Ji Wang

Bone Bioengineering Laboratory,
Department of Biomedical Engineering,
Columbia University,
New York, NY 10027

Bin Zhou

Bone Bioengineering Laboratory,
Department of Biomedical Engineering,
Columbia University,
New York, NY 10027

Yizhong Jenny Hu

Bone Bioengineering Laboratory,
Department of Biomedical Engineering,
Columbia University,
New York, NY 10027

Zhendong Zhang

Bone Bioengineering Laboratory,
Department of Biomedical Engineering,
Columbia University,
New York, NY 10027;
Department of Orthopedic Surgery,
First Affiliated Hospital,
School of Medicine,
Shihezi University,
Shihezi, Xinjiang, China

Y. Eric Yu

Bone Bioengineering Laboratory,
Department of Biomedical Engineering,
Columbia University,
New York, NY 10027

Shashank Nawathe

Orthopaedic Biomechanics Laboratory,
Department of Mechanical Engineering,
University of California,
Berkeley, CA 94720

Kyle K. Nishiyama

Division of Endocrinology,
Department of Medicine,
Columbia University,
New York, NY 10032

Tony M. Keaveny

Orthopaedic Biomechanics Laboratory,
Department of Mechanical Engineering,
University of California,
Berkeley, CA 94720

Elizabeth Shane

Division of Endocrinology,
Department of Medicine,
Columbia University,
New York, NY 10032

X. Edward Guo¹

Bone Bioengineering Laboratory,
Department of Biomedical Engineering,
Columbia University,
351 Engineering Terrace,
New York, NY 10027
e-mail: exg1@columbia.edu

Accurate and Efficient Plate and Rod Microfinite Element Models for Whole Bone Segments Based on High-Resolution Peripheral Computed Tomography

The high-resolution peripheral quantitative computed tomography (HR-pQCT) provides unprecedented visualization of bone microstructure and the basis for constructing patient-specific microfinite element (μ FE) models. Based on HR-pQCT images, we have developed a plate-and-rod μ FE (PR μ FE) method for whole bone segments using individual trabecula segmentation (ITS) and an adaptive cortical meshing technique. In contrast to the conventional voxel approach, the complex microarchitecture of the trabecular compartment is simplified into shell and beam elements based on the trabecular plate-and-rod configuration. In comparison to voxel-based μ FE models of μ CT and measurements from mechanical testing, the computational and experimental gold standards, nonlinear analyses of stiffness and yield strength using the HR-pQCT-based PR μ FE models demonstrated high correlation and accuracy. These results indicated that the combination of segmented trabecular plate-rod morphology and adjusted cortical mesh adequately captures mechanics of the whole bone segment. Meanwhile, the PR μ FE modeling approach reduced model size by nearly 300-fold and shortened computation time for nonlinear analysis from days to within hours, permitting broader clinical application of HR-pQCT-based nonlinear μ FE modeling. Furthermore, the presented approach was tested using a subset of radius and tibia HR-pQCT scans of patients with prior vertebral fracture in a previously published study. Results indicated that yield strength for radius and tibia whole bone segments predicted by the PR μ FE model was effective in discriminating vertebral fracture subjects from nonfractured controls. In conclusion, the PR μ FE model of HR-pQCT images accurately predicted mechanics for whole bone segments and can serve as a valuable clinical tool to evaluate musculoskeletal diseases.

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¹Corresponding author.

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Introduction

High-resolution peripheral quantitative computed tomography (HR-pQCT) is an exciting new technology in the field of musculoskeletal imaging. It provides unprecedented three-dimensional (3D) visualization of the human bone at limited radiation for in vivo scanning. The XtremeCT I (Scanco Medical AG, Bassersdorf, Switzerland) system, for instance, can achieve an isotropic voxel size of $82\text{ }\mu\text{m}$, resolving fine details in cortical and trabecular microstructure that allow for accurate and reproducible morphological measurements [1–5]. Despite its recent development, HR-pQCT has already demonstrated unprecedented utility in analyzing bone microstructure and biomechanics in clinical studies of musculoskeletal diseases such as osteoporosis [6–13].

Characterized by deterioration in bone microstructure and compromised bone strength, osteoporosis is a global health concern. Vertebral fragility fracture alone, just one manifestation of osteoporosis, contributes significantly to the increased mortality rate in the population [14]. Currently, osteoporotic fracture risk is solely assessed by measuring areal bone mineral density (aBMD) using dual-energy X-ray absorptiometry (DXA) [15]. However, bone strength is not only dependent on density and mineral content, but also dictated by bone geometry, as well as cortical and trabecular microarchitecture [16,17]. Indeed, recent HR-pQCT studies have identified that bone microstructural changes associated with osteoporosis can predispose patients to fracture, and can serve as additional predictors of fracture risk independent of aBMD [18–20]. Specifically, using individual trabecula segmentation (ITS), an advanced and quantitative algorithm that decomposes the trabecular microstructure into a collection of individual trabecular plates and rods [21], reductions in the volume, number, and connectivity of trabecular plates were found in fracture subjects regardless of changes in aBMD [11]. These plate and rod trabecular parameters were also found to be better predictors of mechanical competence than overall bone volume fraction [21].

Another exciting advancement made possible by the HR-pQCT is the ability to create 3D patient-specific microfinite element

(μ FE) models that allow clinicians to directly predict the mechanical competence of bone and implement appropriate intervention treatments [22]. From HR-pQCT images of trabecular subvolumes and whole bone segments, μ FE models have been generated to assess patient-specific mechanical properties. These models have shown excellent predictive power at the distal radius and tibia compared to experimental (mechanical testing) and computational (μ CT-based μ FE analysis) gold standards [5,8,23,24]. Studies of fragility fracture using HR-pQCT-based μ FE models have also identified reduced bone stiffness that can effectively distinguish fracture subjects [23].

