specific stress states down to those of single crystals, will then allow determining not only the fracture safety factor in each and every voxel but also the orientation of the corresponding most endangered crystal phase within that voxel. This will allow for unprecedented insight into the loading of tissue engineering constructs, up to a sophistication level that is sometimes attained in civil or geotechnical engineering,^{9,10} a level which, as for now, remains an extraordinary exception in the field of regenerative medicine. Details of underlying methods and results are given in the remainder of the present paper, along the following structure: The paper starts by reviewing the microCT- and micromechanics-supported, elastic finite-element analysis (FEA) of Dejaco *et al.*,⁴ which serves as the basis for the subsequent developments. Thereafter, the FE-specific stresses are ‘downscaled’ into the (sub-FE) polycrystal microstructure, to allow for strength analysis

and safety assessment at the subvoxel/subelement level. This is followed by an elaboration on numerical challenges and corresponding remedies in form of cluster computing strategies; the latter allow for obtaining interesting results, the discussion of which concludes the paper.

2. CT- and micromechanics-supported elastic FEA of Dejaco *et al.*

In this section a biomaterial class appearing as almost spherical granules 40–2000 μm in size is analyzed. The production of these biomaterials is based on the effect of liquid immiscibility as described in detail by Komlev *et al.*² The investigated materials exhibit pores at two different length scales (see Figures 1 and 2): In the scanning electron micrography (SEM) pictures (Figure 1), the micropores appear between the single hydroxyapatite crystals with a characteristic length of a few microns, while these micropores are not any more discernible in micro-CT scans with 3–49 μm voxel size (see Figure 2). In such micro-CT images (for

more details on the scanning device and parameters used, see the paper of Dejaco *et al.*)⁴ the micropores rather determine the ‘density’, or more precisely, the gray value-indicated X-ray attenuation coefficient of the voxels making up the solid portion of the scanned object. The latter appears to also host many ‘macropores’ with a characteristic length of some tens to hundreds of micrometers, as well as ‘macrocracks’ with a length in the same order of magnitude.

Following the procedure outlined by Dejaco *et al.*,⁴ the voxel-specific gray values GV are converted into voxel-specific ‘microporosities’ ϕ according to

$$1. \quad \phi(GV) = \frac{GV - GV_{HA}}{GV_{air} - GV_{HA}}$$

with GV_{air} and GV_{HA} respectively denoting the gray values of voxels that would be filled only by air or only by hydroxyapatite.

Figure 1. (a) SEM pictures of hydroxyapatite granules; (b) zoom-in to resolve the single crystals with microporosity in between

Figure 2. Reconstructed micro-CT images, obtained by a SkyScan 1172 desktop micro-CT device: (a) three-dimensional intransparent illustration of a whole globule; (b) orthogonal slices through the center

of the granule; (c) semitransparent illustration in order to display the macroporosity and macrocracks

Both follow from evaluation of a normalized histogram (i.e. by a probability density function) of all the voxels contained in the scanned object:⁴ GV_{air} relates to the leftmost peak of such a histogram ($GV_{air} = 100$ in the present case), and GV_{HA} follows from summing up, throughout all voxels, the microporosity found in the object (including the 100% microporosity values associated with the voxels representing macropores and cracks inside the scanned granule) and identifying this sum as the overall porosity Φ_{total} , which according to weighing experiments, is equal to $\Phi_{total} = 0.55$. In mathematical terms, this reads as

$$GV_{HA} = \frac{1}{1 - \Phi_{total}} \left[GV_{air} (\Phi_{macro} - \Phi_{total}) + \int_{GV_{thr}}^{255} p(GV) GV dGV \right]$$

2. $= 257.9$

where $GV_{thr} = 139$ is the threshold gray value related to the minimum between the air and scaffold peak in the histogram, $p(GV)$ denotes the probability density function of gray values according to the aforementioned histogram and Φ_{macro} is the macroporosity. It is retrieved from the histogram as well, according to

$$3. \quad \Phi_{macro} = \int_0^{GV_{thr}} p(GV) dGV$$

resulting in the present case, in $\Phi_{macro} = 0.189$. The method described by Equations 1–3 does not require any phantom- or dual energy-based calibration.

