

Bone strength at the distal radius can be estimated from high-resolution peripheral quantitative computed tomography and the finite element method

Joshua A. MacNeil, Steven K. Boyd*

Department of Mechanical and Manufacturing Engineering, Schulich School of Engineering, University of Calgary, Calgary, Canada

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Abstract

Bone strength is a fundamental contributor to fracture risk, and with the recent development of *in vivo* 3D bone micro-architecture measurements by high-resolution peripheral quantitative computed tomography, the finite element (FE) analysis may provide a means to assess patient bone strength in the distal radius. The purpose of this study was to determine an appropriate FE procedure to estimate bone strength by comparison with experimental data. Models based on a homogeneous tissue modulus or a modulus scaled according to computed tomography attenuation were assessed, and these were solved by linear and non-linear FE analyses to estimate strength.

The distal radius from fresh, human cadaver forearms (5 male/5 female, ages 55 to 93) was dissected free and four 9.1 mm sections were cut beginning at the subchondral plate to provide 40 test specimens. The sections were scanned using an *in vivo* protocol providing 3D image data with an 82 μm voxel size. All specimens were mechanically tested in uniaxial compression, and elastic and yield properties were determined. Linear FE analyses were performed on all specimens ($N=40$), and non-linear analyses using an asymmetric, bilinear yield strain criteria were performed on a sub-sample ($N=10$) corresponding to the normal clinical measurement site.

Experimentally determined apparent elastic properties correlated highly with ultimate stress ($R^2=0.977$, $p<0.05$, $N=31$) for the 31 specimens tested to failure. Subsequently, a linear FE analysis estimating apparent elastic properties also correlated highly with failure, and the correlation was higher when moduli were determined from scaled CT-attenuation values than a homogeneous modulus ($R^2=0.983$ vs. $R^2=0.972$, $p<0.05$, $N=31$). A non-linear analysis based on tensile and compressive yield strains of 0.0295 and 0.0493 for homogeneous models, and 0.0127 and 0.0212 for scaled models directly estimated ultimate stress, and correlated highly ($R^2=0.951$ vs. $R^2=0.937$, $p<0.05$, $N=5$).

The linear relation between stiffness and strength may be unique to radius compressive loading. It supports the use of a linear FE analysis to determine bone strength by regression equations established here. Scaled tissue modulus models performed better than homogeneous modulus models, and the advantage of a scaled model is its potential to account for mineralization changes. The combined numerical–experimental procedure for FE model validation on the patient micro-CT technology demonstrated that bone strength can be estimated non-invasively, and this may provide important insight into fracture risk in patient populations.

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Keywords: Model validation; Bone strength; Experimental–numerical comparison; Micro-CT; Finite element model; Distal radius

Introduction

Osteoporosis is a common multi-factorial disorder of reduced bone mass and micro-architectural deterioration of bone tissue, manifesting clinically as a concurrent increase in fragility and fracture risk [1–3]. The definition of osteoporosis, according

to WHO, is a hip bone mineral density (BMD) measured by dual X-ray absorptiometry (DXA) of more than 2.5 SD below the mean for young, Caucasian adult women [4]. Although DXA-based BMD is used as a surrogate measure of bone strength, it cannot account for bone micro-structure and tissue density variations, and it has limited ability to assess compartmental differences (cortical versus cancellous). Osteoporosis is a disease of low bone strength, not low bone mass as has been previously pointed out [5], therefore more direct surrogates for bone strength should be considered [6]. One promising approach is the use of patient-specific finite element (FE) analysis.

* Corresponding author. Department of Mechanical and Manufacturing Engineering, University of Calgary, 2500 University Drive, N.W., Calgary, Alberta T2N 1N4, Canada. Fax: +1 403 282 8406.

E-mail address: skboyd@ucalgary.ca (S.K. Boyd).

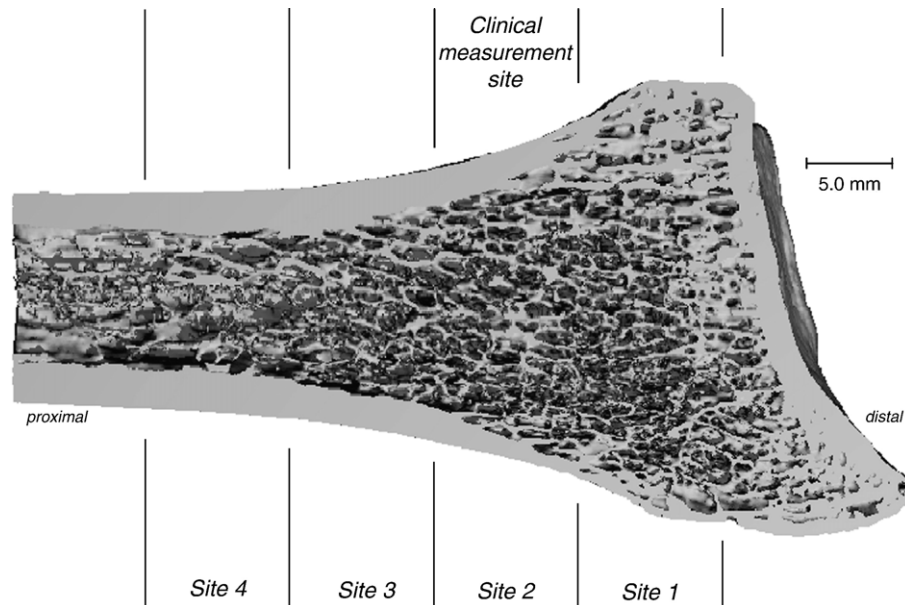


Fig. 1. Each of the 10 radii was evaluated at four adjacent sites resulting in a total of 40 specimens. The first site is most distal, the second site corresponds to normal clinical measurement, and the third and fourth sites are located proximally as shown on this sample 3D HR-pQCT image of a cadaver radius.

