Morphology Based Anisotropic Finite Element Models of the Proximal Femur Validated with Experimental Data

W S Enns-Bray^{1*}, O Ariza^{1,2,3,4}, S Gilchrist^{2,3,4,5}, R P Widmer¹, P J Vogt¹, H
Palsson⁶, S K Boyd⁷, P A Guy^{3,5}, P Crompton^{2,3,4,5}, S J Ferguson¹, B Helgason¹

¹Institute for Biomechanics,
ETH-Zürich, Switzerland.

²Orthopaedic and Injury Biomechanics Group

³Centre for Hip Health and Mobility

⁴Department of Mechanical Engineering

⁵Department of Orthopedics

University of British Columbia, Vancouver, Canada.

⁶Faculty of Industrial Engineering, Mechanical Engineering and Computer
Science, School of Engineering and Natural Sciences

University of Iceland, Reykjavik, Iceland

⁷Department of Radiology, Faculty of Medicine, McCaig Institute for Bone and
Joint Health

University of Calgary, Calgary, Canada

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*Corresponding author

William Enns-Bray (willame@ethz.ch)

Institute for Biomechanics

ETH Zürich

Schafmattstrasse 30, HPP-O23

CH-8093 Zürich

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Abstract

Finite element analysis (FEA) of bones scanned with quantitative computed tomography (QCT) can improve early detection of osteoporosis. The accuracy of these models partially depends on the assigned material properties, but anisotropy of the trabecular bone cannot be fully captured due to insufficient resolution of QCT. The inclusion of anisotropy measured from high resolution peripheral QCT (HR-pQCT) could potentially improve QCT-based FEA of the femur, although no improvements have yet been demonstrated in previous experimental studies.

This study analyzed the effects of adding anisotropy to clinical resolution femur models by constructing six FE models (two isotropic & four anisotropic) for each specimen from a set of sixteen femurs that were experimentally tested in sideways fall loading with a strain gauge on the superior femoral neck. Two different modulus-density relationships were tested, both with and without anisotropy derived from mean intercept length analysis of HR-pQCT scans.

Comparing iso- and anisotropic models to the experimental data resulted in nearly identical correlation and highly similar linear regressions for both whole bone stiffness and strain gauge measurements. Anisotropic models contained consistently greater principal compressive strains, approximately 14% in magnitude, in certain internal elements located in the femoral neck, greater trochanter, and femoral head.

In summary, anisotropy had minimal impact on macroscopic measurements, but did alter internal strain behavior. This suggests that organ level QCT-based FE models measuring femoral stiffness have little to gain from the addition of anisotropy, but studies considering failure of internal structures should seriously consider including anisotropy to their models.

Introduction

Finite element (FE) models of the proximal femur derived from clinical Quantitative Computed Tomography (QCT) rely on realistic material properties to accurately predict patient-specific bone strength *in vivo* [1]. The trabecular bone within the proximal femur exhibits anisotropic mechanical behavior due to its complex microarchitecture, which is difficult to resolve at clinical resolutions and therefore unavailable *in vivo*. Several studies have attempted to construct anisotropic FE models of the proximal femur with widely varied methods [2][3][4][5][6][7][8][9], however there is little agreement in the resulting outcome or the optimal approach, which can be partly attributed to a shortage of experimental validation studies focusing on anisotropy. Hence, the question remains whether anisotropic material properties improve QCT-based FE models of the proximal femur, which is highly relevant to the overall goal of translating this modelling technique into clinical practice.

The anisotropy of large anatomical regions can be measured incrementally from subsections taken from high-resolution peripheral QCT (HR-pQCT) scans with voxel sizes below 100 μ m. The morphological anisotropy can be described using a fabric tensor [10], which can be measured using surface analysis tools such as the mean intercept length (MIL) method [11]. When implemented in organ-level FE models, elements representing trabecular bone are typically assigned orthotropic material properties. This requires a realistic degree of anisotropy (DA) and directionality that accurately reflects the mechanics of the underlying microarchitecture. The DA represents the ratio of material stiffness between orthogonal planes, while the directionality represents the three-dimensional orientation of those planes, also referred to as the material's principal directions. The anisotropy of an orthotropic stiffness tensor can be described using its eigenvalues and eigenvectors. The ratios between the first and second, and

first and third eigenvalues together describe the DA of the tensor, while the eigenvectors describe its directionality.