In order to convert the microCT scan into an FE model of a still tractable size, neighboring voxels of the microCT scan were merged together. In more details, $4 \times 4 \times 4 = 64$ neighboring voxels were combined into one cubic trilinear FE measuring $14 \times 14 \times 14 = 2744 \mu m^3$, their gray values were averaged, and a corresponding microporosity assigned according to Equations 1–3. This resulted in an element-specific microporosity distribution across the object. The corresponding microporosities are then converted into FE-specific isotropic elastic properties (in terms of Young's modulus and Poisson's ratio), by means of the self-consistent micromechanical model of Fritsch *et al.*,⁷ which was developed in the framework of so-called random homogenization theory or continuum micromechanics,^{11,12} for porous polycrystals built up by elongated hydroxyapatite crystal phases oriented in all space directions (see Figure 3 for the microstructure envisioned in each FE and Figure 4 for the elasticity relations applied to each and every FE).

This resulted in an FE model consisting of 1171176 FEs. As far as loading boundary conditions are concerned, uniaxial compression on the order of magnitude of physiological strain (0.1% of the granule's diameter) was imposed in the form of

Figure 3. Illustration of a porous polycrystal built up by needle-shaped single crystals oriented in all space directions; in the shown case, the microporosity is around 60%

slightly distributed forces at the poles of the granule. Resulting stress and strain fields, based on the 1.2 million element mesh, turned out to be satisfactorily converged.⁴

3. Sub-FE strength analysis and safety assessment

The aforementioned FEA delivers ‘macroscopic’ element-specific stress tensors that are related to the representative volume elements (RVEs) of porous polycrystals. Thus, the micromechanical representation of these porous polycrystals allows for further downscaling of these stresses from the level of the overall porous polycrystal to that of single crystal phases, the orientations of which are defined by the Euler angles φ and ϑ as indicated in Figure 5. The corresponding concentration relation reads as

$$4. \quad \sigma_{HA}(\varphi, \vartheta) = \mathbf{B}_{HA}(\varphi, \vartheta) : \boldsymbol{\Sigma}$$

with $\sigma_{HA}(\varphi, \vartheta)$ as the microscopic stresses in the (φ, ϑ) -oriented crystal phase, $\boldsymbol{\Sigma}$ as the second-order macroscopic stress tensor and $\mathbf{B}(\varphi, \vartheta)$ as the corresponding stress concentration tensor, reading as⁷

$$\mathbf{B}_{HA}(\varphi, \vartheta) = \mathbf{c}_{HA} : \{ [\mathbf{I} + \mathbf{P}_{cyl}^{poly}(\varphi, \vartheta) : (\mathbf{c}_{HA} - \mathbf{c}_{poly})]^{-1} : \\ : \{ (1 - \phi) \langle [\mathbf{I} + \mathbf{P}_{cyl}^{poly}(\varphi, \vartheta) : (\mathbf{c}_{HA} - \mathbf{c}_{poly})]^{-1} \rangle \\ + \phi (\mathbf{I} - \mathbf{P}_{sph}^{poly} : \mathbf{c}_{poly})^{-1} \} : \mathbf{c}_{poly}^{-1}$$

5.

Figure 4. Elastic properties as functions of X-ray attenuation-related gray values GV, according to Dejaco *et al.*⁴: (a) Young's modulus E ; (b) Poisson's ratio ν

where $\mathbf{c}_{\text{HA}}$ is the fourth-order stiffness tensor of pure hydroxyapatite,^{13,14} $\mathbf{I}$ is the fourth-order identity tensor, $\mathbf{C}_{\text{poly}}$ is the fourth-order stiffness tensor of the overall porous polycrystalline biomaterial made of hydroxyapatite (see Fritsch *et al.*⁷), and $\mathbf{P}_{\text{cyl}}^{\text{poly}}$ and $\mathbf{P}_{\text{sph}}^{\text{poly}}$ are the Hill or morphology tensors for cylindrical or spherical inclusions respectively, embedded in a fictitious

matrix with stiffness $\mathbf{C}_{\text{poly}}$. Inspired by the well-known failure criterion named after Mohr and Coulomb, particularly unfavorable ('critical') stress states are characterized by a combination of normal stresses oriented in the needle direction