The current standard for patient-specific analysis of strength by FE is to use clinical computed tomography (CT) to provide three-dimensional (3D) data for generation of continuum-level models [7,8]. This approach has been applied to clinical studies [9] where it was determined that upon drug treatment both the degree of density change and the density distribution affects predicted vertebral strength. Although clinical CT has the advantage that central skeletal sites can be assessed, it is limited by image resolution. The continuum models do not include micro-architectural features, and special care must be taken in the analysis of the cortical region, particularly when it is thin. Despite these limitations, a good estimate of apparent-level bone strength can be achieved.

Bone micro-architecture can be incorporated into large-scale FE models when high-resolution image data is available, and those data can be obtained through the use of micro-computed tomography (μ CT). The typical approach is to directly convert the 3D image data to FE meshes on a voxel-by-voxel basis [10,11] resulting in models that have millions of degrees of freedom and require specialized FE solvers [11,12]. Most frequently, these models are limited to a linear analysis to estimate elastic properties (i.e., elastic modulus) [13–15] because they are computationally intensive. However, non-linear analyses of these model types have been applied when model sizes were considerably smaller, for example, representing cancellous sub-volumes [16]. The advantage of a non-linear FE approach is that the bone strength properties can be predicted directly [16] when an appropriate failure criterion is used, as opposed to a linear model which must assume a relation between apparent elastic properties and failure strength. But, the reason that non-linear FE models are not used more often is because they are computationally demanding. Therefore, it has been attractive to assess strength from linear, large-scale FE models despite their intrinsic inability to model strength directly. One approach has

been to approximate yield load by estimating the force required for a pre-defined tissue volume to exceed a preset strain magnitude, and this approach has been promising based on cadaver validation studies [17].

Nevertheless, a non-linear FE analysis is better suited for estimations of bone strength and post-yield behaviour than a linear model. The choice of a failure criterion is an important consideration when developing such a model, and many different failure criteria have been proposed, and each have advantages and

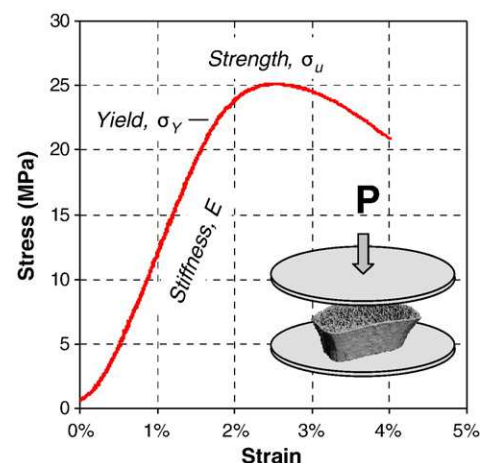


Fig. 2. Uniaxial compression was performed on each section of the radii (inset), and the force-displacement data was used to determine the stress-strain plots. Stress was determined by dividing the platen force by the average cross-sectional area, and strain was determined by normalizing the platen displacement by the undeformed specimen thickness. The slope of the linear elastic region corresponds to the apparent stiffness (E) of the bone, the yield stress (σ_Y) is reached at the end of the elastic region, and the ultimate strength (σ_U) corresponds to the peak stress.



Fig. 3. Finite element voxel-based meshes of the same specimen. A typical mesh with a homogeneous tissue elastic modulus (left) and a mesh with a modulus scaled according to the CT-attenuation (right) are shown. Note that although the scaled modulus model represents the bone as a continuum, the micro-architecture is still incorporated into the model as can be clearly seen.

disadvantages [18], partially depending on whether they are applied to continuum or micro-structural FE models. Some examples include the von Mises [9], maximum principal strain [19], and the Tsai-Wu [20] failure criteria, and recently criteria that incorporate damage accumulation [21]. Although there is no consensus regarding which is the most appropriate criterion, an asymmetric tissue yield strain criterion, with a ratio of principal tensile to compressive yield strains of ~ 0.6 has worked well for micro-structural models [16]. The apparent ultimate stress was not determined directly by this model; instead apparent yield properties are based on the 0.2% offset rule [16].

Another important consideration for voxel-based FE models is whether to apply a homogeneous tissue modulus for the min-

eralized phase, or whether to adjust the tissue modulus according to CT-based density data. A homogeneous tissue modulus works well for high-resolution image data to describe apparent-level mechanical properties [11,22], but it cannot account for spatial variations of tissue modulus. Converting CT-attenuation data to a tissue modulus [23] can account for spatially varying moduli and performs well to predict cancellous apparent modulus [24]; however, it is sensitive to partial volume effects, and is resolution dependent [23]. When gray-scale voxel conversion is applied to continuum models (from clinical CT image data) the conversion from CT-attenuation to modulus of elasticity has resulted in good estimations of apparent strength [7] and implicitly accounts for partial volume effects. An important motivation to use a gray-scale conversion is that treatments for osteoporosis may result in changes in tissue mineralization and strength — this may be accounted for *a priori* by converting the CT-attenuation to moduli of elasticity.

