

Mapping the Multi-Directional Mechanical Properties of Bone in the Proximal Tibia

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The remodeling behavior of bone is influenced by its mechanical environment. By mapping bone's mechanical properties in detail, orthopedic implants with respect to its mechanical properties could stimulate and harness remodeling to improve patient outcomes. In this study, multiaxial apparent modulus and strength of cadaveric proximal tibial bone are mapped and predicted from computed tomography (CT) derived apparent density. Group differences are identified from testing order, subchondral depth, condyle, and sub-meniscal bone with covariates; age and gender. Axial modulus is 50% greater than the transverse modulus. Medial axial modulus is 30% greater than the lateral side. On the lateral side, axial modulus decreases by 50% from proximal to 25 mm distal. On the medial side, axial modulus remains relatively constant. Differences are quantified for density and multiaxial modulus across all subchondral depths, and different power law relationships are provided for each location. Density explains 75% of variation when grouped by subchondral depth and condyle. Yield strength is well-predicted across all test directions, with density predicting 81% of axial strength variation and no differences over subchondral depth. Quantified mapping of bone multiaxial modulus based on condyle and subchondral depth is shown for the first time in a clinically viable protocol using conventional CT.

This can explain desirable results such as bone formation within a scaffold and fracture healing as the activity of osteoblasts and osteoclasts are stimulated by localized strain gradients.^[1] It also explains undesirable results such as stress shielding and bone resorption.^[2] To optimize this natural mechanoresponse, it is critical to control the strain field in the bone.^[3] Strains of between 0.1% and 1% have been reported as the lower threshold of lamellar bone formation.^[1,4] To generate these desirable levels of strain in the bone, it is first necessary to know the stiffness tensor of bone as a relationship of Hooke's Law.

Measuring the mechanical properties of bone is made difficult given its structural anisotropy and mechanical heterogeneity.^[5] With such complex behavior it is useful to be able to simply express mechanical properties as a function of density, accounting for spatial variation and whether the bone is trabecular or cortical.^[6] This can be measured from quantitative computed tomography (qCT) imaging.^[7] A broad range of

1. Introduction

Bone is a remarkable dynamic material with coupled remodeling mechanisms closely linked to its strain response. These are well described as Frost's Mechanostat, Wolff's Law, and Perren's strain theory, all of which propose that bone mechanical properties can be influenced by its mechanical environment.

power-law models predicting apparent modulus from apparent density exist, however these are limited to uniaxial testing.^[8,9] Some authors have shown that consideration and quantification of orthotropic properties in the proximal tibia may be necessary to determine strains and regions of high strength more accurately.^[10,11] Comparing existing models for axial apparent modulus can yield variations in apparent modulus prediction of a factor of 15 even within the same anatomical site.^[12,13]

The proximal tibia is a site of popular interest for arthroplasty solutions, owing to the prevalence of osteoarthritis in the knee joint. Common successful procedures include total knee arthroplasty, partial knee arthroplasty, and tibial osteotomy. Although these procedures are all promising, the long-term function and implant stability are suboptimal as none of them take advantage of the mechanoresponse of bone and result in bone resorption, implant loosening, and failure.^[14,15] There may be an opportunity for these treatments to harness bone's natural mechanoresponse by invoking a localized increase in strain in the range of 1% to 8% to maintain or improve the quality of the bone in which they are placed.^[1] Implants with apparent modulus designed to control bone mechanobiology would benefit from improved prediction and refined knowledge of the spatial variation of multi-axial bone properties within the proximal tibia. This could be particularly useful for early intervention treatments that are likely to be revised in the patient's lifetime.

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Table 1. Summary of the calculated apparent density and measured apparent modulus and yield strength for all cubes, reporting median and (range) values.

Mechanical Property	Apparent density [mg cm ⁻³]	n	Test direction		
			X	Y	Z
Apparent modulus [GPa]	384 (106–957)	195	0.304 (0.053–1.302)	0.362 (0.021–1.49)	0.509 (0.081–1.50)
Yield strength [MPa]		194	1.81 (0.188–4.60)	1.57 (0.139–3.53)	2.97 (0.257–15.9)

In order to do this, it is necessary to understand and predict mechanical properties, such as apparent modulus and strength, in a clinically viable workflow.

The aim of this study is to provide a detailed map of multi-axial bone apparent modulus and strength in the proximal tibia. These data will enable the calculation of strain fields in the bone and the definition of implant mechanical properties that control strain and better enable the mechanoresponse of bone. Mechanical properties will be discussed in terms of their variation across the proximal tibia and their dependencies on apparent density and other factors.