$$6. \quad \sigma_{\text{HA,NN}}(\varphi, \vartheta) = \mathbf{N}(\varphi, \vartheta) \cdot \boldsymbol{\sigma}_{\text{HA}}(\varphi, \vartheta) \cdot \mathbf{N}(\varphi, \vartheta)$$

and shear stresses oriented orthogonal to $\sigma_{\text{HA,NN}}$

$$7. \quad \sigma_{\text{HA,Nn}}(\varphi, \vartheta, \psi) = \mathbf{N}(\varphi, \vartheta) \cdot \boldsymbol{\sigma}_{\text{HA}}(\varphi, \vartheta) \cdot \mathbf{n}(\varphi, \vartheta, \psi)$$

reading as

$$8. \quad \sigma_{\text{HA}}^{\text{crit}} = \max_{\varphi, \vartheta} \{ \beta \max_{\psi} |\sigma_{\text{HA,Nn}}(\varphi, \vartheta, \psi)| + \sigma_{\text{HA,NN}}(\varphi, \vartheta) \}$$

with $\mathbf{N}(\varphi, \vartheta)$ as the elongation direction of the needle-shaped crystal phase oriented in the (φ, ϑ) direction (see Figure 5), with $\mathbf{n}$ being located orthogonal to $\mathbf{N}$ and oriented in the ψ direction (see Figure 5) and with β as the ratio between the uniaxial tensile strength $\sigma_{\text{HA}}^{\text{ult,t}}$ and the pure shear strength $\sigma_{\text{HA}}^{\text{ult,s}}$ of the single crystal phase; $\beta = 0.65$ in the present case.⁷ Failure at the single-crystal level (which due to the quasi-brittle failure of the overall porous polycrystal, triggers failure of the latter as well) occurs on

$$9. \quad \sigma_{\text{HA}}^{\text{crit}} - \sigma_{\text{HA}}^{\text{ult,t}} = 0$$

while

$$10. \quad \sigma_{\text{HA}}^{\text{crit}} - \sigma_{\text{HA}}^{\text{ult,t}} < 0$$

Figure 5. Schematic illustration of the reference frame, with a needle-like hydroxyapatite inclusion oriented along vector $\mathbf{e}_r = \mathbf{N}$, inclined by angles ϑ and φ with respect to the reference frame ($\mathbf{e}_x$, $\mathbf{e}_y$ and $\mathbf{e}_z$), and with the local base frame $\mathbf{e}_r$, $\mathbf{e}_\varphi$ and $\mathbf{e}_\vartheta$ being attached to the needle

refers to elastic behavior. This induces an element-specific safety factor S reading as

$$11. \quad S = \frac{\sigma_{HA}^{ult,t}}{\sigma_{HA}^{crit}}$$

which is larger than 1 for non-failing crystals and approaches 1 for crystals being loaded up to failure. This element-specific safety factor is associated with a critical direction $(\varphi, \vartheta, \psi)$ stemming from the maximum value in Equation 8. Distribution of these safety factors and the corresponding critical needle orientations are given in Section 5, together with corresponding statistical analyses.

4. Computational strategy for high-resolution safety analyses

The employed safety analysis is based on downscaling FE-related stresses (see Figure 6(b)), which were computed from the structural analysis of the entire granule (see Figure 6(a)), to the level of intravoxel/intraelement microstress-related needle-shaped single crystals (see Figure 6(c)), which are then assessed in terms of the Mohr-Coulomb-type criterion (see Equation 8), yielding a safety factor according to Equation 11 (see Figure 6(d)).