An important drawback to assessing bone strength by FE is that critical parameters affecting the model inputs are not standardized. Failure criterion, appropriate failure parameters (i.e., yield strains), CT-attenuation to modulus conversions, and bone measurement site vary from experiment to experiment. The results of one study are unlikely to be directly applicable to others. Recently, however, a new high-resolution peripheral quantitative computed tomography scanner (HR-pQCT; XtremeCT, Scanco Medical) has been introduced that provides high-resolution 3D image data at the distal radius and tibia with an isotropic voxel size of 82 μm , and these systems have a well defined measurement protocol. Previous prototypes of this system providing a 165 μm isotropic voxel size have been used to demonstrate that bone strength predicted by a linear FE analysis corresponds well with experimental testing [17,25,26]. With the advent of these new micro-CT patient scanners, there is an opportunity to apply appropriate FE methods to non-invasively assess strength for patient monitoring because the scanning procedure for the HR-pQCT scanners is standardized (bone measurement site, resolution, density calibration). The development of appropriate protocols and FE model parameters can be applied more universally for all users of HR-pQCT technology with the potential prospect of accurately assessing bone strength in patients non-invasively.

The purpose of this study is to explore the use of both linear and non-linear FE models for predicting bone strength, and whether to base those models on homogeneous versus scaled

Table 1
Morphological indices at each measurement site ($N=10$ /site, mean and standard deviation in brackets)

Site	Area	D100	Dcomp	Ct.Th	Dtrab	BV/TV	Tb.N	Tb.Th	Tb.Sp	Tb.1/N.SD
	[mm ²]	[mg/cm ³ HA]	[mg/cm ³ HA]	[mm]	[mg/cm ³ HA]	[%]	[/mm]	[mm]	[mm]	[mm]
1	470 (123)	122 (49)	424 (112)	0.08 (0.08)	91 (38)	7.6 (3.2)	1.35 (0.27)	0.054 (0.01)	0.72 (0.17)	0.45 (0.24)
2	281 (117)	221 (107)	755 (116)	0.53 (0.30)	89 (42)	7.5 (3.5)	1.12 (0.27)	0.064 (0.02)	0.88 (0.25)	0.52 (0.25)
3	197 (80)	311 (124)	907 (56)	0.92 (0.27)	57 (40)	4.7 (3.4)	0.80 (0.34)	0.052 (0.04)	1.47 (0.75)	0.78 (0.44)
4	168 (69)	373 (133)	949 (47)	1.05 (0.24)	57 (37)	4.7 (3.1)	0.70 (0.27)	0.065 (0.05)	1.62 (0.84)	0.90 (0.50)

Measurements are provided for average cross-sectional area (Area), volumetric bone mineral density (D100), cortical density (Dcomp), cortical thickness (Ct.Th), cancellous density (Dtrab), bone volume ratio (BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp) and the standard deviation of the trabecular separation (Tb.1/N.SD).

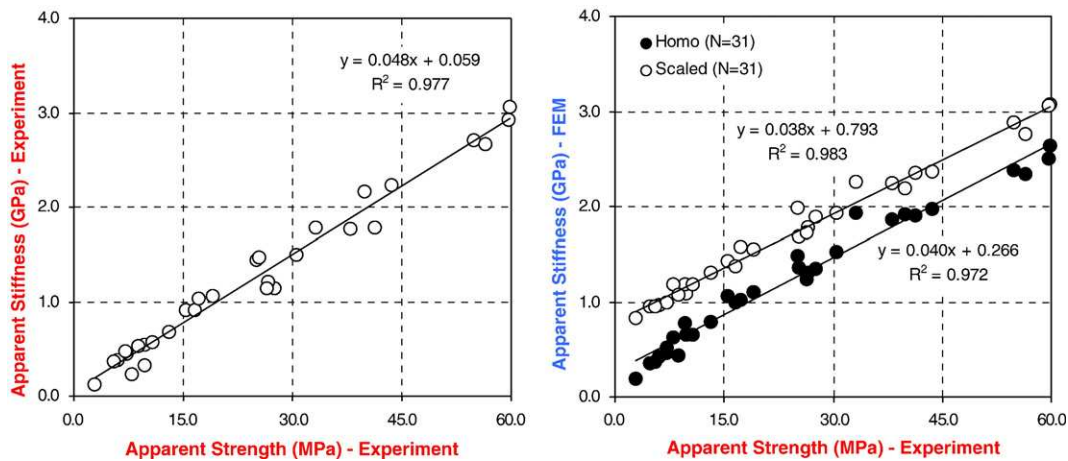


Fig. 4. Correlations and regression equations of apparent stiffness against strength. In all cases, strength data is obtained from uniaxial compression tests ($N=31$). The stiffness of the bone specimens is an excellent predictor of bone strength as shown for both experimentally and computationally (right) determined stiffness.

elastic moduli. Experimental testing of human cadaver bones will be used to evaluate the selection of these FE modeling approaches and appropriate FE parameters for measuring bone strength.

Methods

The study includes both experimental and computational analysis of bone specimens from the distal radius. The finite element models were generated from the 3D image data with either homogeneous or scaled tissue elastic moduli (based on CT-attenuation), and subsequently solved using linear and non-linear FE analyses and compared to experimental results.

Specimens

Fresh human cadaver forearms (5 male and 5 female) with ages ranging from 55 to 93 were obtained from the Gross Anatomy Lab at the University of Calgary. No specific criteria were used for selection and no medical history was available. The radii were fresh frozen until 48 h before scanning and were allowed to thaw at room temperature. The distal radius was dissected free from each forearm, and four adjacent 9.1 mm sections were cut starting at the subchondral plate (Fig. 1). There were a total of 40 specimens, 10 of which corresponded to the site normally measured during *in vivo* scans. The site of these 10 scans, corresponding to the normal patient measurement area, is termed throughout this work as the ‘clinical’ site [27]. All procedures were approved by the Office of Medical Bioethics at the University of Calgary.