While a variety of modulus-density relationships exist in literature [12] no consistent model has been used in studies developing anisotropic organ-level models of the femur. A study by [5] constructed anisotropic femur models from QCT scans by combining the modulus-density relationship proposed by [13] with the FE-based, density-DA relationships proposed by [14] and found differences in strain up to 14% between isotropic and anisotropic models. Another study, using directionality determined using simulated mechanical loading of micro-FE models of small bone volumes within the femur [15], found an average 26% decrease in whole bone stiffness (n=7) between model types when loaded in a sideways fall, but no improvement in correlation between experimental and FE predicted whole bone stiffness [2]. An alternative approach combines fabric tensors with CT density to calculate the element compliance tensor [16]. This has improved proximal femur stiffness prediction by 4% and 42% for a single healthy and osteoporotic specimen, respectively, when compared to a micro-FE model gold standard [4]. Another study, using similar fabric anisotropy, found an improvement in ultimate strength prediction over isotropic models for stance but not sideways fall loading for 36 experimentally tested femur specimens [3], suggesting, conversely, that anisotropy does not improve these organ-level FE models. Thus it remains unclear which anisotropic model is optimal for the proximal femur, and more specifically, which strategy results in the best prediction of whole bone stiffness. Furthermore, it is also unclear which modulus-density relationship and material mapping strategy provides an optimal combination with anisotropic properties, with a variety of previously published combinations available [3][5][6].

The purpose of this study was to investigate two important knowledge gaps surrounding

anisotropic organ-level FE modelling of the femur. The first was to determine whether anisotropy improves whole bone stiffness prediction, instead of just ultimate strength, since stiffness is a closer indicator of whether the energy absorption properties are being modeled correctly, which is particularly important in an impact loading event such as a sideways fall [17]. The second was to determine the effect of combining morphometric anisotropy with different modulus-density relationships and material mapping strategies that have yielded good whole bone and local validation outcomes. This was done by testing two material mapping strategies that represent extremes of possible modulus-density relationships and partial volume artifact correction, instead of arbitrarily selecting from one of the numerous available methods. We hypothesized that anisotropic material properties will result in different local stress and strain behavior and improve the correlation between the FE models and experimental results.

Materials and Methods

Specimens and Experimental Testing

A detailed description about the experiment has been published elsewhere [18]. Briefly, sixteen fresh frozen human femurs (15 women, 1 man, average age: 76 +/- 10 years) were acquired from a commercial tissue donation bank (National Disease Research Interchange, Philadelphia, PA) with no reported history of musculoskeletal or metabolic disease. Specimens were thawed at room temperature wrapped in saline-soaked gauze and scanned in HR-pQCT (XtremeCT, Scanco Medical, Switzerland) at 41µm voxel size calibrated with a standardized hydroxyapatite phantom (0, 100, 200, 400 and 800 mg HA/cm³). Specimens were potted in polymethylmethacrylate (PMMA), with a hinge at the distal ends that allowed free rotation in the anatomical frontal plane. The specimens were also imaged using dual-energy X-ray

absorptiometry (DXA) as described in [19]. PMMA pads, approximately 4 cm in diameter and 1.5 cm in height, were molded to the greater trochanter and femoral head for each specimen and acted as loading surface for the material testing system (8874, Instron Inc., Norwood, MA). Specimens were tested in a fall configuration [20] (Fig. 1), and were preloaded to 100 N over 5 repetitions then compressed at 0.5 mm/s up to half of the failure load predicted using areal bone mineral density (aBMD) [21]. Whole bone stiffness was calculated from load-displacement data adjusted for estimated cartilage deformation at the femoral head and machine compliance, which was measured directly by applying known loads to the frames and fixators [22]. A separate FE model was used to estimate cartilage compliance as described in [18], assuming the femoral head was a spherical shape with a cartilage layer 1.47 mm thickness, based on average thickness of harvested specimens in a previous study [23]. Average cartilage deformation was between 0.11 mm – 0.20 mm at max experimental load [18]. Local changes in surface strain were measured with a rosette strain gauge (FRA-2-11-3LT Tokyo Sokki Kenkyujo Co., Tokyo, Japan) mounted on the anterior-superior surface of the femoral neck using cyanoacrylate and a standard mounting protocol [Chapter Strain gauge analysis of hard tissues: factors influencing measurements [24]]. This experimentally validated method has been effective for measuring external strains at this critical location known for fracture initiation [25], and was therefore useful for comparing the local mechanical behavior predicted by models with different material properties.