The conventional approach for image-based μ FE analyses is direct conversion of image voxels to elements [25]. Although this voxel-based approach rigorously preserves the original microstructure, the resulting models may contain hundreds of millions of elements and require prohibitive computation time and costs [22]. More importantly, the ability of these models to compute yield strength, a property directly related to bone's resistance to fracture, is significantly limited by the large model size arising from the voxel-based meshes. Biomechanically, although bone exhibits fully linear behavior upon initial loading, accumulation of microstructural damage as the tissue strains results in yielding and reduced tissue modulus prior to failure [26]. Accurate computation of yield strength from μ FE models require nonlinear analyses based on assumptions of more complex constitutive laws, at the cost of taking days to weeks to compute [5,22,27–29], significantly limiting the clinical application of HR-pQCT-based nonlinear μ FE analysis. Several recent studies have attempted to address this issue by estimating yield strength based on linear analysis. Pistoia et al. constructed linear models of simple axial compression tests, and estimated yield strength by assuming a critical strain limit. Although the technique offered improved correlation to yield strength measured from mechanical testing in comparison to aBMD, accuracy was still lacking compared to nonlinear simulations [30]. Using homogenized models, Hosseini et al. similarly developed a technique to estimate yield strength based on the

Fig. 1 (a) Radius and tibia segments subjected to HR-pQCT and μ CT scanning. (b) Illustration of mechanical testing setup. (c) Construction of μ FE models using the voxel-based and PR-based meshing techniques.

homogenization method. Their results demonstrated excellent agreement between linearly computed yield strength, nonlinearly computed yield strength, and mechanical testing results while achieving significant reduction in computation time. However, the technique was highly dependent on the subvolume assessment of bone volume fraction and fabric tensor across specimens [31]. In addition, the homogenized procedure does not allow easy and direct quantitative assessments of mechanical parameters in individual trabeculae. With the enhanced image resolution of the second-generation HR-pQCT and potential applications to new sites such as the knee [32–34], the need to improve efficiency for nonlinear HR-pQCT-based μ FE analyses is immense.

The recent development of the trabecular plate and rod (PR) μ FE modeling technique based on ITS offers an alternative approach that may address this problem. By meshing the decomposed trabecular plates and rods with shell and beam elements, the PR μ FE approach achieved significant reductions in model size and computation time for nonlinear analyses of trabecular bone [21,35–37]. Predictions from PR models based on μ CT images of trabecular subvolumes highly agreed with mechanical testing results at the proximal tibia, femoral neck, and greater trochanter [35]. Furthermore, application of the PR approach to HR-pQCT trabecular images in a clinical study of vertebral fracture showed promising results in discriminating postmenopausal vertebral fractures despite the reduced resolution [36]. This technique, however, has been limited to analyzing the trabecular bone, despite the significant contributions of cortical bone to whole bone mechanics [38–41]. Due to the high density of cortical bone, however, model size for whole bone segments, incorporating both the trabecular and cortical bone, would be substantially larger. The distinctive microstructure of the trabecular bone and cortical bone would also require separate meshing procedures for each compartment and reattachment of the meshes, introducing additional complexity.

The goal of this study was therefore to develop and validate a computationally efficient (reduced computation time and model size) μ FE modeling approach for whole bone segments based on the PR approach. Its accuracy in predicting nonlinear mechanical properties based on HR-pQCT scans will be examined relative to the computational and experimental gold standards using human radius and tibia specimens. The ability of these models to identify bone changes from in vivo HR-pQCT scans of the radius and tibia will also be tested using a subset of data from a previously published study of vertebral fracture. We hypothesize that modeling whole bone segments using the PR μ FE technique will accurately and efficiently predict stiffness and yield strength, as well as effectively distinguish vertebral fracture status in postmenopausal women.

Materials and Methods

Specimen Preparation. Thirty sets of radius and tibia bones from the same donors (72 ± 11 yr old, 15 male/15 female) were obtained from the Life Legacy Foundation (Tucson, AZ). Contact X-ray radiography was performed by placing the specimens on the X-ray film to ensure that no fractures were present. A 9.02 mm bone section along the axial direction at the distal end was extracted from each radius and tibia, corresponding to the standard scanning region in clinical HR-pQCT. The bone segments were cut using a band saw, with the specimens secured in a customized clamping jig that ensures precise cutting and alignment between the two end surfaces of the segment. The cutting surfaces were polished using sandpaper to remove unevenness at both ends. The specimens were wrapped in wet gauze and stored in airtight plastic bags at -20°C between procedures for preservation of biomechanical properties [42–44].

Image Acquisition. Each radius and tibia segment was first scanned by HR-pQCT (XtremeCT I, Scanco Medical AG,

Fig. 1(a)) using clinical settings (60 KVp, 1 mA, 100 ms integration time). Bone segments were immersed in saline solution during HR-pQCT scanning to simulate in vivo conditions. The reconstructed images had an isotropic voxel size of $82\ \mu\text{m}$. Each segment was then wrapped in gauze and scanned by μ CT (μ CT 80, Scanco Medical AG, Fig. 1(a)) using ex vivo settings (70 KVp, $114\ \mu\text{A}$, 700 ms integration time). The reconstructed μ CT images had an isotropic voxel size of $37\ \mu\text{m}$.

The cortical and trabecular compartments were automatically segmented from the HR-pQCT and μ CT scans using a validated custom method implemented in Image Processing Language (IPL V5.07, Scanco Medical AG) [45]. A specimen-specific threshold was then applied to convert the grayscale images into binary images. For the HR-pQCT scans, the threshold was selected according to the standard patient evaluation protocol: a Laplace–Hamming filter was applied, and a fixed value of 40% of maximal gray-scale value of the filtered images was used [3]. For the μ CT scans, the minimum between the bone and bone marrow peaks was visually determined from the voxel grayscale value histogram by three researchers independently, and the average of the three chosen thresholds was used [21,43].

Mechanical Testing

After HR-pQCT and μ CT imaging, uniaxial compression tests were performed to directly measure mechanical properties of the radius and tibia whole bone segments (Fig. 1(b)). Using a material testing system (MTS 810, MTS, Eden Prairie, MN), bone segments were loaded to 0.5 mm displacement following three cycles of preconditioning with a loading speed of 5 mm/min. An extensometer (MTS 634.11F-24) was attached at the compression platens to directly measure the displacement between the two end surfaces of the specimens. Load force was measured using a 100 kN load cell (MTS 661.20E-03). Stiffness was calculated from the linear region of the load–displacement curve, and yield strength was determined using the 0.2% offset technique for comparison with the nonlinear μ FE predictions [26].