HR-pQCT Scanning

Each radius section ($N=40$) was scanned by HR-pQCT (XtremeCT, Scanco Medical, Bassersdorf, Switzerland) in saline solution (to simulate soft tissue) using the default human *in vivo* scanning protocol (60 kVp, 1000 μ A, 100 ms

integration time, 750 projections). Each measurement took approximately 3 min and resulted in a 9.02 mm thick stack of cross-sectional images of the forearm (110 slices, voxel size of 82 μ m) taken from the centre of the 9.1 mm specimens. Standard morphological analysis of these scans was performed [28] and averages at each of the four measurement sites were determined.

Experimental mechanical testing

Each radius specimen was destructively loaded (MTS Bionix 2, MTS Systems Corporation, Eden Prairie, USA) in compression to determine the linear elastic and failure regions. See Fig. 2 for an illustration of some key mechanical characteristics and terminology. The loading protocol was initiated with a manual increase to 100 N followed by a decrease to 0 N to ensure no movement of the sample would occur during testing. The boundary conditions consisted of a platen uniaxial test using smooth polished plates. Test methods other than a platen test (e.g., end caps) could not be used due to specimen height restrictions. The loading protocol applied was 3% strain per second until failure. The load cell limit was 10 kN, therefore if samples did not fail before applying 9.5 kN of load the test was halted (for safety reasons) and only the linear region of those tests was obtained. The experimentally determined apparent modulus and ultimate strength were measured from the linear region and peak load from the experimental data, respectively. Knowing the original specimen height and average cross-sectional area, force-displacement data was converted to stress–strain curves for each of the 40 specimens tested. The apparent stiffness and ultimate stress obtained for each specimen were compared to the results of the finite element modeling. The correlation between experimentally determined apparent stiffness and ultimate stress was determined.

Meshes for finite element models

The 3D image data for each specimen from HR-pQCT was prepared for finite element meshing by two methods — either for generation of ‘homogeneous’ or

Table 2
Average finite element model size for homogeneous and scaled meshes

Site	Homogeneous				Scaled			
	Elements	Nodes	DOF	Fractal	Elements	Nodes	DOF	Fractal
1	1,640,929	2,879,327	8,637,981	2.19	7,375,697	7,555,419	22,666,257	2.97
2	1,257,958	1,871,026	5,613,077	2.44	4,420,291	4,534,877	13,604,630	2.96
3	1,066,949	1,391,326	4,173,977	2.64	3,087,563	3,186,855	9,560,564	2.95
4	1,012,782	1,259,340	3,778,020	2.70	2,631,124	2,718,238	8,154,714	2.95

Model size is reported in terms of the number of elements, nodes and degrees of freedom and fractal dimension as averages for each of the four measurement sites ($N=10$ /site).

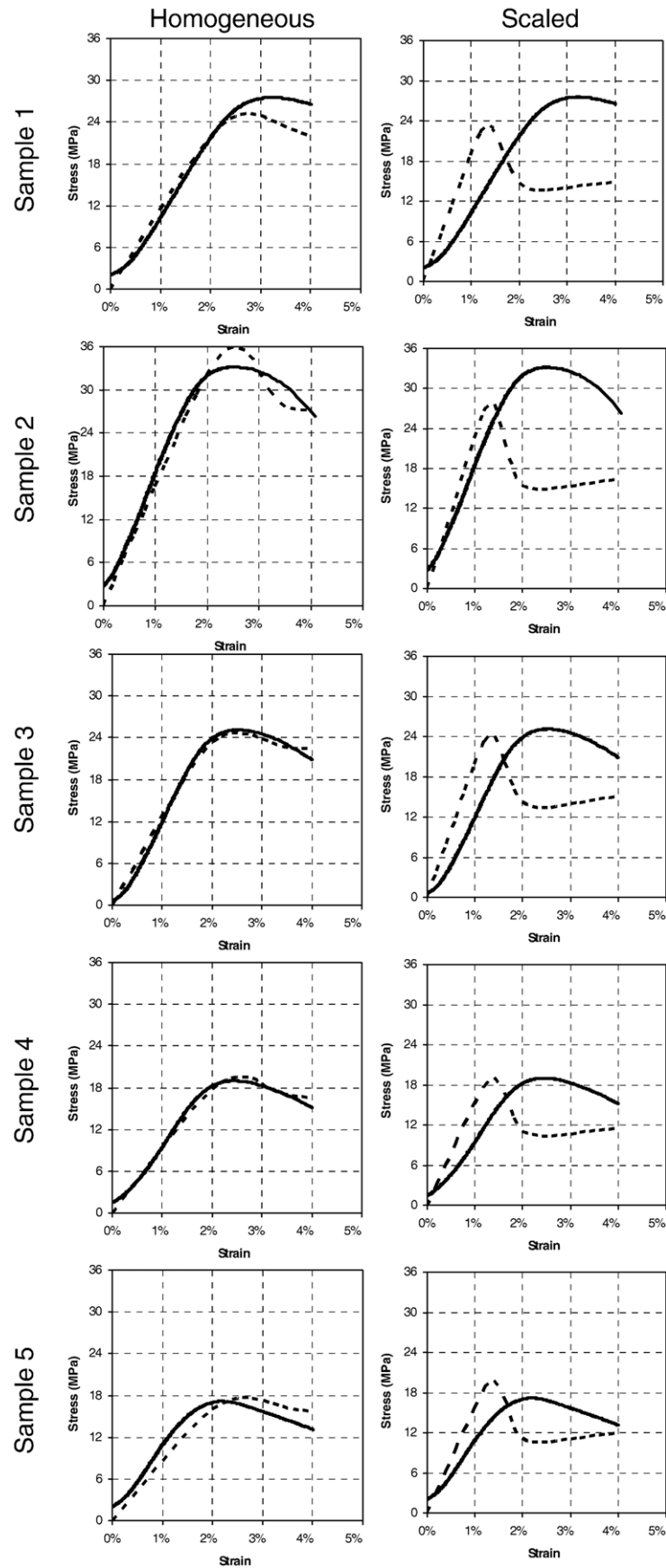


Fig. 5. Stress–strain plots for five specimens from the clinical measurement site. The results of the non-linear finite element analysis (dashed lines) are compared with the experimentally determined stress–strain data (solid lines) for both homogeneous and scaled finite element models (left and right columns, respectively).