2. Results and Discussions

Cubes were extracted from seven cadaveric human knees and a total of 195 measurements were collected for apparent modulus and 194 measurements were collected for yield strength across three subchondral depths in three test directions. Test directions were described by three mechanical axes: X along the posterior–anterior direction, Y along the medial–lateral direction and Z along the distal–proximal direction. Observed apparent density ranged from 106 to 957 mg cm⁻³. The range of observed values is summarized in Table 1.

2.1. Apparent Modulus

The apparent modulus depended on orientation (Table 1) and location in the tibia (Table 2). The following four sections quantify the differences and separate power law relationships for each direction and location.

2.1.1. Differences between Axial and Transverse Modulus

When all anatomical locations of cubes were pooled, all combinations of the three test directions for the apparent modulus data (Table 1) showed that the mean apparent modulus in the Z direction is 68% greater than that in the X direction ($p < 0.001$) and 40% greater than that in the Y direction ($p < 0.001$), through an independent sample *t*-test comparison. No difference was observed between mean apparent modulus in the X and Y direction ($p = 0.07$). Across the X, Y, and Z test directions, 100, 101, and 142 measurements for apparent modulus were made respectively from 195 cubes.

Table 2. Summary of *p*-values for apparent density and modulus of each group factor and the covariates; gender and age. Effect sizes: Medium $\dagger \eta^2 > 0.06$ and large $\ddagger \eta^2 > 0.14$. Statistical significance * $p < 0.05$, ** $p < 0.01$.

Factor	Apparent density	Apparent modulus		
		X	Y	Z
Subchondral depth ^{a)}	<0.001 $\ddagger$ **	<0.001 $\ddagger$ **	<0.001 $\ddagger$ **	0.001 $\ddagger$ **
Condyle ^{b)}	0.111	0.381	0.228	0.011 $\dagger$ *
Sub menisci ^{c)}	0.094	0.482	0.331	0.270
Order of testing ^{d)}	-	0.524	0.607	0.303
Gender ^{e)}	0.447	0.680	0.235	0.055
Age ^{f)}	0.802	0.546	0.458	0.121

^{a)}5, 15, 25 mm; ^{b)}medial, lateral; ^{c)}yes, no; ^{d)}1, 2, 3; ^{e)}male, female; ^{f)}32, 34, 41, 50, 59, 61, 65.

For data along all three directions, regression analysis showed that power-law models fit between apparent density and apparent modulus had good correlation, with at least 52% of variation explained by apparent density and root mean squared error (RMSE) of 0.05 MPa. Apparent modulus in the Z direction was most accurately predicted by apparent density for the observed data ($n = 139$) with $R^2 = 0.57$ and RMSE of 0.042 MPa. These models are summarized in Table S1, Supporting Information.

2.1.2. Modulus and Density Vary with Location in the Proximal Tibia

Apparent density and apparent modulus in all three tested directions differed across subchondral depths (Table 2). Similarly, whether the specimen was taken from the medial or lateral condyle had an effect on the apparent modulus in the Z direction. There were no differences between order of testing and whether the bone was beneath the menisci on the bone apparent density or apparent modulus across any test direction (partial $\eta^2 < 0.06$; Table 2). No differences were observed for the covariates specimen age or gender.

2.1.3. Multi-Axial Modulus Varies with Subchondral Depth

Mean apparent modulus in the X direction of bone in the most proximal slice was 2.7 times greater than bone 10 mm more distal and 3.1 times greater than that taken 25 mm below the tibial plateau. Mean apparent modulus in the Y direction of bone in the most proximal slice was 1.3 times greater than bone 10 mm more distal and 3.5 times greater than that taken 25 mm below the tibial plateau. Mean apparent modulus in the Z direction of bone in the most proximal slice was 1.59 times greater than bone 10 mm more distal and 1.6 times greater than that taken 25 mm below the tibial plateau (Figure 1). Within the data for each subchondral depth, variance in apparent modulus was well explained by apparent density as per the statistics in Tables S2 and S3, Supporting Information.

Apparent density-modulus relationships were formed for the collected data for X, Y, and Z apparent modulus, grouped by the significant factor, subchondral depth. Apparent density correlated well with apparent modulus across all test directions