Continuum Finite Element Models

The base FE models used in the present study are the same as the ones used in Helgason et al., 2016. The description of the FE mesh generation is only briefly described here for clarity. Reconstructed HR-pQCT scans were resampled to clinical CT resolution (0.615 mm) and

segmented semi-automatically by identifying the periosteal surface (ITK SNAP, v2.2.0). Resampled HR-pQCT gray levels were converted to ash density based on hydroxyapatite (HA) content according to $\rho_{\text{ash}} = (\text{mgHA}/1000 + 0.09)/1.14$ [25]. Segmented images were meshed into 10-node tetrahedral elements (Ansys Workbench, v14.0, Altair Engineering Inc., USA). A mesh convergence analysis determined that 2.0 mm was the best compromise between computation cost and relative accuracy, as smaller elements were found to increase whole bone stiffness by approximately 4% at the cost of nearly eight times the computational time. Element modulus of elasticity was assigned using nodal interpolation of ash density values [26] and then averaging the nodal modulus into a single value per element which corresponds to material mapping method A according to the study of Helgason et al., 2016. When selecting candidates for modulus-density-relationships, only studies that effectively captured both local deformation and whole bone properties from *in vitro* validation experiments were considered [25][27][28][29]. Two previously validated relationships were selected from studies that represent the softest [29] and stiffest [28] extremes. In the first, the ash density of each element was adjusted to apparent density according to $\rho_{\text{ash}} = 0.6 \rho_{\text{app}}$ [25] then converted to a Young's modulus using the relatively stiff femur-specific relationship proposed by [30]. In the second, the ash density was converted to modulus using a combination of the relatively soft modulus-density relationships proposed by [31] and [13].

Due to the difference in element modulus resulting from these two methods, each material property included a different partial volume artifact correction method. The first method used no partial volume artifact correction, since the modulus-density relationship already maps a relatively high modulus to the elements. The second method results in a softer element modulus, and therefore partial volume correction was applied over the thin cortices by adding triangular

shell elements with 0.4 mm thickness over the entire femur as described by [29]. Surface elements were assigned a modulus equal to the nearest internal element, but never less than 10 GPa. The material properties are summarized in Table 1, where the first and second method was referred to as ‘NoShell’ and ‘Shell’, respectively. For FE models with isotropic material properties assigned, Poisson’s ratio was set to 0.3.

The distal part of the FE model was modelled with beam elements with hollow cylindrical cross sections closely representing the experimental setup as described in detail in Helgason et al., 2016. Frictionless sliding was permitted at the PMMA-bone contact at the femoral head and the PMMA-platen contact at the greater trochanter. The distal end of the model was fully translationally constrained, while rotation was only allowed about an axis corresponding to the hinge joint at the distal. The length of the femoral shaft not captured by CT was modelled using beam elements representing a hollow cylinder with properties of fully mineralized bone. Models of the PMMA pads on the femoral head and greater trochanter included subject-specific diameter and thickness, based on geometry digitized from the experiment, and were assigned a modulus of 3.1 GPa and Poisson’s ratio of 0.3 [32]. The rigid plate above the greater trochanter was displaced by 1 mm and femoral stiffness was calculated by summing reaction forces over the displaced plate nodes and dividing by the applied displacement.

Anisotropic Material Mapping

The anisotropic model was designed by combining previously published methods. This section gives an overview of the steps and their source material, followed a brief description of each step, which proceeded as follows: First, HR-pQCT image subdivision [2], then MIL

analysis of each sub-volume [33], next interpolation of fabric tensor eigenvectors and eigenvalues from HR-pQCT into clinical resolution FE models at the element centroids [2], and finally the element orthotropic stiffness tensors were constructed by combining isotropic mechanical properties with interpolated fabric data [4] [16].