'scaled' tissue modulus finite element meshes by the voxel conversion approach [10,11] (Fig. 3).

Homogenous models were based on the segmented image representing the bone mineral phase, and these files were created using a Laplace–Hamming filter (cutoff frequency, $f_c=0.4$) as per the standard HR-pQCT analysis protocol. A single homogeneous tissue modulus, $E_{t,homo}$, was determined by back-calculation [11] against the apparent stiffness measured from the experimental stress–strain curves ($N=40$). The best value for $E_{t,homo}$ describing the stiffness characteristics of all specimens (by least-squares fit) was used for all 'homogeneous' finite element models (both linear and non-linear models). A Poisson's ratio of 0.3 was used.

Models with scaled tissue moduli were based on the attenuation values of the bone and marrow phases extracted from the whole 3D images. The CT-attenuation to modulus conversion used the following relation developed by Homminga et al. [23],

$$E_{element} = E_{tissue} \cdot (GV_{element})^\gamma, \quad (1)$$

where each element was assigned an elastic modulus ($E_{element}$) based on the relative gray-value of that element ($GV_{element}$) normalized to a range from 0 (marrow) to 1 (bone). The gray-value data was normalized to 1754 mg HA/cm³ (corresponding to 12,000 CT number), and negative moduli were removed. Trabecular and cortical bone types were treated the same. The elastic modulus (E_{tissue}) and exponent (γ) constants depend on the image resolution and structure size, and were determined using back-calculation against the experimentally determined apparent modulus. The pair of constants that best described all specimens ($N=40$) was used to define the moduli in the finite element meshes (Poisson's ratio of 0.3). The tissue moduli were binned to 8-bit data (127 possible moduli) for all the 'scaled' finite element models (both linear and non-linear models).

The generation of both 'homogeneous' and 'scaled' finite element models resulted in a total of 80 models to be solved (40×2) by either linear or non-linear analyses. The boundary conditions were the same for all models and represented the experimental uniaxial compression tests. Nodes at the bottom platen surface were fixed in the Z direction (i.e., uniaxial testing direction), but free to move in the XY plane, and nodes at the top surface were free to move in the XY plane while a displacement in the Z direction was applied corresponding to 1% strain for the linear finite element models, and 4% for the non-linear models.

Finite element modeling

Linear finite element models were solved using custom large-scale finite element software [29] that was modified for parallel processing for this study on a parallel shared memory supercomputing system using 16 processors (64 bit 1.9 GHz processors, 4 GB of RAM per processor). The apparent modulus, E_{app} , of the specimens was calculated based on the reaction force determined by the finite element model at 1% strain, and specimen average cross-sectional area. The apparent modulus was determined for the 'scaled' and 'homogeneous' models ($E_{a,homo}$ and $E_{a,scaled}$, respectively).

The non-linear finite element analysis was performed on the 10 distal radius specimens corresponding to the 'clinical' site. The yield criterion was based on maximum compressive and tensile yield strains incorporated into the constitutive model. When the tissue maximum principal tensile or compressive strain exceeded those yield values, the elastic properties of the tissue were reduced by 95% [16]. The tensile-compressive yield strength asymmetry was set to 0.6 which is similar to values reported for cortical and trabecular bone [30,31]. The resulting bilinear, asymmetric constitutive model for the tissue [16] was incorporated into our custom large-scale finite element software and solved with 20 steps of incrementing strain to a maximum of 4% apparent strain. The number of steps was determined by ensuring the force-deformation results were stable, while balancing the available computational capacity (i.e., a <5% change in peak load occurred when increasing the number of steps from 15 to 20). The tissue yield tensile (ϵ_t) and compressive (ϵ_c) strains needed to be determined so that the experimental data could be simulated by the finite element model. Similar to the approach for determining the elastic moduli, the 'clinical' site models were solved with a range of yield parameters while maintaining the 0.6 asymmetry until a single set of values could be determined that best represented the experimentally determined yield strength. A set of tensile and compressive yield strains was determined for the homogeneous and scaled finite element model types. The finite element solver was run on a non-shared memory supercomputing system using 16 processors (64 bit 2.4 GHz processors, 4 GB of RAM per 2 processor node).

Statistics

Correlations and regression equations between the experimental measurements and the corresponding finite element predictions were determined (SPSS 14.0, Chicago, USA). A modified *t*-test for significant differences between the correlations was determined based on a significance level of $p < 0.05$. The mean and standard error of the ultimate strength prediction compared to the gold-standard experimental results was reported.

Results

Average morphological indices were determined for each of the four measurement sites ($N=10$ /site) (Table 1). The physical size, volumetric density and cortical thickness varied considerably among the four sites providing a wide range of specimen morphology (and strength).

Experimental testing data provided apparent modulus for all 40 specimens. Failure data was obtained for 31 of those specimens from which the ultimate stress (ultimate strength) was determined. The nine specimens could not be tested until failure since the failure load that would have been needed exceeded the load cell capacity (9.5 kN). Eight of those specimens were from measurement sites 3 and 4, and one specimen was from the clinical site (site 2). Correlations between the apparent modulus (stiffness) and apparent strength (ultimate stress) determined experimentally were $R^2=0.977$ ($N=31$) indicating that stiffness has a strong predictive ability for strength (Fig. 4a).