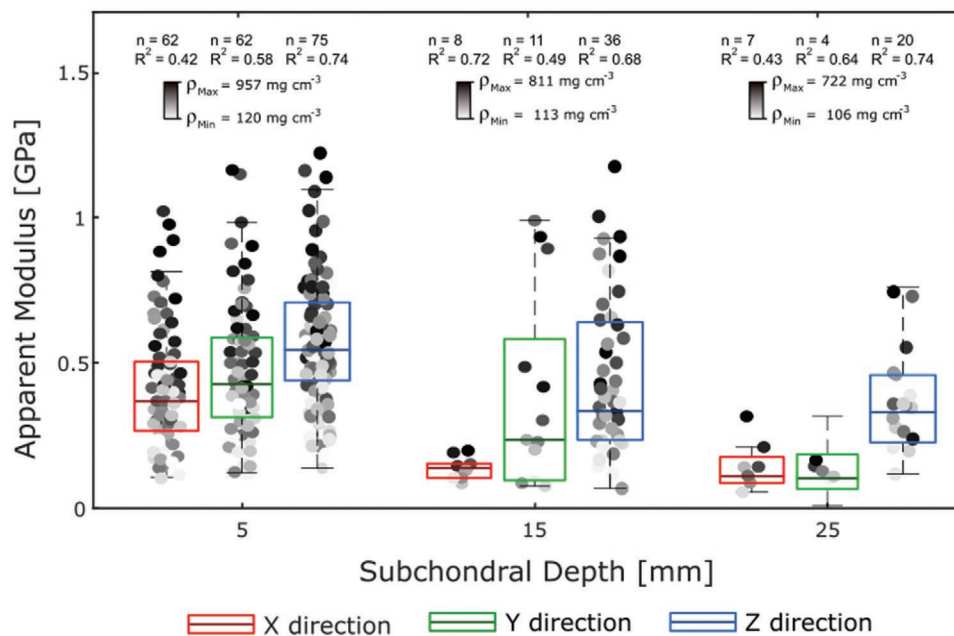


Figure 1. Boxplots for apparent modulus across all three test directions grouped by subchondral depth and pooled from both condyles, with modulus median and quartiles indicated. Marker colors correspond to apparent density, ranging from minimum (white) to maximum (black) density for each depth. n and R^2 values are indicated for density-modulus correlation.

(Figure 1). Relationships for apparent modulus in terms of apparent density in the X and Y directions explained at least 42% and 49% of the variations in apparent moduli in the respective directions. When grouped by subchondral depth, regression values increased to an average of 52% and 57% (Figure 1). A leave-one-out analysis indicated the model would work with a similar accuracy for additional samples (Tables S2, S3, and S4, Supporting Information). For both transverse test directions RMSE were comparable to models in literature (Tables S3 and S4, Supporting Information).

2.1.4. Axial Modulus Varies with Subchondral Depth and Condyle

Bone beneath the medial condyle proved on average to have an apparent modulus in the Z direction 33% more than bone of the same density beneath the lateral condyle ($p = 0.03$). Mean apparent modulus was observed to be relatively consistent in the medial condyle, with apparent modulus of bone in the most proximal slice being 7% greater than bone 10 mm more distal and 15% greater than bone 25 mm more distal (Figure 2a). For the lateral condyle, mean apparent modulus in the Z direction of bone in the most proximal slice was 64% greater than bone 10 mm more distal and 93% greater than bone 25 mm more distal (Figure 2b). Within these subgroups, apparent density was very well correlated to the apparent modulus as per the statistics in Figure 2 and Table S4, Supporting Information.

Apparent density-modulus relationships were formed for the collected data, grouped by the significant factors; subchondral depth and condyle. These relationships explained at least 64% of the variation in data with RMSE comparable to models in literature. Details of these models are summarized in Table S4, Supporting Information.

2.2. Yield Strength

None of the grouping parameters (order of testing, condyle, whether the bone was beneath the menisci) or covariates (age, gender) were significant in explaining any variation between subgroups in the data for strength in the X, Y, and Z directions. Yield strength was predicted in all three test directions, with at least 65% of variation explained by apparent density and RMSE of at most 3.2 MPa (Figure 3). In these power law relationships, axial strength was significantly more dependent on bone density than transverse strength, this is likely due to the greater range of loading which is seen along the axial direction compared to the transverse directions. Apparent modulus in the Z direction was most accurately predicted by apparent density for the observed data ($n = 33$) with $R^2 = 0.81$ and RMSE of 3.2 MPa. The power law relationships (Figure 4) provided predictive models and had the model parameters in Table S5, Supporting Information.

2.3. Comparison with Prior Work and Limitations of Study

To compare our data to prior work, we compared the power law relationships of seven previous studies to predict axial modulus from our CT measured density values (Figure 4). These predicted the apparent modulus value with R^2 correlation coefficients between 0.53 and 0.57 and RMSE between 106 and 5,500 MPa. Our findings align very closely to this—especially if a single power law is to describe the entire axial modulus/density relationship across the proximal tibia we get an R^2 value of 0.57 and RSME of 42 MPa. However, we improved the fit (R^2) in predictive models (Tables S2, S3, and S4, Supporting Information) by accounting for the condyle from which bone was