Voxel-Based Microfinite Element Models of Whole Bone Segments. The voxel-based μ FE models were first constructed from the HR-pQCT and μ CT images for each radius and tibia bone segment (Fig. 1(c)). Each bone voxel in the cortical bone and trabecular bone compartment was converted to an eight-node brick element. Therefore, each element had a side length of $82\ \mu\text{m}$ for the HR-pQCT-based models and $37\ \mu\text{m}$ for the μ CT-based models. Each model was subjected to nonlinear FE analyses using the Finite Element Analysis Program (FEAP, Berkeley, CA) implemented into the super-computation system at Texas Advanced Computing Center (Stamper, Austin, TX). During the simulation, each model was loaded at the distal end to a displacement equal to 1.2% apparent strain along the axial direction, while the proximal end was imposed with zero axial displacement [26]. The bone tissue constitutive law was prescribed based on the rate-independent elasto-plastic material model that incorporates geometric large deformations and material nonlinearity [46,47]. Tissue elastic modulus and Poisson’s ratio were defined as 15 GPa and 0.3, respectively [48]. The tissue-level yield strains were assumed to be 0.33% in tension and 0.81% in compression [49]. The postyield tissue modulus was reduced to 50% of the original modulus. Stiffness was calculated from the linear region of the force displacement curve, and yield strength was calculated using the 0.2% offset technique [26] (Fig. 1(c)).

Plate and Rod Microfinite Element Models of Whole Bone Segments. A PR μ FE model was then generated from each HR-pQCT image (Fig. 1(c)). The segmented trabecular bone compartment was first subjected to ITS decomposition and meshed with shell and beam elements according to previously established

Table 1 Prediction of stiffness and yield strength by HR-pQCT-based PR μ FE model in comparison to three reference methods: the HR-pQCT voxel-based model, the μ CT voxel-based model, and results from mechanical testing

	HR-pQCT PR model	HR-pQCT voxel-based model	μ CT voxel-based model	Mechanical testing
Radius				
Stiffness (N/mm)	66,555 $\pm$ 26,940	64,468 $\pm$ 24,925	54,408 $\pm$ 22,968 ^a	53,146 $\pm$ 23,251 ^a
Yield strength (N)	3715 $\pm$ 1594	3508 $\pm$ 1431	2601 $\pm$ 1171 ^a	4165 $\pm$ 1688 ^a
Tibia				
Stiffness (N/mm)	158,509 $\pm$ 50,227	155,767 $\pm$ 53,774	122,988 $\pm$ 47,139 ^a	136,763 $\pm$ 57,688
Yield strength (N)	9050 $\pm$ 2944	8900 $\pm$ 3200	7248 $\pm$ 2822 ^a	10,236 $\pm$ 4273 ^a

Note: Data are shown as mean $\pm$ SD.

^a $p < 0.05$ for paired t -test between the HR-pQCT-based PR μ FE model and this reference method.

Fig. 2 Linear regressions of stiffness and yield strength between HR-pQCT-based PR model and ((a) and (b)) HR-pQCT voxel-based model, ((c) and (d)) μ CT voxel-based model, and ((e) and (f)) mechanical testing for pooled data at the distal radius and tibia

procedures [21,35]. Briefly, the trabecular bone underwent an iterative thinning process and was converted to a surface-curve skeleton. The entire skeleton was then decomposed into individual plates and rods with every voxel uniquely classified as inner plate, plate edge, inner rod, rod end and junction points [50,51]. In addition, shape-refining nodes were identified from the key turning points on plate edges and rod curves, providing finer meshing of the trabecular plates and rods. Eventually, each trabecular rod was meshed into beam elements with circular cross section, connected to neighboring elements via two nodes. A curvy rod was further divided into several beams by the key turning points on the rod curve to preserve the original curvature. Each trabecular plate was meshed into multiple triangular shell elements through Delaunay triangulation [52], identified by the node set of plate–plate junction, plate–rod junction, plate–edge junction, and turning points on the plate edges. The thickness of each trabecular plate and the diameter of each trabecular rod were further calculated from its volume divided by the total area of shell elements or total length of beam elements, respectively. Each shell and beam element was then assigned a corresponding thickness or cross-sectional

diameter, preserving the original volume of each trabecula. The segmented cortical bone compartment was coarsened twofold to 164 μm voxel size to further reduce model size. Each coarsened voxel was then converted into an eight-node brick element. Finally, to combine the two compartments, nodes from the shell and beam elements on the outer surface of the trabecular bone mesh were reconnected to the closest nodes on the inner surface of the cortical bone mesh. The location of the cortical nodes was slightly adjusted to meet the closest trabecular element to ensure connectivity of elements, but the overall structure on the intracortical surface was preserved as much as possible. The combined bone segment PR μFE models were implemented in ABAQUS 6.10 (Dassault Sytemes USA, Waltham, MA) and subjected to nonlinear FE analyses. An axial compression test up to 1.2% apparent strain was simulated. The tissue elastic modulus, shear modulus, and Poisson's ratio for the shell and beam elements were 15 GPa, 7 GPa, and 0.3, respectively [48]. Boundary conditions and postyield behavior were kept consistent with the voxel-based models. Stiffness and yield strength were determined from the force–displacement curves, as described above.

Fig. 3 Bland–Altman plots of stiffness and yield strength between HR-pQCT-based PR model and ((a) and (b)) HR-pQCT voxel-based model, ((c) and (d)) μCT -voxel-based, and ((e) and (f)) mechanical testing for pooled data at the distal radius and tibia

Table 2 Comparison of model size and computation time between the PR μ FE models and voxel-based μ FE models based on HR-pQCT images

	# Trabecular element	# Cortical element	# Whole bone segment element	Central processing unit hours
Radius				
PR model	26,567 $\pm$ 12,523	95,754 $\pm$ 33,272	122,321 $\pm$ 40,505	1.64 $\pm$ 1.20
Voxel-based model	882,878 $\pm$ 380,907	766,033 $\pm$ 266,179	1,648,911 $\pm$ 555,954	36.74 $\pm$ 12.71
Tibia				
PR model	72,681 $\pm$ 28,625	165,695 $\pm$ 68,181	238,376 $\pm$ 81,029	5.87 $\pm$ 5.80
Voxel-based model	2,328,900 $\pm$ 845,229	1,325,563 $\pm$ 545,448	3,654,463 $\pm$ 1,122,342	78.60 $\pm$ 24.90

Note: Data are shown as mean $\pm$ SD.

