Elastic Anisotropy of Trabecular Bone in the Elderly Human Vertebra

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*Knowledge of the nature of the elastic symmetry of trabecular bone is fundamental to the study of bone adaptation and failure. Previous studies have classified human vertebral trabecular bone as orthotropic or transversely isotropic but have typically obtained samples from only selected regions of the centrum. In this study, the elastic symmetry of human vertebral trabecular bone was characterized using microfinite element (μ FE) analyses performed on 1019 cubic regions of side length equal to 5 mm, obtained via thorough sampling of the centrams of 18 human L1 vertebrae (age = 81.17 ± 7.7 yr; eight males and ten females). An optimization procedure was used to find the closest orthotropic representation of the resulting stiffness tensor for each cube. The orthotropic elastic constants and orientation of the principal elastic axes were then recorded for each cube and were compared to the constants predicted from Cowin's fabric-based constitutive model (Cowin, 1985, "The Relationship Between the Elasticity Tensor and the Fabric Tensor," *Mech. Mater.*, 4(2), pp. 137–147.) and the orientation of the principal axes of the fabric tensor, respectively. Deviations from orthotropy were*

*quantified by the "orthotropic error" (van Rietbergen et al., 1996, "Direct Mechanics Assessment of Elastic Symmetries and Properties of Trabecular Bone Architecture," *J. Biomech.*, 29(12), pp. 1653–1657), and deviations from transverse isotropy were determined by statistical comparison of the secondary and tertiary elastic moduli. The orthotropic error was greater than 50% for nearly half of the cubes, and the secondary and tertiary moduli differed from one another ($p < 0.0001$). Both the orthotropic error and the difference between secondary and tertiary moduli decreased with increasing bone volume fraction (BV/TV; $p \leq 0.007$). Considering only the cubes with an orthotropic error less than 50%, only moderate correlations were observed between the fabric-based and the μ FE-computed elastic moduli ($R^2 \geq 0.337$; $p < 0.0001$). These results indicate that when using a criterion of 5 mm for a representative volume element (RVE), transverse isotropy or orthotropy cannot be assumed for elderly human vertebral trabecular bone. Particularly at low values of BV/TV, this criterion does not ensure applicability of theories of continuous media. In light of the very sparse and inhomogeneous microstructure found in the specimens analyzed in this study, further work is needed to establish guidelines for selecting a RVE within the aged vertebral centrum. [DOI: 10.1115/1.4031415]*

Keywords: cancellous bone, microfinite element models, fabric, constitutive models, orthotropic error

1 Introduction

Knowledge of the nature of the elastic symmetry of trabecular bone is fundamental to the study of bone adaptation and failure. The evidence that bone adapts to its mechanical environment suggests strongly that the anisotropy of trabecular bone reflects the habitual stresses and/or strains that this tissue experiences, including the extent to which this loading is multiaxial. Moreover, the deformation and failure behaviors of trabecular bone in response to a given stress state also depend heavily on the trabecular anisotropy. As the use of computational modeling, such as finite-element modeling, to address questions regarding bone adaptation and failure has grown, there is a heightened need to understand the type of anisotropy, or class of elastic symmetry, exhibited by trabecular bone at a given anatomic site so that this tissue can be accurately represented in the model.

Prior studies of trabecular anisotropy have concluded that the specimens examined exhibit orthotropy and, in some cases such as vertebral trabecular bone, transverse isotropy in their elastic behavior [1]. The orthotropic elastic properties have been described well by constitutive models [2,3] based on the use of the fabric tensor as an orthotropic representation of the specimen microstructure. However, prior investigations of the mechanical behavior of trabecular bone have typically used rather sparse sampling of a metaphysis (e.g., proximal tibia) or cuboidal bone (e.g., vertebra) and have often sought to sample regions that exhibit homogeneous microstructure [4–6]. Particularly with human trabecular bone, which exhibits substantial deterioration in microstructure and microstructural organization during aging, the type of anisotropy exhibited throughout the trabecular compartment of a whole bone has not been established. This information is important for finite element modeling of whole bones, with respect to using accurate data on the elastic constitutive behavior of trabecular bone for the purpose of obtaining meaningful simulations of whole-bone behavior.