The finite element meshes generated with both homogeneous and scaled tissue moduli resulted in models with up to 11.7 and 31.8 million degrees of freedom, respectively. The average number of elements, nodes and degrees of freedom for each site is presented in Table 2. The elastic tissue properties determined by back-calculation against the experimental data for the homogeneous models ($E_{t,homo}$) were 6829 MPa. The parameters determined for the scaled model (Eq. (1)) were an elastic modulus (E_{tissue}) of 15,004 MPa, and an exponent (γ) of

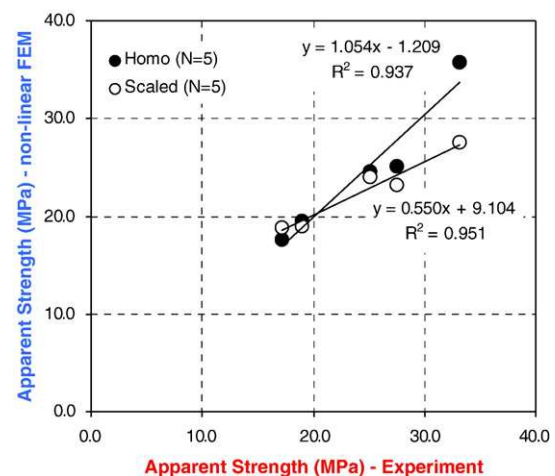


Fig. 6. Correlations and regression equations of non-linear finite element analysis determined apparent strength determined from homogeneous ($N=5$) and scaled ($N=5$) models against the experimentally determined apparent strength for the same specimens.

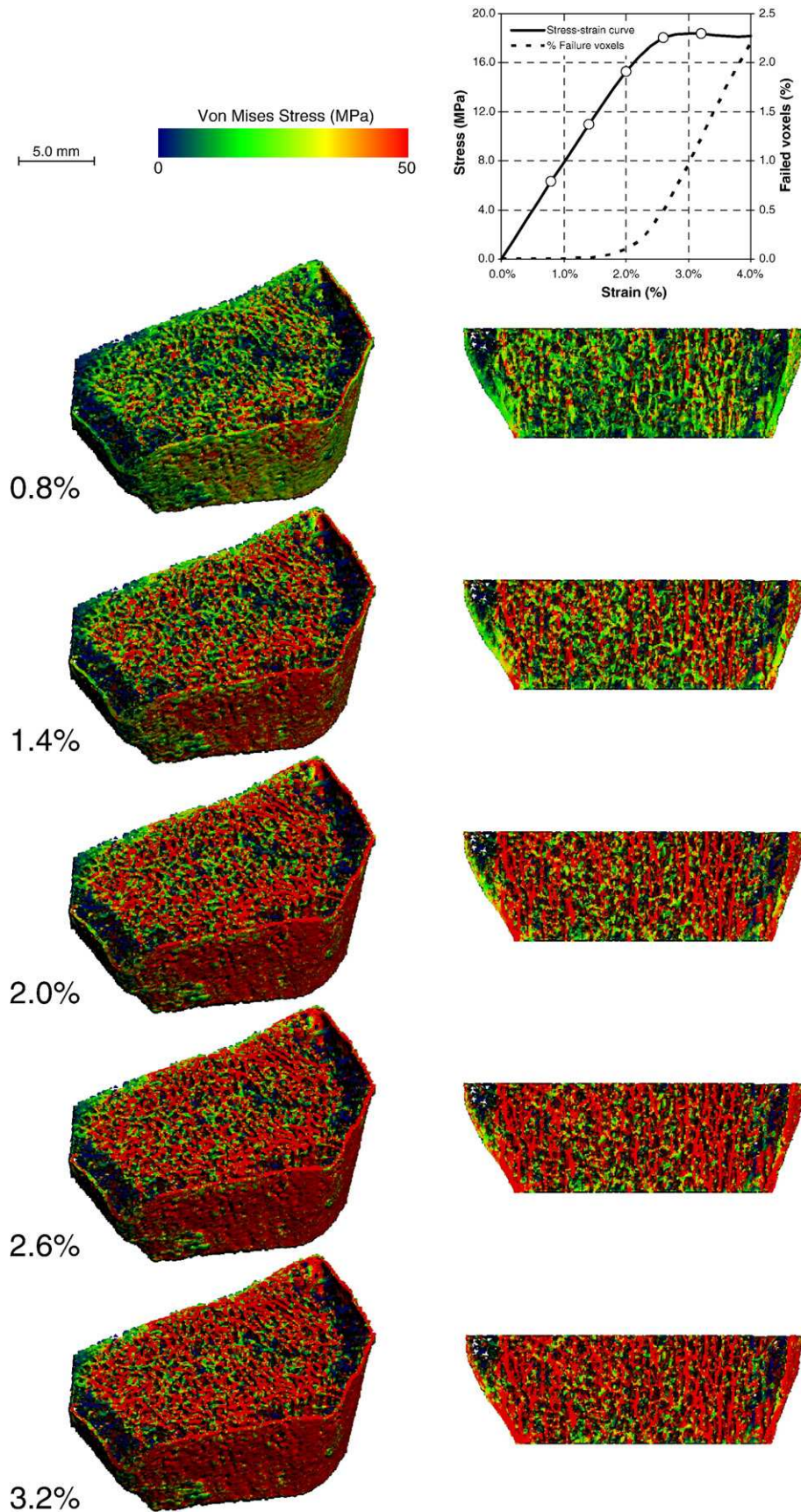


Fig. 7. Visualization of the von Mises stress (represented as color scalars) from a typical non-linear analysis of a model with a homogeneous tissue modulus. The visualizations represent the state of tissue stress at five key steps during the uniaxial compression.