Distinguishing Vertebral Fracture With Plate and Rod Microfinite Element Models of Whole Bone Segments. The ability of the PR μ FE models to identify differences in whole bone segments from clinical HR-pQCT scans was tested using a subset of data from a previously conducted study of vertebral fractures in postmenopausal women [11,19,20]. In this study, 45 vertebral fracture subjects and 45 nonfracture controls (age- and gender-matched) were included. Briefly, postmenopausal women (more than 10 years postmenopause or over the age of 60 years) were recruited at the Columbia University Medical Center (CUMC; New York, NY) or Helen Hayes Hospital (HHH West Haverstraw, NY). Subjects with a history of low-trauma vertebral fracture that occurred after menopause or were found to have vertebral fractures by spine X-ray were included as fracture cases. Subjects with no history of fracture at any site or vertebral deformity confirmed by lateral radiograph were included as control. Exclusion criteria for both fracture and control group included any history of metabolic bone diseases or bone cancers, or drug exposures that could affect bone metabolism. From these subjects, aBMD was measured by DXA (QDR-4500, Hologic, Inc., Walton, MA at CUMC; Lunar Prodigy, GE, Pewaukee, WI at HHH) at multiple sites including the total hip and ultradistal radius. Standard HR-pQCT (XtremeCT I, Scanco Medical AG) images of the nondominant distal radius and tibia were acquired at CUMC as previously described [1,8,20]. From the reconstructed 3D HR-pQCT images, PR μ FE models were created for whole bone segments as described in the Plate and Rod Microfinite Element Models of Whole Bone Segments section to compute stiffness and yield strength. Model predictions were compared between fracture and nonfracture groups. All subjects provided written informed consent and the Institutional Review Board of Columbia University Medical Center approved this study.

Statistical Analyses

Statistical analyses were performed using the NCSS software (NCSS 2007, NCSS Statistical Software, Kaysville, UT). In the ex vivo validation section, data are presented as mean $\pm$ standard deviation (SD). Stiffness and yield strength predicted by PR models were correlated with those derived from voxel-based models and measured from mechanical testing experiments. Paired *t*-test was used to examine differences between the HR-pQCT-based PR

model predictions and each reference method. Two-sided *p*-values < 0.05 were considered to indicate statistical significance. To assess agreement of the HR-pQCT-based PR model to the three reference methods, HR-pQCT voxel-based model, μ CT voxel-based model, and mechanical testing, Bland–Altman plots were constructed to observe the relative difference between HR-pQCT-based PR model results and each reference method. Differences are presented as ratios, calculated by (HR-pQCT-based PR method-reference method)/(mean of HR-pQCT-based PR method and reference method), and plotted against the mean. The 95% confidence intervals (CI) were calculated from the mean relative error ± 1.96 SD.

In the vertebral fracture section, data are presented as mean $\pm$ standard error of the mean (SEM). Differences in stiffness and yield strength between fracture and nonfracture subjects were assessed by Student's *t*-test. Analysis of covariance was further used to evaluate differences at the radius or tibia after adjustment for aBMD *T*-score at the ultradistal radius or total hip, respectively. Two-sided *p*-values < 0.05 were considered to indicate statistical significance. Odds ratios (OR) per SD were calculated by performing logistic regression analysis to estimate the relative risk of fracture associated with parameters predicted by PR models. Fracture status was the dependent variable, while stiffness and yield strength were the potential predictors. The ability of the PR model predictions in discriminating fracture status in comparison to and in combination with aBMD and ITS morphological parameters, published previously [11], were assessed by calculating area under the curve (AUC) from receiver operating characteristic (ROC) analysis. In this type of analysis, higher AUC indicate enhanced ability to discriminate an outcome.

Results

Plate and Rod Models Accurately Predicted Stiffness and Yield Strength. Predictions of stiffness and yield strength at the distal radius and tibia from HR-pQCT images were indistinguishable between the PR models and voxel-based models (Table 1). Strong correlations were found between these two methods for pooled data from the two sites (stiffness: $R^2 = 0.9373$, Fig. 2(a); yield strength: $R^2 = 0.9226$, Fig. 2(b)). In comparison to μ CT voxel-based models and mechanical testing, the HR-pQCT PR model predictions were significantly different. Correlation

Table 3 Prediction of stiffness and yield strength using PR μ FE models based on HR-pQCT images of vertebral fracture subjects and nonfracture controls

	Vertebral fracture	Control	<i>p</i> -value	OR (95% CI)	AUC
Radius					
Stiffness (N/mm)	60,971 $\pm$ 2193	72,399 $\pm$ 2418	$< 0.001^a$	2.39 (1.37, 4.18)	0.71
Yield strength (N)	3468 $\pm$ 129	4173 $\pm$ 151	$< 0.001^a$	2.48 (1.39, 4.43)	0.73
Tibia					
Stiffness (N/mm)	167,536 $\pm$ 5101	201,369 $\pm$ 6424	$< 0.001^a$	3.47 (1.63, 5.40)	0.75
Yield strength (N)	9816 $\pm$ 299	12,078 $\pm$ 418	$< 0.001^a$	4.46 (1.84, 6.83)	0.78

Note: Data are shown as mean $\pm$ SEM. *p*-values for student's *t*-test comparing the fracture group and control group, OR and AUC from ROC analysis for each potential predictor are shown.

^aGroup difference remains significant ($p < 0.05$) after adjusting for aBMD.