The overall goal of this study was to characterize the elastic symmetry of human trabecular bone throughout the elderly vertebral centrum. The class of elastic symmetry was determined using μ FE analyses and subsequent optimization [7] on a comprehensive sample of regions of trabecular bone within the trabecular centrum. Specifically, the objectives were to quantify: (1) the extent to which human vertebral bone exhibits transverse isotropy and orthotropy and (2) for the regions that display orthotropy,

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Fig. 1 Schematic representation of the procedure adopted to find the best orthotropic representation of each cube of trabecular bone: All δ_{ij} terms in C^{OPT} (d) are set to zero to obtain C^{ORT} (e); no other changes are made when obtaining C^{ORT} from C^{OPT} . (a) μ CT image of vertebra, (b) micro-FE analyses of the cube, (c) trabecular fabric-Eigenvectors of the cube, (d) nearly orthotropic stiffness matrix after optimization, and (e) orthotropic stiffness matrix after assigning nonorthotropic terms of zero.

correlations between orthotropic elastic properties calculated from μ FE and those calculated from a fabric-based constitutive model [2,8], and the extent of alignment between the principal elastic and fabric directions.

2 Methods

2.1 Specimen Preparation and Micro Computed Tomography (μ CT) Imaging. Eighteen L1 spine segments (age = 81.17 ± 7.7 yr; eight males and ten females) were harvested from fresh-frozen spines. The L1 vertebra was scanned (μ CT80, Scanco Medical, Brüttisellen, Switzerland) at the maximum possible resolution of $37 \mu\text{m}/\text{voxel}$.

2.2 μ FE Modeling. From the μ CT images, multiple cubes of size $5.032 \times 5.032 \times 5.032 \text{ mm}^3$, oriented along the anatomic axes, were created from the trabecular centrum of each vertebra (Fig. 1(a)). The 5 mm size was chosen based on prior evidence that regions of this size are RVEs for trabecular bone with the typical magnitudes of intertrabecular spacing seen in the human vertebra [9]. No image coarsening was used, resulting in finite elements that were $37 \mu\text{m}$ on a side. A total of 1628 μ FE models (34–155 per vertebra) were created. BV/TV was calculated for each cube. Each of the cubes was segmented using a global threshold value of 15% of the maximum gray value on a 16-bit scale ($0.15 \times 2^{15} = 4915$) and filtered using a Gaussian filter (Sigma=0.8, and support=1) (IPL, Scanco Medical, Brüttisellen, Switzerland). The global threshold value was obtained using an adaptive, iterative method [10].

2.3 Determination of Orthotropic Material Properties. Six hundred and nine cubes were excluded because the trabecular microstructure contained in these cubes did not meet the continuum requirements [9], primarily due to sparse and highly inhomogeneous microstructure. Specifically, cubes that did not contain at least five intertrabecular spacings along each face, and cubes for which at least one intertrabecular spacing was greater than approximately 2 mm, were excluded. The percentage of excluded cubes was larger in the inferior versus midtransverse plane of the vertebrae ($p=0.003$) as determined by repeated-measures

analysis of variance); no other regional differences in the exclusion of cubes were found.

For the remaining cubes, a linear elastic, isotropic material, with a Poisson's ratio of 0.3 and a Young's modulus of 13,000 MPa [11] was assigned to each element. Six linear, static, FE analyses were conducted (ABAQUS v6.8-4, SIMULIA, Providence, RI) (Fig. 1(b)) on each cube to determine the anisotropic stiffness matrix (C^{ANISO}) in the anatomic coordinate system (Table 1).

In this study, the numerical optimization procedure was implemented in MATLAB [7], using the *FMINSEARCH* algorithm to minimize the objective function defined by

$$\text{Obj} = \frac{\sum_{i,j} \delta_{ij}^2}{\sum_{i,j} c_{ij}^2}, \quad i, j = 1, \dots, 6 \quad (1)$$

where δ_{ij} represents the nonorthotropic terms and c_{ij} represents the orthotropic terms of the transformed stiffness matrix. The transformed matrix was obtained through a series of rotations, as defined by the Euler angles, about the coordinate axis. Through the optimization approach, the Euler transformation angles that yielded the best possible orthotropic representation of the stiffness matrix (C^{OPT}) were determined. The Euler angles relating the anatomic coordinate system and the principal directions of the trabecular architecture, represented by the eigenvectors of the

Table 1 Summary of μ FE analyses ($N = 1019$)

	Range
BV/TV	0.03–0.23
Trabecular thickness (Tb·Th*) [12]	0.08–0.33 mm
Trabecular spacing (Tb·Sp*) [12]	0.59–1.99 mm
Number of finite elements	74,689–578,641
Number of nodes	149,429–926,809
Solution time for a single μ FE analysis (T5400 Desktop computer (Dell Inc., Round Rock, TX))	3.7–317.1 min