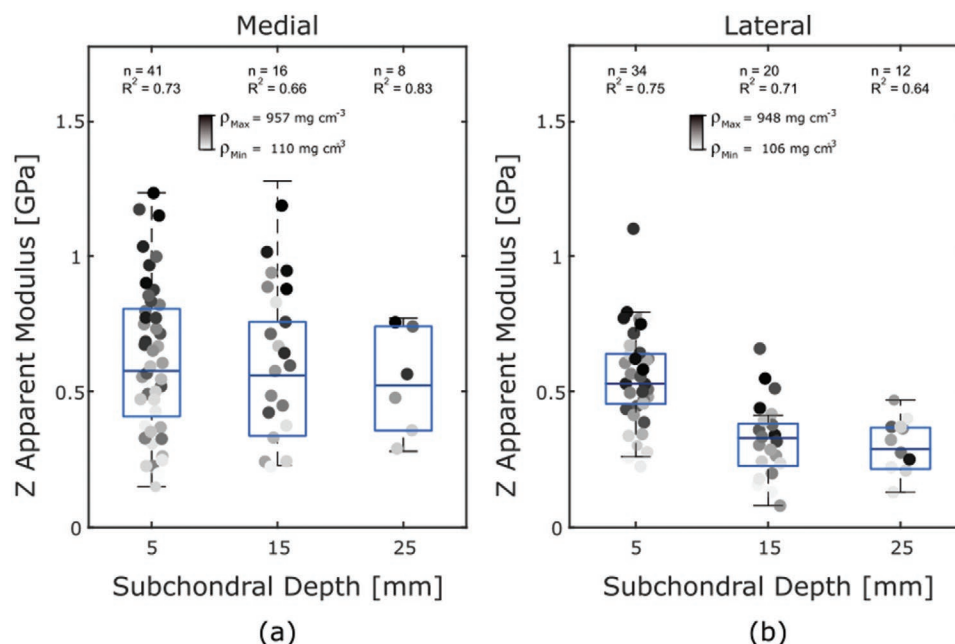


Figure 2. Boxplots for Z apparent modulus grouped by subchondral depth for the a) medial and b) lateral condyles, with modulus median and quartiles indicated. Marker colors correspond to cube apparent density, ranging from minimum (white) to maximum (black) density for each depth. n and R^2 values are indicated for density-modulus correlation.

taken, yielding power laws with R^2 of 0.75 and RSME of 34 MPa for the medial side and R^2 of 0.74 and RSME of 14 MPa for the lateral side. These data indicate that accounting for sample location within the tibia is needed to fully characterize behavior, but also there are some factors which cannot be detected in CT scans affect these properties. For example, bone apparent density, trabecular volume, modulus, strength, and strain energy are all affected by medication.^[16]

Axial (Z) apparent modulus of the proximal tibia has been recorded by numerous authors with values ranging from 2.5–3780 MPa which agrees well with our data.^[5,6,12,17–31] It is noted that a number of studies report apparent modulus to be significantly less or greater than our study, which may be due to differences in experimental method, small samples sizes of predominantly young males or inclusion of cortical bone regions within cubes.^[5,22,30,32,33] Studies such as those by

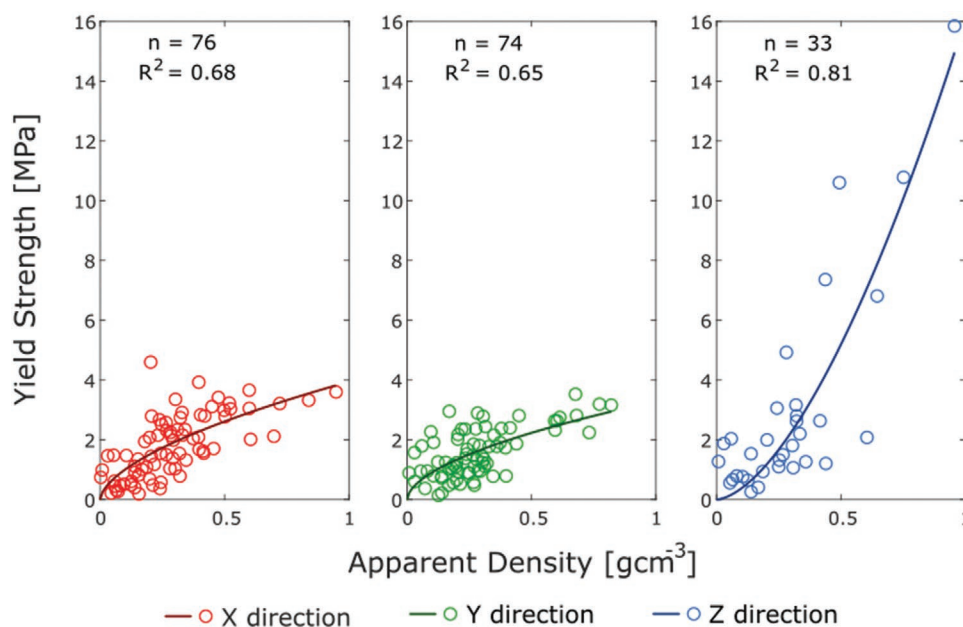


Figure 3. Yield strength against apparent density for direction X, Y, and Z.