Table 4 Area under the curve values indicating the ability to discriminate fracture status using aBMD, ITS morphological parameters, and mechanical parameters from PR μ FE analysis

Independent variables	Radius	Tibia
aBMD	0.71	0.71
aBMD + ITS	0.81	0.77
aBMD + ITS + PR μ FE	0.86	0.86

coefficients, however, remained high for both stiffness (to μ CT voxel-based models: 0.9409, Fig. 2(c); to mechanical testing: 0.8781, Fig. 2(e)) and yield strength (to μ CT voxel-based models: 0.9476, Fig. 2(d); to mechanical testing: 0.9403, Fig. 2(f)). Furthermore, the slopes of the linear regression with all three references methods were near 1 for stiffness (0.9802 for HR-pQCT voxel-based models, 0.9620 for μ CT voxel-based models, and 0.9462 for mechanical testing), indicating that the HR-pQCT PR models can accurately predict stiffness for whole bone segments by adjusting baseline offset. Calculated from the Bland–Altman plots, relative errors of the HR-pQCT-based PR model predictions were the lowest in comparison to the voxel-based models constructed based on the same HR-pQCT images, with 95% confidence interval of 0.0413 ± 0.2963 for stiffness and 0.0697 ± 0.3323 for yield strength (Figs. 3(a) and 3(b)). Compared to μ CT voxel-based models, relative error remained low for stiffness with confidence interval of 0.0176 ± 0.2767 (Fig. 3(c)), while increased slightly for yield strength with 0.1060 ± 0.3631 (Fig. 3(d)). Compared to mechanical testing results, however, prediction of stiffness by HR-pQCT-based PR models generated a mean error of 0.2167 ± 0.377 (Fig. 3(e)), and prediction of yield strength generated a mean error of -0.0996 ± 0.2917 (Fig. 3(f)), indicating an over-estimation of stiffness and an under-estimation of yield strength.

Plate and Rod Models Dramatically Increased Computation Efficiency. The PR modeling approach dramatically increased computation efficiency by reducing model size and computation time. Voxel models generated from HR-pQCT images of the distal radius and tibia segments contained on average $2\text{--}4 \times 10^6$ elements, whereas the PR models generated from the same images reduced model size to 1–2 hundred thousand elements (Table 2). Furthermore, the PR modeling approach achieved nearly a 20-fold reduction in computation time for nonlinear μ FE analyses. Central processing unit time per analysis was reduced to 1.6 and 5.9 h using PR models for the radius and tibia, respectively, in contrast to 36.7 and 78.6 h using voxel-based models.

Plate and Rod Models of Whole Bone Segments Predicted Fracture Risk. Nonlinear μ FE analysis using PR models of whole bone segments found significant differences in stiffness and yield strength between vertebral fracture subjects and nonfracture controls (Table 3). At the radius, stiffness and yield strength were lower in fracture subjects by 16% and 17%, respectively. At the tibia, stiffness and yield strength were lower by 17% and 19%. After adjustment for aBMD, stiffness and yield strength remained significantly lower in fracture subjects at both sites. Logistic regression analyses revealed that yield strength at the distal tibia had the highest odds ratio (OR) of 4.46 ± 2.62 among all the independent variables such that each SD decrease in yield strength was associated with an approximately 4.5-fold increase in the risk of vertebral fracture. ROC analyses at the tibia demonstrated AUC of 0.78 for yield strength and 0.75 for stiffness. ROC at the analyses at the radius demonstrated AUC of 0.73 for yield strength and 0.71 for stiffness. Additionally, ROC analyses were performed for three models: aBMD measurements by DXA only, aBMD with ITS parameters, and aBMD, ITS, and μ FE parameters from PR models combined. The model using aBMD alone resulted in an AUC of 0.71 at both sites, whereas the model using

aBMD and ITS parameters had an AUC of 0.81 at the radius and 0.77 at the tibia. Incorporating the PR μ FE analysis parameters to the multiparametric model resulted in the highest AUC of 0.86 at both sites (Table 4).

Discussion

In this study, a new PR μ FE modeling approach for whole bone segments was developed for clinical HR-pQCT scans. In comparison to the voxel-based approach, fast and accurate prediction of nonlinear mechanics for whole bone segments from HR-pQCT scans was achieved within hours, a significant improvement from several days.

This substantial reduction in computation time was attained through a nearly 20-fold reduction in model size. Each step in the procedure, however, was carefully designed to maintain key features from the original bone microstructure. Decomposing the trabecular compartment into individual trabecular plates and rods using ITS enabled subsequent meshing with shell and beam elements which allowed for significant reduction in the number of trabecular elements while rigorously preserving the original trabecular plate-and-rod microstructure. In addition, the thickness of each element was carefully calculated to ensure preservation of the original volume, as described in our previously established trabecular PR μ FE study [35,36]. In the cortical compartment, bone voxels were optimally coarsened to a level that further reduced model size while simultaneously maintaining key features such as cortical thickness and porosity. Finally, when reconnecting the cortical and trabecular meshes, the algorithm was carefully designed to identify the nearest cortical node for each external trabecular element such that the intracortical surface could be preserved as much as possible while ensuring connectivity. Consequently, the PR μ FE models accurately predicted nonlinear mechanics for whole bone segments from HR-pQCT images despite significant reduction in model size.

Using these PR models, predicted stiffness and yield strength for whole bone segments were strongly correlated to mechanical testing measurements and results from conventional voxel-based models, the experimental and computational gold standards. In addition, by applying the PR μ FE modeling technique to in vivo HR-pQCT scans of the radius and tibia, we confirmed its ability to detect pathological changes in bone mechanics and to discriminate fracture subjects from nonfracture controls. Significant reductions in stiffness and yield strength at both distal sites were found in fracture individuals, and these differences remained significant after adjustment for variability due to aBMD. Furthermore, ROC analysis found increased AUC when incorporating results from the PR μ FE models, indicating that the presented approach enhances the ability to discriminate vertebral fracture status.

One of the limitations of this study is that uniform and isotropic material properties were assumed for the trabecular and cortical bone tissue, while both are heterogeneous and anisotropic in reality. It is interesting to note, however, that despite this simplification, the PR μ FE models predicted accurate stiffness for whole bone segments in comparison to all three reference methods. How these tissue-level inhomogeneity and anisotropy affect the apparent mechanical behavior is yet to be elucidated. Prediction of yield strength, on the other hand, deviated slightly from μ CT voxel-based model results and mechanical testing results, in which PR models underestimated yield strength. This could arise from several sources. Partial volume effects from the reduced resolution of HR-pQCT scans, a result of multiple materials represented as an average in a single voxel, may lead to blurred bone boundaries and altered microarchitecture after thresholding. Different identification of the intracortical surface and segmentation of cortical and trabecular bone may therefore also introduce an additional source of error. With the enhanced resolution of the second-generation HR-pQCT, errors from these sources will likely be reduced.