The determination of the FE- and orientation-specific safety factor S according to Equation 11 together with Equations 4–8 requires multiply repeated evaluation of the expression

$$12. \quad S = \frac{\sigma_{HA}^{ult,t}}{\{\mathbf{N} \cdot \mathbf{B}_{HA}(\varphi, \vartheta) : \boldsymbol{\Sigma} \cdot \mathbf{n}(\psi)\} + \mathbf{N} \cdot \mathbf{B}_{HA}(\varphi, \vartheta) : \boldsymbol{\Sigma} \cdot \mathbf{N}}$$

Actually, Equation 12 together with Equation 5 needs to be evaluated N_{eval} times, where the number of needed evaluations N_{eval} follows from

$$13. \quad N_{eval} = k \times \frac{\pi/2}{\vartheta_{step}} \times \frac{2\pi}{\varphi_{step}} \times \frac{2\pi}{\psi_{step}}.$$

In this study, the number of FEs amounts to $k = 1\,171\,176$ and the increments of the orientation angles amount to $\vartheta_{step} = \varphi_{step} = 0.5^\circ$ and $\psi_{step} = 1^\circ$, leading to $N_{eval} = 290\,510\,457$ needed evaluations. This proved to be appropriate in terms of processing time and accuracy.

Partitioning the terms in the expression for $\mathbf{B}_{HA}(\varphi, \vartheta)$ (see Equation 5) into those that depend only on the gray value GV, those that depend on GV and on the orientation angles φ and ϑ and finally those that depend on the element-specific stresses reduced the computational load significantly.

The terms in Equation 12 together with Equation 5, which depend only on the gray values GV are (a) the microporosity ϕ , (b) the overall

Figure 6. Downscaling from granules to single crystals: (a) FEM of porous polycrystalline biomaterial granule, (b) zoom-out of batch of FEs at the surface of the granule, (c) schematic representation of microstructure within one FE and (d) orientation of the least favorably

loaded needle phase within the RVE associated with the FE of (c). Top row shows a needle where failure does not occur ($S > 1$); bottom row refers to the case of needle failure ($S \leq 1$)

polycrystal stiffness $\mathbf{C}_{\text{poly}}$, and (c) the lengthy inverted term $\{(1-\phi)(\mathbf{I} + \mathbf{P}_{\text{cyl}}^{\text{poly}}(\phi, \vartheta) : (\mathbf{C}_{\text{HA}} - \mathbf{C}_{\text{poly}}))^{-1}\} + \phi(\mathbf{I} - \mathbf{P}_{\text{sph}}^{\text{poly}} : \mathbf{C}_{\text{poly}})^{-1}\}^{-1}$, since its subterm $\langle \mathbf{I} + \mathbf{P}_{\text{cyl}}^{\text{poly}}(\phi, \vartheta) : (\mathbf{C}_{\text{HA}} - \mathbf{C}_{\text{poly}}))^{-1} \rangle$ follows from averaging over all needle orientations and is therefore independent of the angles ϕ and ϑ . These gray value-dependent terms need to be evaluated only 256 times, once for each gray value of the 8-bit gray scale.

The terms in Equation 12 that are gray value *and* orientation dependent are the morphology tensor $\mathbf{P}_{\text{cyl}}^{\text{poly}}$; hence, the term $[\mathbf{I} + \mathbf{P}_{\text{cyl}}^{\text{poly}}(\phi, \vartheta) : (\mathbf{C}_{\text{HA}} - \mathbf{C}_{\text{poly}}))^{-1}]$. These terms are evaluated $256 \times \pi^2/(\phi_{\text{step}}\vartheta_{\text{step}}) = 33\,177\,600$ times.

Finally, the following terms needed to be really evaluated N_{eval} times: $\sigma_{\text{HA}}(\phi, \vartheta) = \mathbf{B}_{\text{HA}}(\phi, \vartheta) : \boldsymbol{\Sigma}$ (see Equation 3), $\sigma_{\text{HA},\text{NN}}(\phi, \vartheta) = \mathbf{N}(\phi, \vartheta) \sigma_{\text{HA}}(\phi, \vartheta) \mathbf{N}(\phi, \vartheta)$ (see Equation 6) and $\sigma_{\text{HA},\text{Nb}}(\phi, \vartheta, \psi) = \mathbf{N}(\phi, \vartheta) \sigma_{\text{HA}}(\phi, \vartheta) \mathbf{n}(\phi, \vartheta, \psi)$ (see Equation 7).