Fig. 2 Histogram of orthotropic error (a) and correlations between orthotropic error and BV/TV (b) and between E_2/E_1 and BV/TV (c)

fabric tensor (mean intercept length [13,14] as calculated using the Scanco software for the 5 mm sphere circumscribed by the cube), were selected as the initial guess for the optimization procedure in order to avoid local optima in the optimization. In the resulting $\mathbf{C}^{\text{OPT}}$, the nonorthotropic terms were set to zero to produce a corresponding orthotropic matrix ($\mathbf{C}^{\text{ORT}}$). The accuracy of the orthotropic assumption of the optimized stiffness matrix was quantified using the orthotropic error, defined as $\text{Error} = \|\mathbf{I} - (\mathbf{C}^{\text{ORT}})^{-1}\mathbf{C}^{\text{OPT}}\|$ [15]. Both $\mathbf{C}^{\text{OPT}}$ and $\mathbf{C}^{\text{ORT}}$ were checked to confirm that they were each positive definite.

For cubes with an orthotropic error less than 0.5, the following were calculated from ($\mathbf{C}^{\text{OPT}}$): the nine elastic constants and the principal elastic directions. For these cubes, orthotropic elastic constants were also determined using Cowin's morphology–elasticity constitutive model [2,8]. The orientations of the fabric axes (as determined above for the optimization procedure that produced $\mathbf{C}^{\text{OPT}}$) and principal elastic directions with respect to anatomic axes (superior–inferior (SI), anterior–posterior (AP), and medial–lateral (ML)) were calculated, as were the differences between the principal elastic and fabric directions.

2.4 Statistical Analysis. The following statistical analyses were carried out (JMP 10.0, SAS Institute Inc., Cary, NC) with an experimentwise significance level of 0.05:

- correlation between BV/TV and the orthotropic error, as an indicator of orthotropy;
- a paired t -test to determine equivalence between E_1 and E_2 , as an indicator of transverse isotropy;
- correlations among the orientations of the fabric, elastic, and anatomic axes, and correlations between the differences between these orientations and BV/TV; and
- correlations between fabric- and μFE -based elastic constants, between the differences in these constants and the

orthotropic error, and between the differences in these constants and BV/TV.

In preparation for the correlation analyses, log transformations were used where appropriate.

3 Results

3.1 Orthotropy and Transverse Isotropy of Human Vertebral Trabecular Bone. The median value of the orthotropic error for the cubes was 0.459 (interquartile range (IQR) = 0.641) (Fig. 2(a)). Elastic properties and orthotropic error for all cubes ($n = 1109$) are provided on the ASME digital collection under the “Supplementary Data” tab. Considering all cubes analyzed ($n = 1019$), the orthotropic error decreased with increasing BV/TV ($R^2 = 0.234$; $p < 0.0001$) (Fig. 2(b)). A total of 479 cubes (18.56–81.97% of the cubes per vertebra) had an orthotropic error greater than or equal to 0.5.

Table 2 Orthotropic elastic constants computed by μFE for the specimens with orthotropic error <0.500 ($N = 540$)

Elastic property	Median	Interquartile range	Minimum	Maximum
E_1 (MPa)	26.07	36.06	1.61	535.10
E_2 (MPa)	44.92	58.26	3.11	558.87
E_3 (MPa)	239.38	171.24	11.19	764.58
G_{23} (MPa)	66.12	80.06	0.79	285.51
G_{13} (MPa)	58.01	44.63	6.25	385.46
G_{12} (MPa)	60.65	46.34	8.58	352.53
ν_{23}	0.048	0.047	−0.643	0.369
ν_{13}	0.051	0.044	−0.392	0.366
ν_{12}	0.244	0.136	−0.808	0.565
E_3/E_1	8.78	8.92	1.04	54.34
E_2/E_1	1.49	0.92	1.00	8.72
E_3/E_2	5.28	4.84	1.00	27.70

Table 3 Orthotropic axial alignment for the specimens with orthotropic error <0.500 ($N=540$): The angles presented compare the primary direction to the SI direction, secondary to the ML direction, and tertiary to the AP direction

	Axis	Median (deg)	Interquartile range (deg)
Elastic modulus	Primary	1.63	1.85
	Secondary	2.51	87.84
	Tertiary	1.07	88.35
Fabric	Primary	7.25	7.04
	Secondary	21.88	29.74
	Tertiary	24.22	34.67

The vast majority of the remaining 540 cubes (Table 2) were not transversely isotropic ($E_1 \neq E_2$, $p < 0.0001$). However, for this reduced set ($n=540$) the ratio E_2/E_1 decreased very mildly toward unity with increasing BV/TV ($R^2=0.014$; $p=0.007$) (Fig. 2(c)), indicating that the higher density cubes tended to be more transversely isotropic.