Nevertheless, the PR μ FE technique for whole bone segments adds to the field of image-based μ FE modeling and enhances the

utility of HR-pQCT. Previously, the PR μ FE technique has demonstrated excellent accuracy and efficiency in predicting trabecular bone biomechanics based on high-resolution μ CT images [35]. Performance of the model at reduced HR-pQCT resolution was assessed for small cubic subvolumes of the trabecular bone, but never for whole bone segments including the cortical compartment [36]. In this study, the previously established PR modeling technique was further refined to achieve fine meshing for whole bone segments captured by the HR-pQCT at reduced resolution. With the current approach, nonlinear HR-pQCT-based μ FE analyses, which provide essential information of bone strength and bone mechanics, can be readily extended to larger scale problems or incorporated into onsite clinical diagnosis. In combination with the second-generation HR-pQCT, which offer enhanced resolution up to an isotropic voxel size of 61 μ m that can capture fine microstructural details even at the knee joint [32], the presented method can be applied to exciting new areas of musculoskeletal research such as knee osteoarthritis.

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References

- [1] Boutroy, S., Bouxsein, M. L., Munoz, F., and Delmas, P. D., 2005, "In Vivo Assessment of Trabecular Bone Microarchitecture by High-Resolution Peripheral Quantitative Computed Tomography," *J. Clin. Endocrinol. Metab.*, **90**(12), pp. 6508–6515.
- [2] Burghardt, A. J., Buie, H. R., Laib, A., Majumdar, S., and Boyd, S. K., 2010, "Reproducibility of Direct Quantitative Measures of Cortical Bone Microarchitecture of the Distal Radius and Tibia by HR-pQCT," *Bone*, **47**(3), pp. 519–528.
- [3] MacNeil, J. A., and Boyd, S. K., 2007, "Accuracy of High-Resolution Peripheral Quantitative Computed Tomography for Measurement of Bone Quality," *Med. Eng. Phys.*, **29**(10), pp. 1096–1105.
- [4] Krause, M., Museyko, O., Breer, S., Wulff, B., Duckstein, C., Vettorazzi, E., Glueer, C., Püschel, K., Engelke, K., and Amling, M., 2014, "Accuracy of Trabecular Structure by HR-pQCT Compared to Gold Standard μ CT in the Radius and Tibia of Patients With Osteoporosis and Long-Term Bisphosphonate Therapy," *Osteoporosis Int.*, **25**(5), pp. 1595–1606.
- [5] Zhou, B., Zhang, X. H., Sekhon, K. K., Adams, M. F., McMahon, D. J., Bilezikian, J. P., Shane, E., and Guo, X. E., 2016, "High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT) Can Assess Microstructural and Biomechanical Properties of Both Human Distal Radius and Tibia: Ex Vivo Computational and Experimental Validations," *Bone*, **86**, pp. 58–67.
- [6] Nishiyama, K. K., Macdonald, H. M., Buie, H. R., Hanley, D. A., and Boyd, S. K., 2010, "Postmenopausal Women With Osteopenia Have Higher Cortical Porosity and Thinner Cortices at the Distal Radius and Tibia Than Women With Normal aBMD: An In Vivo HR-pQCT Study," *J. Bone Miner. Res.*, **25**, pp. 882–890.
- [7] Macdonald, H. M., Nishiyama, K. K., Kang, J., Hanley, D. A., and Boyd, S. K., 2011, "Age-Related Patterns of Trabecular and Cortical Bone Loss Differ Between Sexes and Skeletal Sites: A Population-Based HR-pQCT Study," *J. Bone Miner. Res.*, **26**(1), pp. 50–62.
- [8] Boutroy, S., Van Rietbergen, B., Sornay-Rendu, E., Munoz, F., Bouxsein, M. L., and Delmas, P. D., 2008, "Finite Element Analysis Based on In Vivo HR-pQCT Images of the Distal Radius Is Associated With Wrist Fracture in Postmenopausal Women," *J. Bone Miner. Res.*, **23**(3), pp. 392–399.
- [9] Liu, X. S., Cohen, A., Shane, E., Yin, P. T., Stein, E. M., Rogers, H., Kokolus, S. L., McMahon, D. J., Lappe, J. M., Recker, R. R., and Lang, T., 2010, "Bone Density, Geometry, Microstructure, and Stiffness: Relationships Between Peripheral and Central Skeletal Sites Assessed by DXA, HR-pQCT, and cQCT in Premenopausal Women," *J. Bone Miner. Res.*, **25**(10), pp. 2229–2238.
- [10] Nishiyama, K. K., Macdonald, H. M., Hanley, D. A., and Boyd, S. K., 2013, "Women With Previous Fragility Fractures Can Be Classified Based on Bone Microarchitecture and Finite Element Analysis Measured With HR-pQCT," *Osteoporosis Int.*, **24**(5), pp. 1733–1740.
- [11] Liu, X. S., Stein, E. M., Zhou, B., Zhang, C. A., Nickolas, T. L., Cohen, A., Thomas, V., McMahon, D. J., Cosman, F., Nieves, J., and Shane, E., 2012, "Individual Trabecula Segmentation (ITS)-Based Morphological Analyses and Microfinite Element Analysis of HR-pQCT Images Discriminate Postmenopausal Fragility Fractures Independent of DXA Measurements," *J. Bone Miner. Res.*, **27**(2), pp. 263–272.
- [12] Vilaythiou, N., Boutroy, S., Szulc, P., van Rietbergen, B., Munoz, F., Delmas, P. D., and Chapurlat, R., 2011, "Finite Element Analysis Performed on Radius and Tibia HR-pQCT Images and Fragility Fractures at All Sites in Men," *J. Bone Miner. Res.*, **26**(5), pp. 965–973.
- [13] Vilaythiou, N., Boutroy, S., Sornay-Rendu, E., Munoz, F., Delmas, P. D., and Chapurlat, R., 2010, "Finite Element Analysis Performed on Radius and Tibia HR-pQCT Images and Fragility Fractures at All Sites in Postmenopausal Women," *Bone*, **46**(4), pp. 1030–1037.
- [14] Johnell, O., and Kanis, J. A., 2006, "An Estimate of the Worldwide Prevalence and Disability Associated With Osteoporotic Fractures," *Osteoporosis Int.*, **17**(12), pp. 1726–1733.
- [15] Miller, P. D., and Leonard, M. B., 2006, "Clinical Use of Bone Mass Measurements in Adults for the Assessment and Management of Osteoporosis," *Primer on the Metabolic Bone Disease and Disorders of Mineral Metabolism*, 6th ed., American Society for Bone and Mineral Research, Washington, DC, pp. 150–161.