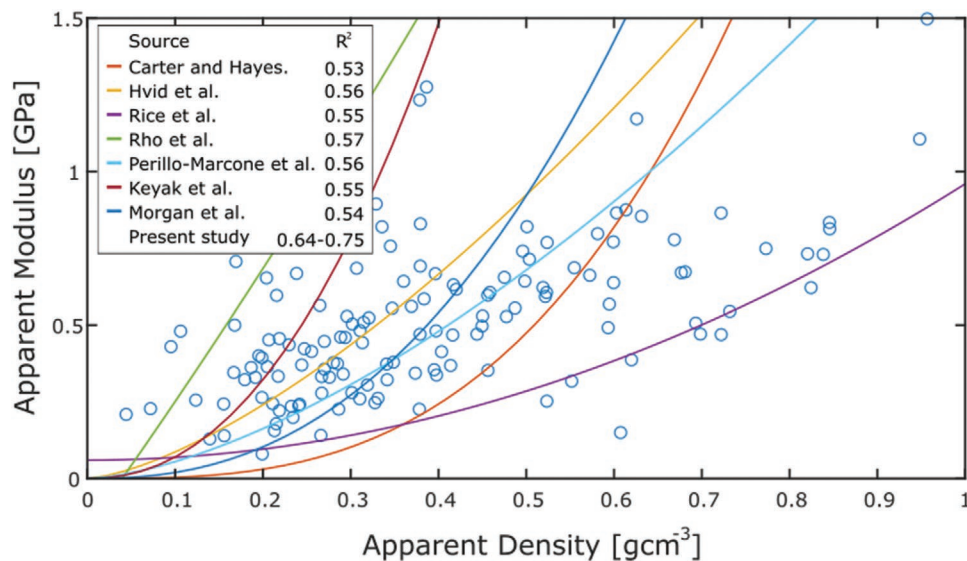


Figure 4. Commonly used power-law models for bone apparent modulus alongside their respective R^2 values for the observed data. Values for the present study refer to grouped data for each condyle and subchondral depth.

Johnston et al., Nazemi et al., and Ashman et al. have found apparent modulus from alternative methods (e.g., indentation testing, finite element simulations combined with neural networks or ultrasound testing). In all cases, the results were similar to that found here with from compression testing. Our findings, that there are differences in apparent modulus between the medial and lateral condyle are also supported in literature, but this has not previously been quantified.^[34,35] Previous work has also quantified orthogonal properties of the proximal tibia.^[18–22,35] Apparent modulus in the transverse directions is reported between 51 and 553 MPa with a degree of anisotropy ranging from 1.1 to 4.3, but this has not previously been analyzed for variation across the tibial plateau. The anisotropy and transverse moduli data observed here coincides with that in literature, as well as indicating that average anisotropy is greater on the medial side than the lateral side (1.9 and 1.4, respectively). Our study also introduces the relationships for transverse moduli in terms of apparent density from CT, the variation of transverse modulus with distal depth and a statistical comparison and quantification of the transverse and axial moduli.

There are limitations to consider from this study. First, the main limitation of the study is the data was generated from cadaveric specimens and assumes these properties translate to living bone. To minimize this limitation we used fresh frozen specimens, not embalmed or fixed in any way. Second, it is widely accepted that mechanical properties vary between males and females and it is noted that the effect of gender on the Z apparent modulus resulting from the analysis of variance (ANOVA) shown in Table 2 may be underpowered ($p = 0.055$) as the number of male donors was low compared to female donors.^[36] Third, it is noted that in addition to strain, the mechanoresponsiveness of bone depends patient biology and the power-law relationships found in this study may not account for differences in bone properties in patients with metabolic diseases which affect bone formation. Fourth, the resultant

power law exponent value was less than one, where previous work reported different values greater than one. This may be because all our specimens were <1.3 GPa and exclusively contained cancellous bone with no cortical, or higher stiffness cancellous volume included in the specimens.^[8,12] Previous literature suggests that apparent modulus and strength of bone correlate with fabric tensor data for the micro-structure, however no correlation between mechanical properties in the three orthogonal directions and corresponding fabric data was observed.^[24] This may be due to our clinically focused workflow which used clinical CT whereas the fabric tensor data is usually created from micro CT methods.^[37] Fifth, specimens had to be frozen once sliced into cubes and thawed before testing, however, the effects of this were mitigated by ensuring that the minimum number of freeze-thaw cycles were used and that all cubes from a given specimen were tested in the same testing session. There may also have been errors introduced by non-parallel cube geometry. We recorded errors in cube dimensions of $\pm 1.7\%$, but consistency of the observed data from this study and good comparison with results from literature suggests that the measures taken to generate specimen specific cutting guides were effective.