3.2 Orthotropic Axial Alignment. The primary, secondary, and tertiary elastic directions were closely aligned to the SI, ML, and AP axes, respectively ($n=540$; Table 3). By comparison, the fabric axes deviated further from the anatomic directions. The

primary elastic and fabric axes were closely aligned with each other, with a median difference of only 5.61 deg (IQR = 8.11 deg). Less strong alignment between elastic and fabric axes was seen for the secondary (median = 20.04 deg; IQR = 30.27 deg) and tertiary (median = 23.00 deg; IQR = 31.29 deg) directions. The extent of alignment among the axes depended on BV/TV: with increasing BV/TV, the secondary elastic axes became more closely aligned with the ML direction ($p < 0.024$) and the secondary and tertiary elastic axes aligned more closely with the fabric axes ($p < 0.015$). In addition, with decreasing BV/TV, the primary elastic axis tended to align more closely with the primary fabric axis ($p=0.090$).

3.3 Correlation of μ FE Elastic Properties With Morphology-Based Elastic Properties. Considering only the cubes for which the orthotropic error was less than 0.500 ($n=540$), moderate correlations were found between the elastic moduli obtained from the μ FE results and those obtained from the morphology–elasticity relationships ($R^2 \geq 0.337$; $p < 0.0001$) (Figs. 3(a)–3(c)). Weaker correlations were found for the shear moduli ($R^2 \leq 0.191$; $p < 0.0001$) (Figs. 3(d)–3(f)). No correlations were observed for Poisson’s ratios ($p > 0.057$). With and increasing orthotropic error, the difference between the μ FE- and fabric-based predictions of E_1 , E_2 , G_{23} increased ($p < 0.021$), and that for G_{12} decreased ($p < 0.0001$). The difference between the

Fig. 3 Correlations of the Young’s moduli ((a)–(c)), shear moduli ((d)–(f)), and Poisson’s ratio ((g)–(i)) from the μ FE model versus the morphology-based model: The correlation coefficients were nearly unchanged when the circled data point was excluded

μ FE- and fabric-based predictions of E_1 and G_{12} increased with increasing BV/TV ($p < 0.002$), while for E_3 the difference decreased with increasing BV/TV ($p < 0.0001$).

4 Discussion

In this study, a comprehensive approach that sampled as many 5 mm cubic regions within the trabecular centrum as possible was adopted to evaluate the elastic symmetry of trabecular bone from human L1 vertebrae. Nearly half of the 1019 cubes considered for the study exhibited an orthotropic error, which quantifies the error due to the orthotropic assumption, greater than 50%, and this error decreased with increasing BV/TV. When comparing E_1 and E_2 to evaluate the extent of transverse isotropy, significant differences were found ($p < 0.001$). The data for cubes that had an orthotropic error less than 50% were further analyzed to compare the orthotropic elastic properties calculated from a fabric-based constitutive model versus those computed from the μ FE analyses. Only moderate correlations between the fabric-based and the μ FE-computed moduli were found, and no correlations were found for the Poisson's ratios. In addition, the orientations of the secondary and tertiary fabric and elastic axes were different. These results indicate that when using a criterion of 5 mm for an RVE, transverse isotropy or orthotropy cannot be assumed for elderly human vertebral trabecular bone. Particularly at low values of BV/TV, this criterion does not ensure applicability of theories of continuous media, such as the morphology–elasticity constitutive theory used here. Indeed, the present data illustrate that substantial discrepancies in elastic constants occur when the criterion that is employed to define an RVE is inadequate.