Reconstructed HR-pQCT scans were downsampled to 82 μm and smoothed with a modest Gaussian filter ($\sigma = 1.2$, kernel size = 1.0). The bone mineral phase of each scan was extracted using a fixed global threshold manually selected to best preserve trabecular connectivity. Thresholded scans were subdivided into 5mm cubic sub-volumes over a uniform grid, where each specimen yielded approximately 8000 cubes. Each individual sub-volume underwent MIL analysis [34] using IPL (Image Processing Language v5.15, Scanco Medical, Switzerland) to determine a second-order fabric tensor describing the morphological anisotropy [10]. Each fabric tensor contained three eigenvectors corresponding to the principal directions of stiffness, and three eigenvalues that together describe the DA of each sub-volume. The map of anisotropy from all collective sub-volumes formed the input for an interpolation volume used to transfer HR-pQCT anisotropy information into the clinical resolution FE models, similar to the approach by [2]. An interpolating volume was generated for the eigenvectors using radial basis functions with a Gaussian basis (ALGLIB v3.7.0, ALGLIB Project; Nizhny Novgorod, Russia) and an additional interpolation volume was generated for the eigenvalues using simple tri-linear interpolation. Subsequently, for each element in the clinical resolution models, the eigenvalues and eigenvectors were interpolated from the map of anisotropy based on the element centroid location. The resulting directionality of the anisotropy mapping process was empirically evaluated by comparing the orientation of primary eigenvectors to the orientation of trabecular microarchitecture visible within the corresponding segmented HR-pQCT scan.

In anisotropic FE models, the orthotropic stiffness tensor of each element was constructed by combining the isotropic elastic constants with the fabric information interpolated from HR-pQCT. The interpolated fabric tensor was reconstructed from the interpolated eigenvectors and eigenvalues at each element centroid and normalized by setting the trace of the tensor equal to three, as described by [16]. In previous studies, the fabric eigenvalues have been adjusted to account for errors resulting from the low resolution of HR-pQCT scans, relative to micro CT. Two such calibration equations were identified in literature:

$$m = 1.75m_0 - 0.75 \quad (1)$$

$$m = 0.96m_0 + 0.04 \quad (2)$$

from [35] and [3], respectively, where m_0 is the raw eigenvalue from the HR-pQCT scan, and m is the eigenvalue calibrated to micro CT that is used to calculate the anisotropic properties. Since it was unclear which calibration law was optimal for our modelling objectives, two types of anisotropic models were tested; one anisotropic model with normalized eigenvalues calibrated with the equation 1 (Aniso 1), and a second anisotropic model using equation 2 (Aniso 2). The calibrated eigenvalues were then used to scale the Young's modulus, Poisson's ratio, and shear modulus in each orthogonal plane to fully define the 3D orthotropic stiffness matrix (Table 2) similar to the approach by [4]. Lastly, the local coordinate system of each element was rotated to align with the corresponding eigenvectors that represent the principal stiffness directions.

For this study, anisotropy was only applied to elements representing trabecular bone [4], and so any elements with a bone volume fraction (BVF) above 1.4 g/cm^3 apparent density, including all shell elements, were assigned isotropic material properties according to table 2. In total, six FE models were constructed for each specimen, including two modulus-density relationships (NoShell & Shell), each with three material types (Iso, Aniso 1, Aniso 2). Apart from the

material properties, the final anisotropic FE models were identical to the isotropic models in every respect.

Comparison between models and experimental testing

Whole bone stiffness predicted by FE models was correlated with experimental stiffness, and linear regression was used to calculate the slope and intercept of a line of best fit between groups. Max and min principal surface strains were measured from the experiment at the maximum applied force, and subsequently compared to FE surface strains by averaging the surface nodal strain over an area corresponding to the size of the strain gauge (radius 1.5 mm) centered on the strain gauge location digitized from the experiments [18]. The root mean square error (RMSE) and maximum error of each regression quantified the variance and bias of each linear model. Bland-Altman plots were also generated to assess the agreement and error bias between the FE and experimental data for each model type. The principal compressive strain of each internal element was calculated throughout the femur geometry for each model type and the element-wise percent difference between isotropic and anisotropic models were also plotted to highlight dissimilarities. Element nodes were manually identified within the femoral neck, and the nodal maximum and minimum strains were correlated between isotropic and anisotropic models, for internal and surface nodes separately.