The evaluation of the safety factor of Equation 12 together with Equation 5 is based on a software written in GNU C.¹⁵ Thereby, memory use is minimized through the use of a storage scheme based on the χ mapping of Nadeau and Ferrari.¹⁶ Symmetric second- and fourth-order tensors are efficiently mapped onto 3×3 and 6×6 matrices, whereby a matrix of size $m \times n$ with elements $a_{ij} \forall i \in \{0, \dots, m-1\}, j \in \{0, \dots, n-1\}$ is stored as an array $\mathbf{A}$ of double-precision floating points, with element a_{ij} being stored row-wise in array element $A(j+in)$, as one contiguous allocated memory block, for fast sequential referencing (reducing page swaps). Several costly arithmetic operations, such as matrix-matrix multiplication, matrix-inversion and tensor component transformation, are required. In order to gain efficacy, the latter operations are implemented in the form of one matrix transpose in combination with two matrix-matrix operations in accordance to Nadeau and Ferrari.¹⁶ The corresponding floating-point operations are summarized in Table 1.

For the realization of the arithmetic operations, the C library Atlas (Automatically Tuned Linear Algebra Software^{19,20}) was used,

providing a C interface to very efficient high-performance Blas (Basic Linear Algebra Subprograms¹⁷) and Lapack (Linear Algebra Package¹⁸) routines; see Table 1 for an overview. Blas is the actual standard for matrix and vector operations,¹⁷ whereas Lapack, among other higher-level routines such as eigenvalue problems and singular problems, implements the necessary matrix-inversion itself using level 3 Blas calls to a large extent. Notably, the level 3 Blas routine Gemm (general matrix multiply and add) plays a major role regarding the efficiency of the whole algorithm. This is partly due to its own complexity $O(n^3)$, but mostly since all other Blas level 3 and Lapack routines (such as matrix inversion) rely heavily on Gemm calls, their own as well as the whole program's efficiency largely depends on the optimization of Gemm. Thus, the computational kernel of level 3 Blas is Gemm,¹⁷ which has great a potential to exploit the hierarchical structure of the modern computers used in this study and allows for minimization of the number of memory transfer operations – for example through the use of block algorithms forcing the data of matrix multiplications to completely reside in level 1 cache memory.²¹ Atlas takes great advantage of this and realizes Gemm as a portable high-performance routine adapting to the machines that run it, depending on the system, often getting close to theoretical peak performance.²⁰

In order to further enhance the computational efficiency of the multiple evaluation of Equation 12 together with Equation 5, the authors resorted to the implementation of a Kerrighed single system image²² (SSI) computing system. An SSI cluster is a clustered computer system that, to the user, behaves as a single high-performance multiprocessor computer while effectively being a cluster of interconnected single- or multiprocessor computers sharing their resources transparently to the operator. Kerrighed delivers SSI functionality, offering scalability, fully transparent shared virtual memory and global process management with a global scheduler using preemptive process migration for load-balancing and dynamic distribution of processes on available cluster nodes.²² The architecture of the Kerrighed cluster used in

Frequency per evaluation of Equation 12 together with Equation 5	Operation	Floating-point operations	Implementation
4	$\mathbf{C} \leftarrow \alpha \text{op}(\mathbf{A})\mathbf{B} + \gamma \mathbf{C}$	$O(n^3)$	Level 3 Blas ¹⁷
1	$\mathbf{C} \leftarrow \mathbf{A}^{-1}$	$O(n^3)$	Lapack ¹⁸
2	$\mathbf{C} \leftarrow \alpha \mathbf{A} + \gamma \mathbf{B}$	$O(n^2)$	Level 2 Blas ¹⁷
2	$\mathbf{C} \leftarrow \alpha \mathbf{A}\mathbf{x} + \gamma \mathbf{y}$	$O(n^2)$	Level 2 Blas ¹⁷

Computational complexity is given in big O notation. $\mathbf{A}$, $\mathbf{B}$ and $\mathbf{C}$ describe $n \times n$ matrices; $\mathbf{x}$ and $\mathbf{y}$ describe vectors of length n ; α and γ describe scalars and $\text{op}(\mathbf{A}) = \mathbf{A}$ or $\mathbf{A}^T$