3. Conclusion

This study quantified the distribution of cancellous bone mechanical properties in the proximal tibia. The most important finding was that the orthotropic modulus and strength properties of the material as well as their dependence on location within bone have been quantified. Average apparent modulus and strength were 1.7 and three times higher in the axial direction compared to the transverse directions, respectively. In the dominant axial direction, the bone was 1.3 times stiffer in the medial condyle than the lateral condyle. This was because the proximal cancellous bone in the medial condyle had an elastic

modulus of 610 MPa that only decreased by 10% over a 25 mm distal depth. In contrast, the proximal cancellous bone in the lateral condyle had an elastic modulus of 562 MPa that decreased by 50% over the same 25 mm distal depth. This map of cancellous bone apparent modulus and strength in axial and transverse directions is required in order to design implantable devices that can safely harness the exciting potential and beneficial characteristics of bone's mechanoresponse. In this way bone remodeling could be stimulated to maintain healthy bone stock post-surgery.

This study also quantified the relationship between density and mechanical properties for cancellous bone in the proximal tibia. The best relationships were found in the axial direction where a power law relationship between apparent modulus and density yielded an R^2 of 0.75, but only after a different power law for the medial and lateral condyle was established. A good power law relationship between density and yield strength in the axial direction was measured with an R^2 coefficient of 0.81. These density/modulus and density/strength relationships enable mechanical properties to be calculated from conventional clinical CT scans in order to tailor any implantable device to influence the local strain distribution in the cancellous bone surrounding the device, whilst not exceeding its strength. Such a device could then take advantage of mechanoresponse to actively increase the strength and modulus of the bone into which it is implanted.

Knowledge of the spatial variation of multi-axial properties of bone within the proximal tibia allows for improved prediction of bone mechanical properties and strain. This is a crucial part of the development of implants with apparent modulus designed to harness bone mechanoresponse. Such treatments could be particularly useful for early intervention treatments that are likely to be revised in the patient's lifetime.

4. Experimental Section

Sample Preparation: Cadaveric human tissue in this study was obtained from seven donors with no prior lower limb pathologies, traumas, surgeries or osteoarthritis (age = 34–65 years; sex = five females, two males; side = four left knees; three right knees). Tissue was frozen within 24 h post-mortem; and were thawed and denuded to the bone prior to the experiments. Ethical permission was granted by the Imperial College Healthcare Tissue Bank Review Committee under a UK Human Tissue Authority License 12 275.

A conventional CT scanner (SOMATOM Definition AS; SIEMENS AG) was used to image all specimens using a clinical imaging protocol (512 × 512 resolution, 140 kVp, 0.6 mm slice thickness, ≈0.5 mm pixel spacing). A 5-material calibration phantom (Model 3; Mindways Software Inc.) was placed under the specimens for bone mineral densitometry and was visible on each CT slice. Following scanning, 3D models of the specimens were segmented from the scan slices using image processing software (Mimics, Materialise) as in **Figure 5a**.