Results

The orientation of the primary fabric eigenvectors showed good empirical agreement with the alignment of the trabecular microarchitecture visible within the segmented HR-pQCT

scan, (Fig. 2). Qualitatively speaking, the DA showed variation throughout the internal architecture. The majority of the femoral head, neck, and greater trochanter contained a DA of approximately 1.5, with values as low as 1.2 and as high as 2.0. The correlation of both isotropic and anisotropic models with experimental whole bone stiffness and strain gauge measurements were similar in all models (Table 3), and the highest coefficients of determination (R^2) were shared by an iso- and anisotropic model. Anisotropy consistently increased the slope and decreased the intercept of the regression line in both material methods (i.e. Shell vs NoShell), but these differences were small relative to the changes due to the type of material method. Bland-Altman plots of Shell and NoShell models showed similar mean differences between FE and experimental whole-bone stiffness with no apparent correlation between the error and average specimen stiffness (Fig. 3).

Visual comparison of the principal compressive strain distribution within anisotropic and isotropic models showed that the highest strains were concentrated in the greater trochanter and femoral neck, with slightly higher strains visible in the anisotropic models (Fig. 4). The percent difference in strain was plotted for each element, revealing maximum differences of approximately 14% in high strain regions in the femoral neck and trochanter, and for some specimens, the femoral head as well (Fig. 5). For the femoral neck specifically, direct comparison of max and min principal strains of the nodes showed strong agreement in external nodes and less agreement in internal nodes, with growing variation within high strain nodes (Fig. 6). Moreover, higher compressive strains were observed in this region than tensile strains, which were also higher in specimens with lower neck aBMD.

Discussion

This study investigated whether adding morphological anisotropy measured from HR-pQCT improves continuum FE models, constructed from clinical resolution CT images of the proximal femur, undergoing sideways fall loading. We found that neither the addition of anisotropy, nor the different modulus-density relationship made much impact on the correlation and linear regressions between FE models and experiments. However, we did observe consistent differences in the strain of internal elements in critical load bearing regions such as the femoral head, neck, and greater trochanter.

Comparing the orientation of the fabric eigenvectors to the trabecular patterns visible in the segmented CT scans, we can conclude that MIL method yields a realistic measure of directionality for cancellous bone. This finding has also been confirmed by studies at the tissue level [34] and organ level [2,2][4]. For trabecular bone volumes extracted from the proximal femur, studies have reported mean fabric-based DA between 1.60-1.97 (Table 4), which is higher than those measured by the mapping process in this study, even after including eigenvalue calibration. A higher DA could amplify the effects of anisotropy, but the true DA in these regions remains uncertain, since fabric tensors are a purely morphological representation of anisotropy and can only approximate mechanical properties. One study found up to 33% difference between MIL and FE-predicted DA for trabecular bone [34], therefore it is possible that the DA is being underestimated by the MIL method.

These results indicate that the addition of anisotropy had minimal to no impact on the correlation between FE and experiments, which is in agreement with other experimental validation studies using sideways fall loading configuration [2][3]. The correlation values for whole bone stiffness were lower than other recently published studies [28][36], which, apart from the different modulus-density relationships, can be largely attributed to the difference in

boundary conditions. Previous studies have used fitted metal cups cemented to the femur at the loading surfaces, whereas this study used PMMA pads, which were included within the model and created a full-contact problem. The local external strains were consistently overestimated by FE, which was also reported in a recent study [28] with comparable correlation coefficient and RMSE magnitude as the present study.

Comparing isotropic to anisotropic correlations, it is possible that the variation inherent within the experimental data could be masking any small improvements made by anisotropy, which is likely only 5-10% in magnitude given the success of prior studies with high stiffness correlations using isotropic properties [36]. Another explanation is that the heterogeneity of the CT density distribution, used to construct the isotropic models, already intrinsically contains the majority of the anisotropy contained by the trabecular bone compartment. In other words, by interpolating additional anisotropy from the HR-pQCT scan into the clinical resolution model, we have not included enough new information to have an impact on these macroscopic outcomes. This can be further illustrated by considering that a 5x5x5 mm cube used to measure anisotropy would also contain multiple elements in the clinical resolution model, and would thus elicit an anisotropic response due to the heterogeneous density distribution alone. It is difficult to say to what extent this property is able to capture the actual anisotropy, especially in real clinical scans where the microarchitecture is even more blurred. Still, the results of this study indicate that slightly altering these material properties will have little impact on whole bone stiffness.