- [16] Ulrich, D., van Rietbergen, B., Laib, A., and Ruegsegger, P., 1999, "The Ability of Three-Dimensional Structural Indices to Reflect Mechanical Aspects of Trabecular Bone," *Bone*, **25**(1), pp. 55–60.
- [17] Schileo, E., Taddei, F., Malandrino, A., Cristofolini, L., and Viceconti, M., 2007, "Subject-Specific Finite Element Models Can Accurately Predict Strain Levels in Long Bones," *J. Biomech.*, **40**(13), pp. 2982–2989.
- [18] Sornay-Rendu, E., Boutroy, S., Munoz, F., and Delmas, P. D., 2007, "Alterations of Cortical and Trabecular Architecture Are Associated With Fractures in Postmenopausal Women, Partially Independent of Decreased BMD Measured by DXA: The OFELY Study," *J. Bone Miner. Res.*, **22**(3), pp. 425–433.
- [19] Stein, E. M., Liu, X. S., Nickolas, T. L., Cohen, A., McMahon, D. J., Zhou, B., Zhang, C., Kamanda-Kosse, M., Cosman, F., Nieves, J., and Guo, X. E., 2012, "Microarchitectural Abnormalities Are More Severe in Postmenopausal Women With Vertebral Compared to Nonvertebral Fractures," *J. Clin. Endocrinol. Metab.*, **97**(10), pp. E1918–E1926.
- [20] Stein, E. M., Sajda, P., Saha, P. K., Wehrli, F. W., Bevil, G., Keaveny, T. M., and Guo, X. E., 2010, "Abnormal Microarchitecture and Reduced Stiffness at the Radius and Tibia in Postmenopausal Women With Fractures," *J. Bone Miner. Res.*, **25**(12), pp. 2572–2581.
- [21] Liu, X. S., Sajda, P., Saha, P. K., Wehrli, F. W., Bevil, G., Keaveny, T. M., and Guo, X. E., 2008, "Complete Volumetric Decomposition of Individual Trabecular Plates and Rods and Its Morphological Correlations With Anisotropic Elastic Moduli in Human Trabecular Bone," *J. Bone Miner. Res.*, **23**(2), pp. 223–235.
- [22] Christen, D., Webster, D. J., and Muller, R., 2010, "Multiscale Modelling and Nonlinear Finite Element Analysis as Clinical Tools for the Assessment of Fracture Risk," *Philos. Trans. R. Soc. A*, **368**(1920), pp. 2653–2668.
- [23] Liu, X. S., Zhang, X. H., Sekhon, K. K., Adams, M. F., McMahon, D. J., Bilezikian, J. P., Shane, E., and Guo, X. E., 2010, "High-Resolution Peripheral Quantitative Computed Tomography Can Assess Microstructural and Mechanical Properties of Human Distal Tibial Bone," *J. Bone Miner. Res.*, **25**, pp. 746–756.
- [24] Macneil, J. A., and Boyd, S. K., 2008, "Bone Strength at the Distal Radius Can Be Estimated From High-Resolution Peripheral Quantitative Computed Tomography and the Finite Element Method," *Bone*, **42**(6), pp. 1203–1213.
- [25] van Rietbergen, B., Weinans, H., Huiskes, R., and Odgaard, A., 1995, "A New Method to Determine Trabecular Bone Elastic Properties and Loading Using Micromechanical Finite-Element Models," *J. Biomech.*, **28**(1), pp. 69–81.
- [26] Keaveny, T. M., Guo, X. E., Wachtel, E. F., McMahon, T. A., and Hayes, W. C., 1994, "Trabecular Bone Exhibits Fully Linear Elastic Behavior and Yields at Low Strains," *J. Biomech.*, **27**(9), pp. 1127–1136.
- [27] Niebur, G. L., Feldstein, M. J., Yuen, J. C., Chen, T. J., and Keaveny, T. M., 2000, "High-Resolution Finite Element Models With Tissue Strength Asymmetry Accurately Predict Failure of Trabecular Bone," *J. Biomech.*, **33**(12), pp. 1575–1583.
- [28] van Lenthe, G. H., and Muller, R., 2006, "Prediction of Failure Load Using Micro-Finite Element Analysis Models: Toward In Vivo Strength Assessment," *Drug Discovery Today Technol.*, **3**(2), pp. 221–229.
- [29] Wolfram, U., Gross, T., Pahr, D. H., Schwiedrzik, J., Wilke, H. J., and Zysset, P. K., 2012, "Fabric-Based Tsai-Wu Yield Criteria for Vertebral Trabecular Bone in Stress and Strain Space," *J. Mech. Behav. Biomed. Mater.*, **15**, pp. 218–228.
- [30] Pistoia, W., Van Rietbergen, B., Lochmüller, E. M., Lill, C. A., Eckstein, F., and Ruegsegger, P., 2002, "Estimation of Distal Radius Failure Load With Micro-Finite Element Analysis Models Based on Three-Dimensional Peripheral Quantitative Computed Tomography Images," *Bone*, **30**(6), pp. 842–848.
- [31] Hosseini, H. S., Dünki, A., Fabeck, J., Stauber, M., Vilaythiou, N., Pahr, D., Pretterklieber, M., Wandel, J., van Rietbergen, B., and Zysset, P. K., 2017, "Fast Estimation of Colles' Fracture Load of the Distal Section of the Radius by Homogenized Finite Element Analysis Based on HR-pQCT," *Bone*, **97**, pp. 65–75.
- [32] Kroker, A., Zhu, Y., Manske, S. L., Barber, R., Mohtadi, N., and Boyd, S. K., 2017, "Quantitative In Vivo Assessment of Bone Microarchitecture in the Human Knee Using HR-pQCT," *Bone*, **97**, pp. 43–48.
- [33] Kroker, A., Bhatla, J. L., Emery, C. A., Manske, S. L., and Boyd, S. K., 2018, "Subchondral Bone Microarchitecture in ACL Reconstructed Knees of Young Women: A Comparison With Contralateral and Uninjured Control Knees," *Bone*, **111**, pp. 1–8.
- [34] Ibanez, L., Schroeder, W., Ng, L., and Cates, J., 2005, "The ITK Software Guide," Kitware, Clifton Park, NY.
- [35] Wang, J., Zhou, B., Liu, X. S., Fields, A. J., Sanyal, A., Shi, X., Adams, M., Keaveny, T. M., and Guo, X. E., 2015, "Trabecular Plates and Rods Determine Elastic Modulus and Yield Strength of Human Trabecular Bone," *Bone*, **72**, pp. 71–80.
- [36] Liu, X. S., Wang, J., Zhou, B., Stein, E., Shi, X., Adams, M., Shane, E., and Guo, X. E., 2013, "Fast Trabecular Bone Strength Predictions of HR-pQCT and Individual Trabeculae Segmentation-Based Plate and Rod Finite Element Model Discriminate Postmenopausal Vertebral Fractures," *J. Bone Miner. Res.*, **28**(7), pp. 1666–1678.