Table 1. Overview of the computationally most expensive floating-point operations required at each evaluation of Equation 12 together with Equation 5

the present case involves one master node and N_{cn} computing nodes with N_{cr} central processing unit (CPU) cores each, leading to the total number of CPUs $N_{cpu} = N_{cn} \times N_{cr} = 70$ on average, depending on current availability. As nodes, desktop workstations running on different hardware, such as AMD Phenom II X6 1090T and Intel Core i7-3930K processing units on Gigabyte GA-890GPA-UD3H and Intel DX79TO motherboards with varying amounts of random-access memory between 8 and 64 GB, were used. The flexibility of this system, allowing for hardware heterogeneity, is one of the advantages of Kerrighed. The master node is running an Ubuntu 10.04 Linux operating system and provides a Debian GNU/Linux 5.0 image with a Kerrighed-patched 2.6.20 kernel for the cluster processing nodes. Nodes boot the remote Debian image by fetching a Preboot Execution Environment boot loader using the trivial file-transfer protocol and connecting to a network file system share holding the root file system, which is all provided by the master node. This way, a (even diskless) node can simply be added to the cluster by booting the Debian Linux image through an Ethernet network, which, as the authors do, can even be done using Oracle VM VirtualBox by Sun Microsystems as a virtual environment, allowing regular desktop computers to participate as cluster nodes while still being available as workstations if necessary. Since all nodes use the one shared root file system, any change to it will obviously affect all the nodes, making administration very practicable.

The aforementioned computing cluster allows for effective parallelization. The latter, however, requires appropriate software

for the execution of parallel programs. A corresponding parallel algorithm was written in GNU C;¹⁶ see Figure 7. It handles the appropriate creation of computing processes and the distribution of work. Note the access point node AP in Figure 7, which is the node to which the operator can connect through the network to manage the whole system. It is also where the master program is run: it starts the cluster as father process, which spawns, by means of the command `fork()`, N_{cpu} child processes. Semaphores are used to synchronize events between father and children: after splitting the N_{eval} needed evaluations of the safety factor (see Equation 12) into small, parallelizable chunks of work and having assigned a small chunk of work to each child process, the father process issues a `sem_wait()` operation, waiting for the first child to issue `sem_post()`. Issuing this semaphore command is what a child having completed its task does before exiting, whereupon its father will spawn a new child if there is still work left and will assign the next chunk of work to it for processing. Having arrived at a point when all work chunks have already been assigned to a process, the father, by means of the command `waitpid()`, simply waits for all children to finish, then merges and postprocesses the results written by the processes and exits. Note that when child processes are created, at first, they all run on the access point node (since that is where the father process is issuing the `fork()`-operation). It is the Kerrighed scheduler,²² which then uses preemptive process migration to distribute the processes appropriately to other nodes. On the other hand, the Debian Linux kernel's completely fair scheduler is responsible for the distribution of processes on a single node over multiple local CPU cores.^{23,24}

Figure 7. Overview of the master algorithm handling the distribution and parallelization of work in the computing cluster

Figure 8. Probability density functions of (a) the element-specific critical microscopic stress σ_{HA}^{crit} (see Equation 8) and (b) the

corresponding safety factor $S = \sigma_{HA}^{ult,t} / \sigma_{HA}^{crit}$ (see Equation 11) over all FEs

5. Results

Normalized histograms (probability density functions) over all 1.2 million element-specific stresses σ_{HA}^{crit} and corresponding safety factors S (see Figure 8) show that 99.4% of the elements behave purely elastically – that is, only 7395 (i.e. 0.6%) out of the 1 171 176 elements exhibit a safety factor smaller than 1. Not only are these failing locations close to the poles where the object was loaded, but also they occur in the inner core of the object, close to the macropores and cracks found there; see Figure 9. The average safety factor is as high as 6.93, while the location-dependent safety factors vary strongly, which is indicated by a standard deviation of 4.93. The orientation angle φ of the crystal phases related to the critical microscopic stress are fairly uniformly distributed, while the orientation angles ϑ are elevated around $\pi/2$; see Figures 10 and 11. This is consistent with the overall mechanical behavior of a brittle material sample in a

splitting test: compression loading in the e_z direction induces (mainly tensile) failure in directions orthogonal to the loading direction – that is, on the $e_x - e_y$ plane.