1.7. The 80 models were solved to determine the apparent modulus and took on average 2.6 h (range 1.4 to 5.0 h) per model. Correlations were performed between the apparent modulus determined by the homogeneous and scaled models with the experimentally determined strength (Fig. 4b), and both types of linear finite element models were excellent predictors of strength although scaled models performed slightly better ($R^2=0.983$ and $R^2=0.972$, respectively, $p<0.05$).

Five non-linear analyses were successfully completed for both homogeneous and scaled models of the clinical site data. Of the nine specimens for which there was experimental data available, three non-linear analyses could not be completed due to hardware constraints, and one model did not converge to a solution. The average solution time was 25 ± 8 and 29 ± 4 h for the homogeneous ($N=5$) and scaled ($N=5$) models. The asymmetric yield strain for tension and compression ($\epsilon_{t,homo}$ and $\epsilon_{c,homo}$) determined for the homogeneous models was 0.0295 and 0.0493, respectively. Similarly, for the scaled models the asymmetric yield strain ($\epsilon_{t,scaled}$ and $\epsilon_{c,scaled}$) was 0.0127 and 0.0212, respectively. A comparison of the stress–strain data determined experimentally and by non-linear analysis is presented for each of the five specimens (Fig. 5) revealing similar patterns up to the ultimate stress. Correlations between the apparent strength determined experimentally and by finite element analysis were $R^2=0.937$ and $R^2=0.951$ for homogeneous and scaled models, respectively, again with scaled models performing slightly better ($N=5$, $p<0.05$, Fig. 6). At the ultimate stress, an average of 1.3% and 7.6% of the tissue volume failed in the homogeneous and scaled models, respectively. The von Mises stress for a specimen illustrating five displacement steps (from 20) in the Z axis by non-linear analysis of a homogeneous tissue modulus model is shown (Fig. 7).

For the five clinical samples, the absolute error in the finite element prediction of strength (ultimate stress) compared with the experiments was determined and summarized in Table 3. The strength estimates were obtained directly from the peak of the stress–strain curves for the non-linear finite element analysis. For the linear analysis, the regression equations (for homo-

geneous and scaled models) between apparent stiffness and apparent strength (Fig. 4b) were used to estimate strength based on the determined apparent stiffness. The coefficient of the errors for the five specimens was $<14\%$ for the linear models, and $<10\%$ for the non-linear model.

Discussion

This study demonstrated that finite element models based on 3D measurements from HR-pQCT can estimate bone strength in the human distal radius. Strength is a fundamental determinant of fracture risk, and the results here suggest that the finite element method is a good surrogate measure for bone strength. Based on experimental testing with the cadaver data, it was demonstrated that stiffness is highly correlated with strength at the distal radius under uniaxial compression. This finding supports the use of linear finite element modeling to predict strength at the radius, and it was also found that excellent correspondence of strength by non-linear analysis could be attained.

There are limitations to this study that should be discussed. Clearly, the boundary conditions utilized here do not necessarily reflect the loading of the radius *in vivo*. However, the goal here was to validate the finite element model results with experimental data, therefore it was crucial that the boundary conditions of the experiments and the models were matched. It was found that the model agreement with the experimental data was high over a wide range of morphological structures, and now future work should consider whether other types of loading can also be modeled effectively. Another consideration is whether the region scanned in patients by HR-pQCT (the clinical region) is representative of the whole radius in a Colles fracture. A preliminary cadaver validation study suggests that it is representative of whole bone strength [32], and recent work in our laboratory using image guided failure assessment also supports that finding (unpublished). Whether the strength of the radius is representative of the strength of central skeletal sites (i.e., lumbar spine, proximal femur) is not clear, and is something that will undoubtedly need to be explored in future research. Although the finite element modeling techniques in this study were not validated on an independent sample cohort from which the model parameters were determined, the goal here was to determine if finite element models could estimate bone strength, and this was clearly the case. A small number of parameters were determined (elasticity and yield parameters) and these provided the finite element models enough versatility to predict bone strength on specimens with a wide range of structures. It is likely that these same parameters could be used to model failure behaviour of other bones measured by HR-pQCT, but further testing and validation is necessary, particularly for the non-linear analyses since five specimens were successfully tested. Finally, the finite element approach used here does not account for damage accumulation (micro cracks) that may compromise bone strength [33]; however, it is still not clear how much damage accumulation occurs in people, and whether at physiological levels it has an impact on bone strength [34,35].

Table 3

Apparent bone strength (ultimate stress, GPa) determined experimentally, and predicted by both linear (via the stiffness–strength regression equations shown in Fig. 3) and non-linear finite element models for the five clinical specimens

Site	Experimental	Linear FEM		Non-linear FEM	
		Homogeneous	Scaled	Homogeneous	Scaled
Mean	24.42	27.83	27.95	24.52	22.54
Min	17.20	18.71	20.00	17.60	18.83
Max	33.20	41.81	38.59	35.77	27.52
SD	6.49	9.12	7.75	7.07	3.67
Mean error	–	3.59	3.53	1.29	2.53
SD	–	3.36	2.30	1.10	2.36
%CV	–	13.75	9.44	4.52	9.66

The mean, minimum, maximum and standard deviation of the apparent strength for the five specimens presented, as well as the Mean error, standard deviation and coefficient of variation of the difference between the finite element model results and the experimental results.