- [37] Wang, H., Liu, X. S., Zhou, B., Wang, J., Ji, B., Huang, Y., Hwang, K. C., and Guo, X. E., 2013, "Accuracy of Individual Trabecula Segmentation Based Plate and Rod Finite Element Models in Idealized Trabecular Bone Microstructure," *J. Biomech. Eng.*, **135**(4), p. 044502.
- [38] Currey, J. D., 1988, "The Effect of Porosity and Mineral Content on the Young's Modulus of Elasticity of Compact Bone," *J. Biomech.*, **21**(2), pp. 131–139.
- [39] McCalden, R. W., McGeough, J. A., Barker, M. B., and Court-Brown, C. M., 1993, "Age-Related Changes in the Tensile Properties of Cortical Bone. The Relative Importance of Changes in Porosity, Mineralization, and Microstructure," *J. Bone Jt. Surg. Am.*, **75**(8), pp. 1193–1205.
- [40] Schaffler, M. B., and Burr, D. B., 1988, "Stiffness of Compact Bone: Effects of Porosity and Density," *J. Biomech.*, **21**(1), pp. 13–16.
- [41] Wachter, N. J., Augat, P., Krischak, G. D., Sarkar, M. R., Mentzel, M., Kinzl, L., and Claes, L., 2001, "Prediction of Strength of Cortical Bone In Vitro by Microcomputed Tomography," *Clin. Biomech.*, **16**(3), pp. 252–256.
- [42] Folsch, C., Mittelmeier, W., Bilderbeek, U., Timmesfeld, N., von Garrel, T., and Matter, H. P., 2012, "Effect of Storage Temperature on Allograft Bone," *Transfus. Med. Hemother.*, **39**, pp. 36–40.
- [43] Hamer, A. J., Strachan, J. R., Black, M. M., Ibbotson, C. J., Stockley, I., and Elson, R. A., 1996, "Biochemical Properties of Cortical Allograft Bone Using a New Method of Bone Strength Measurement. A Comparison of Fresh, Fresh-Frozen, and Irradiated Bone," *J. Bone Jt. Surg. Br.*, **78**(3), pp. 363–368.
- [44] Wieding, J., Mick, E., Wree, A., and Bader, R., 2015, "Influence of Three Different Preservative Techniques on the Mechanical Properties of the Ovine Cortical Bone," *Acta Bioeng. Biomech.*, **17**(1), pp. 137–146.
- [45] Buie, H. R., Campbell, G. M., Klinck, R. J., MacNeil, J. A., and Boyd, S. K., 2007, "Automatic Segmentation of Cortical and Trabecular Compartments Based on a Dual Threshold Technique for In Vivo Micro-CT Bone Analysis," *Bone*, **41**(4), pp. 505–515.
- [46] Papadopoulos, P., and Lu, J., 2001, "On the Formulation and Numerical Solution of Problems in Anisotropic Finite Plasticity," *Comput. Methods Appl. Mech. Eng.*, **190**(37–38), pp. 4889–4910.
- [47] Papadopoulos, P., and Lu, J., 1998, "A General Framework for the Numerical Solution of Problems in Finite Elasto-Plasticity," *Comput. Methods Appl. Mech. Eng.*, **159**(1–2), pp. 1–18.
- [48] Goldstein, S. A., 1987, "The Mechanical Properties of Trabecular Bone: Dependence on Anatomic Location and Function," *J. Biomech.*, **20**(11–12), pp. 1055–1061.
- [49] Bayraktar, H. H., Morgan, E. F., Niebur, G. L., Morris, G. E., Wong, E. K., and Keaveny, T. M., 2004, "Comparison of the Elastic and Yield Properties of Human Femoral Trabecular and Cortical Bone Tissue," *J. Biomech.*, **37**(1), pp. 27–35.
- [50] Saha, P. K., and Chaudhuri, B. B., 1996, "3D Digital Topology Under Binary Transformation With Applications," *Comput. Vision Image Understanding*, **63**(3), pp. 418–429.
- [51] Saha, P. K., Chaudhuri, B. B., and Majumder, D. D., 1997, "A New Shape Preserving Parallel Thinning Algorithm for 3D Digital Images," *Pattern Recognit.*, **30**(12), pp. 1939–1955.
- [52] Delone, B., 1934, "Sur la sphère vide," *A la mémoire de George Voronoi.*, **6**, pp. 793–800.