These findings are in contrast to previous studies, which also used RVEs of approximately 5 mm and found that trabecular bone exhibits orthotropic or greater symmetry [7,8,16,17]. Prior studies also obtained good correlations between the fabric-based and μ FE-computed elastic properties as well as close alignment between the fabric and elastic directions [1,8]. This contrast is likely due to both the thorough sampling of cubic regions throughout the trabecular centrum for the present study and the advanced age of the donors from which the vertebrae were obtained. These two features of the experimental design produced a population of cubes with a median BV/TV of only 0.07. Given the associations found in this study between BV/TV and the extent of material symmetry, studies using higher density specimens would be expected to find greater suitability of the 5 mm criterion for an RVE and, hence, a greater extent of symmetry and better agreement with the fabric-based predictions. Overall, our results together with the earlier published studies on material symmetry in trabecular bone (which selected far fewer specimens per vertebra or metaphysis and with more restrictive exclusion criteria, qualitatively speaking) suggest that stricter exclusion criteria for homogeneity and sparseness will select a larger percentage of specimens that meet the true definition of an RVE.

Some limitations of this study deserve mention. First, although the present results may pertain only to the elderly lumbar spine, this anatomic site and age range are nevertheless consistent with a highly clinically relevant population for the study of vertebral biomechanics. Second, the initial exclusion criterion for homogeneity of the microstructure contained in the cube was only qualitative. We cannot conclude that *none* of the excluded cubes possess orthotropic or higher symmetry; however, our exclusion criteria do not affect the finding that a very large fraction of the 5 mm cubes retained for analysis was not RVEs. Third, we used a fixed size for the cubic regions analyzed, which resulted in excluding some cubes whose microstructure was too sparse within a 5 mm region but not too sparse within an enlarged region. Through ancillary studies, however, we found that using a larger size for all cubes would actually also result in excluding some cubes whose microstructures were gauged to be sufficiently homogeneous at the 5 mm size but too inhomogeneous at larger sizes. Fourth, the elastic constants were not measured directly but rather

computed from the μ FE analyses. Finally, in light of the correlation between the orthotropic error and the deviation of the μ FE-computed moduli from the fabric-based values, the μ FE-computed moduli would be expected to more closely match the fabric-based values if we had used a lower cutoff than 0.500 for the orthotropic error. This expectation is consistent with the continuum requirements on which the morphology–elasticity constitutive model is based. However, changing the cutoff would not change the finding that, at the length scale of 5 mm, many regions of the elderly vertebral trabecular centrum cannot be considered continua.

This finding thus indicates that the criterion for an RVE for trabecular bone should be expanded to include guidelines based on more than size, sparseness, and qualitative assessment of homogeneity. As noted above, simply increasing the region size beyond 5 mm in the elderly vertebral centrum often does not yield an RVE. Our data on the inverse association between orthotropic error and BV/TV (Fig. 2(b)) indicates that a guideline based on BV/TV could be considered. A quantitative guideline for homogeneity may be less straightforward to develop, though approaches such as subsampling the presumptive RVE [17] and examining the dependence of μ FE-derived elastic properties on the extent of intraregional variations in density, trabecular thickness, and trabecular separation are likely to provide insight.

The present results also have implications for modeling of trabecular bone for the purpose of studying vertebral failure. Numerous studies (e.g., Refs. [18,19]) model vertebral trabecular bone as orthotropic or transversely isotropic when constructing finite-element models of the entire vertebral body or vertebra. It is noteworthy that multiple studies that have used this approach have found good agreement between experimentally measured and FE-computed values of vertebral stiffness and also vertebral strength [20,21]. In addition, modeling the majority of the vertebral trabecular centrum as transversely isotropic produces nearly equivalent predictions of vertebral stiffness to those obtained when using orthotropic properties instead [22]. These apparent contradictions to the present data might be resolved by considering the dependence of the orthotropic error (Fig. 2(b)), the ratio of E_2/E_1 (Fig. 2(c)), and the individual moduli [2,3] on BV/TV. Although the cubes of lowest volume fraction tended to exhibit the least material symmetry, these regions of the vertebra, by virtue of their low stiffness, may not be primary load-bearing regions and their contribution to the overall stiffness of the vertebra may thus be small. If that is the case, then errors in constitutive modeling of these regions may be inconsequential for simulating the mechanical behavior of the vertebra. However, this line of reasoning is predicated on Wolff's law, and in a scenario of poor or incomplete adaptation, or unusual loading, the regions of low density may have major structural significance. As an example, lower volume fractions in the anterior region of the vertebra have been postulated to result from adaptation to loads that are shifted more to the posterior regions during erect postures in a segment with degenerated intervertebral disks, and may be a risk factor for fracture during forward flexion [23]. The results of the present study therefore suggest that the question of how to accurately model trabecular bone throughout the entire vertebral centrum is still open and that the choice of model could impact the fidelity of simulations of vertebral mechanical behavior, particularly for nonhabitual loading scenarios.

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