The experimental finding that strength can be predicted from stiffness was unexpected and important. It provides insight into the failure behaviour of the distal radius, and suggests that apparent strain is the limiting factor (i.e., fracture occurs if a certain strain threshold is exceeded). The high correlation indicates that there is a linear relation between stiffness and strength, and this is not a universal relation observed in all engineering materials. For example, the strength of steel can be modified by alloying or heat treatment to modify its strength without affecting stiffness in which case a linear relation would not exist for differently tempered steels. It is not known what effect anti-fracture therapies may have on strength independently from stiffness. Also, at other skeletal sites having different bone types, it is not known whether the linear relation between stiffness and strength would hold true. These relations should be tested at other skeletal sites, as well as with animal bones where drug treatment effects can be investigated. Nevertheless, the fact that apparent strain was a limiting factor of the experimental data supports the choice to use the asymmetric, bilinear maximum principal compressive and tensile yield strain criterion [16] for our non-linear analyses. Strain has been used in linear models as a means to assess maximum load capacity of a bone [17]. It is possible that the high correlation between stiffness and strength is only valid for axial compression in this very specific measurement protocol (HR-pQCT). However, for HR-pQCT measurements specifically, it supports the use of a linear analysis to predict strength via an estimation of stiffness as the correlation with experimentally determined stiffness is high ($R^2 > 0.966$, $N = 31$, data not shown). Thus, the regressions equations for homogeneous and scaled models shown in Fig. 4 can be a basis to estimate strength of the distal radius. Indeed, for the five specimens representing the ‘clinical’ measurement site (Table 3), the error expressed in terms of the coefficient of variation was less than 14%. Notably, the computational cost of the linear models is an order of magnitude less than the non-linear approach.

The use of a scaled modulus in the finite element models has the advantage of being able to partially accommodate for partial volume effects by modulating the modulus according to CT-attenuation values, whereas the homogeneous model can only define each image voxel as bone or marrow. The elastic and yield constants determined through back-calculation are intrinsically adjusted to account for segmentation errors and partial volume effects. Nevertheless, the resolution of HR-pQCT is at the cusp of distinguishing small trabecular structures (or thin cortices), and this may explain why the yield strain constants determined here were higher than previous estimations for models generated from high-resolution micro-CT measurements of trabecular structures (0.60% tension, 1.01% compression) [16]. The lowest yield strain constants determined here were for the scaled models, and this was likely due to its continuum representation of the bone structure. It should be pointed out that finite element simulations based on clinical CT typically use continuum representations [7], but the models based on HR-pQCT are distinguished by that fact that they still incorporate micro-architectural features (Fig. 3). We chose to model the cancellous and cortical bone uniformly using a single

set of elastic and yield parameters; by determining yield characteristics of those tissues separately it may be possible to improve the simulation of the apparent strength behaviour.

The elastic region of the stress–strain curves (Fig. 5) was consistently overestimated by the non-linear scaled model analyses, but not in the homogeneous model analyses. This is related to the fact that the elastic constants were determined from all 40 specimens, but here only five specimens representing the clinical site are shown. The homogeneous models typically overcompensate total bone volume during segmentation by thresholding [27], and this occurs for both the cancellous and cortical regions. In contrast, the scaled models do not involve thresholding, but partial volume effects are more significant in specimens with proportionally more cancellous bone (i.e., sites 1 and 2) compared to the more proximal sites (3 and 4). The five scans representing the ‘clinical’ sites contain a large proportion of cancellous bone (Table 1) leading to the overestimation for specimens. A future study may benefit from focusing on only specimens from the ‘clinical’ site, rather than a range of sites represented in our 40 specimens. Also, improved segmentation strategies could potentially improve the generation of the homogeneous FE models [36,37].

The systematic error in apparent stiffness at the clinical site does not reduce the ability of the finite element method to accurately estimate bone strength. If the error was random, rather than systematic, then there would be more cause for concern. The advantage of scaled models, from a computational perspective, was that they were easier to solve (less iterations for convergence) and their predictive ability performed as well or better than the homogeneous models. An important advantage of using a scaled model is that they have the potential to assess effects of anti-fracture therapies that may influence tissue density (i.e., teriparatide, bisphosphonates) which would not be possible with a homogeneous model. The ultimate goal is to measure bone strength with *a priori* determined constants (elasticity, yield); therefore, the flexibility of a scaled modulus to account for density changes is important. The value of 1.7 found was comparable with others’ findings [23,38], but more work needs to be completed to establish reliable relations between CT-attenuation and elastic modulus in the context of varying bone tissue density due to anti-fracture therapies.

The non-linear FE model required considerably more computational effort than the linear model, but it has the advantage that it can capture the apparent strength behaviour of the tissue. The stress–strain curves extended past the ultimate strength peak, and although it was not the focus of this study, it was notable that the homogeneous model performed better than the scaled models in this region. The sudden drop in strength (Fig. 6) suggests that the reduction in modulus by 95% for failed elements was too severe, and it may require further consideration such as setting a constant rather than proportional post-yield stiffness (perhaps being more representative of the remnant stiffness provided by the collagen network). The determination of ultimate load from non-linear analysis is often based on using yield strength and the 0.2% offset rule, but our model differs somewhat in that the ultimate strength was

determined directly from the peak of the stress–strain curves, and this was performed on a complete section of bone that incorporated both cancellous and cortical compartments. Future improvements of our custom finite element software source code should resolve the computational problems and hardware constraints that prevented a solution for some of the clinical models, and in the future it may be feasible to routinely determine the full apparent strength characteristics of bone *in vivo*.

Finally, osteoporosis is a disease of low bone strength, not low bone mass. The finite element method is a good surrogate of bone strength, and although the non-linear approach provides significant yield behaviour, a linear approach can provide a good estimate of strength with significantly less computational effort. The protocol for HR-pQCT measurement of the distal radius is standardized across research sites, and therefore the finite element approaches and associated model parameters are widely relevant. These data strongly support the use of the finite element approach to estimate bone strength at the distal radius.

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