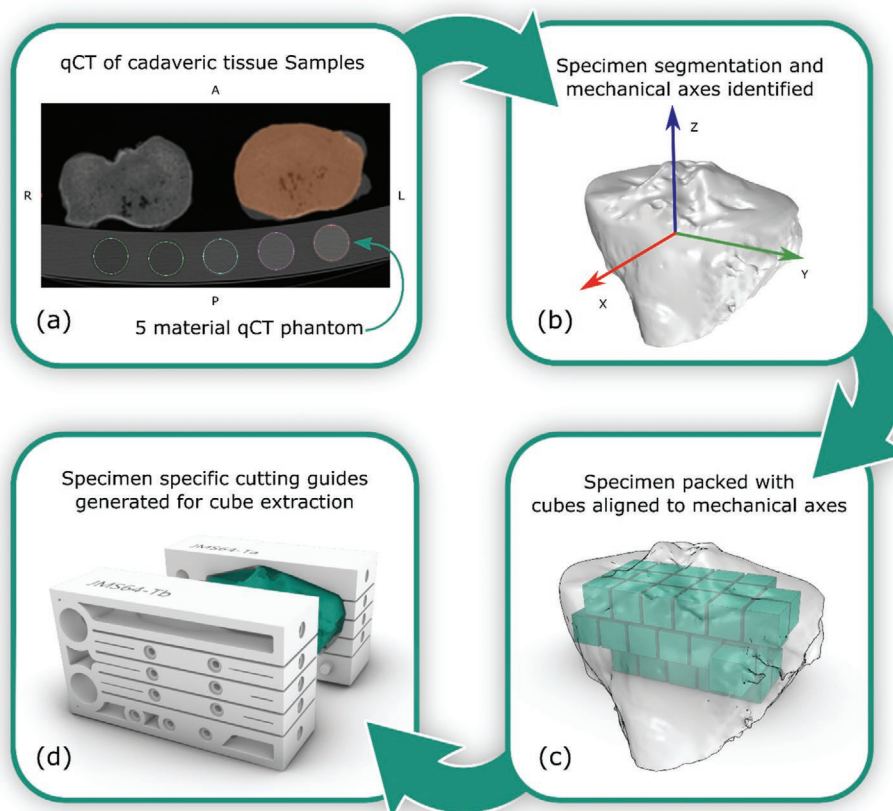


Figure 5. a) Segmented CT scan of two tibia specimens with a five-material calibration phantom. b) Mechanical coordinate frame defined for each specimen with axes based on anatomical landmarks. c) Three layers of cubes (green) packed within the specimen and aligned to the mechanical axes. d) Specimen specific guides to secure each specimen (green) during cutting.

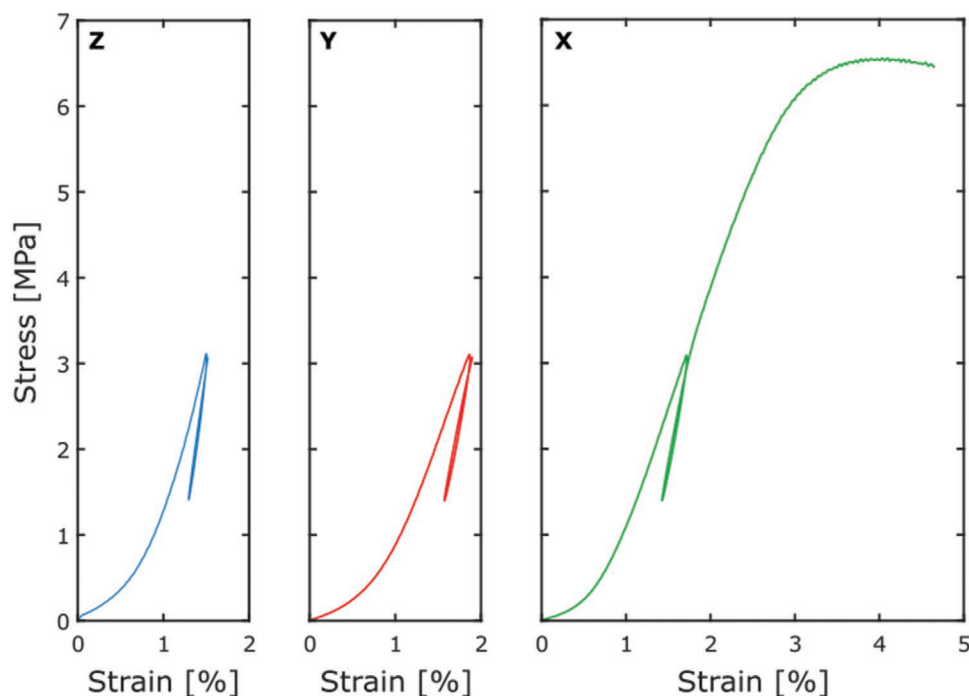


Figure 6. Stress–strain traces for one sample tested in the all three directions in the order; Z, Y, X. Hysteresis loops were taken between σ_{40} and σ_{20} and the sample was yielded on the final test.

Each sample was optimally packed with 9 mm side length cubes aligned to the mechanical axes of the tibial specimens using Rhinoceros 6 and Grasshopper (Robert McNeel & Associates), shown in Figure 5b,c.^[38] The coordinate axis of each specimen was set at the center of the tibial plateau with the X (posterior–anterior), the Y (medial–lateral), and Z axes (distal–proximal) aligned to a conventionally defined vector system.^[38] Specimen specific cutting guides, as in Figure 5d, were generated to fit to each 3D bone surface model to allow the accurate removal of cubes from the proximal tibia over three subchondral depths below the tibial plateau.

Cutting guides were additively manufactured in medical grade nylon (PA 2200) using an industrial 3D printer (P110,EOS). Tibial specimens were clamped in their respective cutting guides and cubes cut from them with a pathology saw (Exakt, Oklahoma, US) along predetermined slots with no fine grinding. Cubes were measured to have mean side lengths of 8.90 ± 0.15 mm. In total, 195 cubes were extracted from the seven specimens (Table S6, Supporting Information).

The cubes had dimensions chosen to comply with existing protocols for testing porous structures.^[8,39] Cubes were removed from both the medial and lateral sides of the proximal tibia, across three layers of material spanning material 30 mm below the tibial plateau.