The predominantly tensile loading of the unfavorably stressed needle-shaped phases within the RVEs or FEs is also evident from the histograms of Figure 12, with average tensile normal microstresses of about 7.26 MPa, as compared to average shear stresses of only 0.41 MPa. It is also interesting to study the actual spatial distribution (resolved to the RVE size) of microstresses of the unfavorably stressed needle phases within these RVEs; see Figure 13. It appears that the highest stresses (and lowest safety factors) occur close to the poles of the granules where the granule was loaded in the present case; see Figure 13(b). There, the unfavorably stressed needle phases are oriented perpendicular to the loading direction (see Figure 13(a)) and they exhibit high tensile normal stresses (see Figure 13(d)) and low shear stresses (see Figure 13(c)). In the domain away from the poles, the needles with highest critical microstress according to Equation 8 exhibit lower tensile normal stress (see Figure 13(d), cross-section 3) and the ones with the least loading are oriented even in the loading direction (see Figure 13(a), cross-section 3). However, close to the macropores found inside the granule, the loading characteristics of the needle-shaped phases are again closer to those encountered at the loaded poles.

Figure 9. Semitransparent illustration of the granule, highlighting elements that exhibit crystal failure ($S \leq 1$) in black

6. Discussion

To the best knowledge of the authors, this is the first time that advanced engineering mechanics principles have been applied to quantify the safety margin of biomaterials used for bone regeneration. As a novelty, the authors resolved the mechanical behavior down to the subvoxel level, which is not shown any more by micro-CT but where one has to resort to electron microscopic techniques such as SEM in order to elucidate microfeatures such as the ones shown in Figure 1. These features explain the heterogeneous distributions of elastic and hardness properties at the single micron scale,^{25,26} which are considered

Figure 10. Probability density functions of the angles (a) φ and (b) ϑ quantifying the orientation of the critically stressed needle phase according to Equation 8, over all FEs (transparent bars) and over only FEs for which the safety factor $S \leq 1$

here by means of poro-micromechanics theory.⁶ They are the source of load-induced heterogeneous stress distributions across the loaded objects, at both the polycrystalline level of the single FEs and the single crystal level within the FEs – that is, within the RVEs on which the porous biomaterial is defined. This heterogeneity feature is what the presently investigated biomaterial granule shares with the biological materials it replaces, and this feature is normally regarded as the key to the astonishing robustness that biological materials exhibit – for example with respect to ductility enhancement or toughness.²⁷ This obviously favorable mechanical characteristic is fully consistent with the very successful use of the investigated granules in mechano-

biological environments as encountered in real-life clinical applications.²⁸

From an engineering mechanics' viewpoint, it is astonishing that normal stresses related to the critical intravoxel/intraelement microstress, as given in Figure 12(a), are virtually exclusively tensile. This results from the fact that for medium to high microporosities, both tension- and compression-dominated principal stresses at the element level (as both typically occurring in porous ceramics; see also e.g. the paper of Lacroix *et al.*²⁹), lead to tensile loading of the critically stressed needle phase at the subvoxel/subelement level; see – for example Figure 9 of Fritsch *et al.*⁷

Figure 11. Two-dimensional probability density function as a color map of the angles φ and ϑ at critical hydroxyapatite needle orientation (resulting in the largest critical needle stresses according to Equation 8) over all FEs

Figure 12. Probability density functions over all FEs of (a) the normal stress $\sigma_{NN}(\varphi, \vartheta)$ and shear stress (b) $\sigma_{Nn}(\varphi, \vartheta, \psi)$ at hydroxyapatite needle orientation resulting in the largest needle stresses according to Equation 8

Figure 13. Results depicted on cross-sections through the granule. All variables correspond to the most unfavorably oriented hydroxyapatite needle (resulting in the largest needle stresses according to Equation 8): (a) angle ϑ is shown in gray scale for FEs where the safety factor $S > 1$ (no needle failure), and in color style for

FEs where the safety factor $S \leq 1$ (needles exhibit failure) is shown in a color scale; (b) safety factor S (see Equation 11) is shown in a color scale, where red-magenta highlights FEs where $S \leq 1$ (needles exhibit failure); (c) shear stress σ_{Nn} ; (d) normal stress σ_{NN}

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