We found that anisotropic models have consistently higher principal compressive strain for certain internal elements in the femoral head, neck, and greater trochanter. This finding was similar in magnitude to another recent study [5], and suggests that some elements are sensitive to

poorly aligned microarchitecture under sideways fall loading. Differences were also observed in the nodal strain of internal femoral neck nodes, suggesting that any failure estimation of internal bone tissue could be sensitive to anisotropic material properties. A recent high resolution FE study also indicated that failure in the proximal femur can start with failure of the internal trabecular structure [37]. Thus anisotropic material properties could be particularly important when modeling implants such as screws, intramedullary nails, and hip prosthesis stems that adhere to the internal trabecular microarchitecture, as well as failure criteria for bone tissue that uses anisotropic information [38].

The anisotropy mapping method presented here has limitations. The cortical bone elements were assigned isotropic material properties, when in reality this compartment is anisotropic as well [39]. This could explain the minimal changes observed in the external regions, yet we expect that the majority of the cortical elements will still be loaded along the principal material direction, thus minimizing the impact of anisotropy. This study did not separate trabecular and cortical compartments prior to anisotropy mapping as performed by other studies [3]. This could affect the directionality in the transition region between compartments, as the primary eigenvector will be artificially pulled parallel to the cortical structure. Yet the anisotropy mapping results presented in Fig. 2 indicated that misalignments in the transition region were minimal, and furthermore it is unlikely that the outcome measurements are sensitive to small changes in local directionality. Since the anisotropy was mapped from HR-pQCT, it cannot be applied to in vivo patient-specific studies. However, with the availability of atlas maps of anisotropy from public databases, it may be possible to include ‘general’ anisotropic information by registering a database model with a patient-specific model [40]. Additionally, the down sampled HR-pQCT scans used in this study were higher resolution than a typical clinical

in vivo QCT scan, which can have voxel sizes greater than 0.615mm, which could affect the material mapping strategy. MIL measurements, however, were designed for micro CT scans, with voxel sizes of 20µm and lower, which is impossible for HR-pQCT. Although we tested two different calibration equations to compensate for larger HR-pQCT voxel size, project-specific calibration protocols using micro CT could provide more accurate fabric anisotropy calibrations for HR-PQCT images.

In conclusion, our data does not support the hypothesis that the addition of anisotropy improves the accuracy of whole bone stiffness and external strain predictions in the femoral neck from femur models in sideways fall loading. However, anisotropy altered the internal strains in specific local areas including the internal femoral neck and greater trochanter, demonstrating that anisotropy plays an important role in modeling the mechanics of these regions. Thus it is clear that the utility of anisotropy depends on the modeling objectives, and future studies can use this information to determine whether including these more complex material properties will have a meaningful impact on their modeling outcomes.

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Fig. 1: Experimental setup (above); corresponding FE model (below-left). The FE model used for estimating cartilage compliance is shown below-right (reprinted from [17] with permission). An Optotrak Certus motion capture system (Northern Digital Inc, Waterloo, ON, Canada, accuracy < 0.1 mm) equipped with a digitizer probe was used to record the locations of landmarks on the femur with respect to the experimental setup to allow for accurate representation of boundary conditions in the FEA. The femur FE models were transferred to the experimental coordinate system through a rigid registration using an iterative closest point algorithm [23] .

Fig. 2: Segmented HR-pQCT scan (left) showing major anatomical trabecular directionality including the primary compression (1) and tension (2) lines, secondary tension (3) and compression (4) lines, and greater trochanter lines (5). Also depicted, the directionality of the primary eigenvectors from the map of anisotropy (middle), and primary eigenvectors interpolated to the individual elements (right). The eigenvectors are colored by the degree of anisotropy (DA), which is the ratio between first and third eigenvalues.