Specimens were kept in gauze saturated in phosphate buffered saline (PBS), to ensure they were hydrated at all times, and stored at -30 °C until mechanical testing.^[39]

Quantifying Bone Density from CT Scan: Inclusion of a phantom in the CT scans allowed for a robust calibration of qCT Hounsfield units (HU) to apparent density. This process followed previous methods whereby regression of the HU values for the phantom materials in the scan and the known densities of the phantom results in a linear relationship between HU and calibrated density ρ_{CT} when water content and displaced volume of phosphate in the phantom was accounted for.^[7,40] This calibration yields calibrated density values independent of any imaging settings used during imaging. Ash density and subsequently apparent density can be determined from the calibrated density as per Equations (1) and (2).^[41,42]

$$\rho_{Ash} = 1.22\rho_{CT} + 52.6 \quad (1)$$

$$\rho_{App} = 1.64\rho_{Ash} + 10 \quad (2)$$

Each voxel was allocated to its relative position inside its cube by importing 3D models of each cube into the CT image processing software and masking out the enclosed region. Voxel meshes for calibrated density of each of the cubes were extracted from these CT masks. The apparent density of bone mineral for each cube was determined by averaging across this voxel mesh applying Equations (1) and (2). There was a good correlation between the calculated CT apparent density (using Equations (1) and (2)) and measured apparent density (by measuring the cubes with a digital caliper and weighing) (Figure S1, Supporting Information).

Mechanical Testing: A materials testing machine (Instron 8872) with a 10-kN load cell was used to perform quasi-static compression testing at an extension rate of 2 mm min^{-1} , which corresponds to a strain rate within standard limits.^[39]

Displacement was measured using linear variable differential transformers attached to the testing platens to reduce any compliance effects from the test apparatus. A sampling rate of 30 Hz was used. The platens of the machine were lubricated to reduce any frictional effects. Stress–strain curves were obtained using the individual macro dimensions of each specimen.

An initial sample of specimens from another specimen donor was tested in the Z direction to failure to establish a relationship between density and yield stress of the cubes. Cubes were tested in all three orthogonal directions (X, Y, Z) sequentially with randomized order of test directions. A preliminary dataset was compressed to 50% strain at 2 mm min^{-1} to find the required reference yield stresses for each cube based on its apparent density. Preliminary testing established that testing up to 40% of the yield stress would not affect the results for elastic modulus or yield strength when testing subsequent directions. The loading regime included a hysteresis loop to account for settling in behavior of the initial toe region within the porous structure. For half of the cubes, this was carried out from 40% of the cube's yield stress (σ_{40}), to 20% of its yield stress (σ_{20}), and then back to σ_{40} . Specimens were tested in this way along each test direction, with the last test of each specimen undergoing a hysteresis loop from σ_{40} to σ_{20} and then being taken to failure as per the traces (Figure 6).

The elastic moduli were then calculated using a linear regression analysis of the hysteresis loop. Yield strength was determined as the 1% offset stress.

In total 343 data points were recorded for apparent modulus, 100 tested in the X direction, 101 in the Y direction, and 142 tested in the Z direction. Similarly, for yield stress, 183 data points were recorded, 76 in the X direction, 74 in the Y direction, and 33 in the Z direction.

Statistical Analysis and Model Fitting: Multiple one-way ANOVA tests were performed to determine which group factors significantly affected the target variables.^[43] The group factors considered for main effects were order of testing, subchondral bone depth, which condyle the specimen was taken from and its location in the metaphyseal cortex, with specimen age and gender as covariates. Target dependent variables were the apparent density and both apparent modulus and strength each in the X, Y, and Z direction. Independent sample *t*-tests were used to determine whether the differences between the three test directions, for apparent modulus and strength, were statistically significant. Holm–Bonferroni post-hoc tests were applied to correct significance values. Significance was indicated by a *p* value <0.05, with partial eta squared values to indicate small (partial $\eta^2 > 0.01$), medium ($\eta^2 > 0.06$), and large ($\eta^2 > 0.14$) effect sizes.

Of the 195 extracted cubes, sequential testing of each direction resulted in 100, 101, and 142 data points for apparent modulus in the X, Y, and Z directions respectively. Similarly, for yield strength, 76, 74, and 33 data points were collected in the X, Y, and Z directions respectively. Based on this data, the commonly implemented power law relationships predicting apparent modulus and strength in terms of apparent density were fit for each test direction, grouped by those variables which proved to be significant in the ANOVA. A leave-one-out cross validation was performed on each power-law relationship to determine sensitivity of the data to the specific datasets which were used.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

anatomical mapping, bone, mechanical properties, mechanobiology

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