Fig. 3: Top: Linear regression between experimental and FE predicted whole bone stiffness for Iso (red), Aniso 1 (blue), and Aniso 2 (green), for Noshell (left) and Shell (right) models. Bottom: Bland-Altman plots showing the percent difference between experimental and FE predicted whole bone stiffness as a function of the average stiffness, for Iso (red O) and Aniso 1 (blue X), for Noshell (left), and Shell (right) models.

Fig. 4: Mid-frontal slice of principal compressive strain within NoShell and Shell models with Iso (top) and Aniso 1 (bottom) properties, for the stiffest (left) and softest (right) specimens.

Fig. 5: Percent difference in principal compressive strain between NoShell models with Iso and Aniso 1 properties, for the stiffest (left) and softest (right) specimens.

Fig. 6: Both max and min nodal principal strains plotted simultaneously for stiffest (left & center left) and softest (center right & right) specimens, for nodes located in the femoral neck, separated into external and internal groups, for NoShell (top) and Shell (bottom) materials.

Table 1: Two material mapping methods using stiffer and softer density modulus relationships, and different partial volume artefact correction for surface elements.

Method Name	Modulus-Density Relationship (MPa)	Densito-metric Range (g/cm ³)	Partial Volume Artefact Correction
NoShell	$E_0 = 6850 * \rho_{app}^{1.49}$ (Morgan et al. 2003)	all	None
Shell	$E_0 = 33900 * \rho_{ash}^{2.20}$ (Keyak et al. 1994)	$\rho_{ash} \leq 0.27$	0.4 mm thick 6-node shell elements with cortical properties added to the surface of the femur (Bessho et al., 2007).
	$E_0 = 5307 * \rho_{ash}$ (interpolation)	$0.27 < \rho_{ash} < 0.6$	
	$E_0 = 10200 * \rho_{ash}^{2.01}$ (Keller 1994)	$0.6 \leq \rho_{ash}$	

Table 2: Isotropic and orthotropic elastic constants used to construct the 3D stiffness tensor for each element. The constants E_0 , ν_0 , and G_0 are identical in both the isotropic and orthotropic models. In the isotropic case the constants are the same in each orthogonal plane, while in the orthotropic case they are scaled by the normalized eigenvalues m corresponding to the specific orthotropic plane.

Elastic constant	Isotropic	Orthotropic
E_{ii}	E_0	$E_0 m_i^2$
ν_{ij}	$\nu_0=0.3$	$\nu_0 m_i/m_j$
G_{ij} (i,j = 1,2,3)	$G_0 = \frac{E_0}{2(1 + \nu_0)}$	$G_0 m_i m_j$

Table 3: Correlation and linear regression between each FE model and experimental whole bone stiffness and strain gauge measurements.

Material Properties		Whole Bone Stiffness [N/mm]					External Strain Gauge [microstrain]				
		R ²	Slope	Intercept	RMSE%	Max Err%	R ²	Slope	Intercept	RMSE%	Max Err%
NoShell	Iso	0.72	1.30	246	26.43	56.68	0.90	1.21	43	19.95	57.75
	Aniso 1	0.71	1.37	113	27.66	63.83	0.87	1.20	42	21.6	64.84
	Aniso 2	0.72	1.40	-25	26.53	62.22	0.88	1.21	80	21.30	64.54
Shell	Iso	0.69	1.12	224	17.26	40.24	0.91	1.17	-93	18.77	59.99
	Aniso 1	0.69	1.18	103	18.45	46.61	0.89	1.15	-91	19.24	61.37
	Aniso 2	0.70	1.19	23	17.63	45.19	0.89	1.16	-70	19.24	60.76

Table 4: Previously published degrees of anisotropy (DA) from MIL analysis of human femoral bone cores scanned in microCT.

Study	Anatomic Location	N	Min	Max	Mean	SD
Charlebois et al., 2010	Femoral Head	44	1.403	2.147	1.679	0.161
Rincon-Kohli et al., 2009	Proximal Femur	28	1.641	2.642	1.641	0.241
Matsuura et al.,2008	Femoral Neck	100	1.17	3.22	1.97	0.38
Matsuura et al., 2008	Greater Trochanter	105	1.19	2.52	1.60	0.23