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CONTRIBUTION OF EXTRAFIBRILLAR MATRIX TO THE MECHANICAL BEHAVIOR OF BONE USING A NOVEL COHESIVE FINITE ELEMENT MODEL

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Abstract

The mechanical behavior of bone is determined at all hierarchical levels, including lamellae (the basic building block of bone) that are comprised of mineralized collagen fibrils and extrafibrillar matrix. The mechanical behavior of mineralized collagen fibrils has been investigated intensively using both experimental and computational approaches. Yet, the contribution of the extrafibrillar matrix to bone mechanical properties is poorly documented. In this study, we intended to address this issue using a novel cohesive finite element (FE) model, in conjunction with the experimental observations reported in the literature. In the FE model, the extrafibrillar matrix was considered as a nanocomposite of hydroxyapatite (HA) crystals bounded through a thin organic interface modeled as a cohesive interfacial zone. The parameters required by the cohesive FE model were defined based on the experimental data reported in the literature. This hybrid nanocomposite model was tested in two loading modes (*i.e.* tension and compression) and under two hydration conditions (*i.e.* wet and dry). The simulation results indicated that (1) the failure modes of the extrafibrillar matrix predicted using the cohesive FE model were closely coincided with those experimentally observed in tension and compression tests; (2) the pre-yield deformation (*i.e.* internal strain) of HA crystals with respect to the applied strain was consistent with that obtained from the synchrotron X-ray scattering measurements irrespective of the loading modes and hydration status; and (3) the mechanical behavior of the extrafibrillar matrix was dictated by the properties of the organic interface between the HA crystals. Taken together, we postulate that the extrafibrillar matrix plays a major role in the pre-yield deformation and the failure mode of bone, thus, giving rise to important insights in the ultrastructural origins of bone fragility.

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Keywords

Bone; Cohesive Finite Element Modeling; Dehydration; Extrafibrillar Matrix; Organic Interface; Tension and Compression Test

INTRODUCTION

Bone is a natural composite of mineral and organic phases with a highly hierarchical structure at multiple length scales from a few millimeters to a few nanometers (Rho et al., 1998). At each length scale, functional adaptations enable bone to exhibit remarkable strength and stiffness to act as a load-bearing structure in the body, yet possess sufficient toughness to avoid brittle failures. At the ultrastructural level, lamella is the basic building block of bone, which is comprised of mineralized collagen fibrils embedded in an extrafibrillar matrix (Deymier-Black et al., 2012). The mechanical behavior of the mineralized collagen fibrils has been well studied by researchers (Burr, 2002; Gupta et al., 2013; Nair et al., 2013; Vercher-Martínez et al., 2015). However, the contribution of the extrafibrillar matrix to the mechanical properties of bone is still poorly understood. An experimental study using a mice model by Karunaratne et al. (Karunaratne et al., 2012) showed that disruption of extrafibrillar mineralization by disease may significantly impact the nano-mechanics of bone. In the absence of a reinforcing extrafibrillar matrix, collagen fibrils were found to deform to a greater extent compared to healthy bone. Further, a computational study by Nair et al. (Nair et al., 2014) showed that the mineralized collagen fibril by itself does not have sufficient stiffness to sustain the compressive forces experienced by bone. These results suggest that the extrafibrillar matrix presumably plays an important role in carrying load at the ultrastructure level of bone.

Structurally, the mineral crystals in the extrafibrillar matrix are most likely granular in shape (McNally et al., 2012) and are interconnected *via* a thin layer of organic matrix. Hence, the extrafibrillar matrix may be considered as a hybrid composite of granular mineral crystals bounded through a thin organic interface. This organic interface contains heterogeneous group of non-collagenous matrix proteins, including osteopontin (OPN) and osteocalcin (OC), bone sialoproteins (BSP), and proteoglycans (PGs) (Sroga and Vashishth, 2012; Wise et al., 2007). Although these non-collagenous proteins account for only a small percentage (less than 10% by volume) of the organic phase in bone, they may play an important role in sustaining the structural integrity of the tissue (Fantner et al., 2007; Huang et al., 2009; Kasugai et al., 1991; Poundarik et al., 2012; Thurner et al., 2010). For instance, a recent study suggests that the mineralized fibrils might be reinforced by dilatational band formation in the extrafibrillar matrix (Nikel et al., 2013; Poundarik et al., 2012).

In addition, it is well known that proteoglycans (PGs) help attract water into the extracellular matrix of tissues, such as cornea and articular cartilage (Bertassoni and Swain, 2014; Gandhi and Mancera, 2008; Heinegård and Oldberg, 1989). Thus, changes of PGs in bone matrix may directly alter the hydration status of bone matrix (Broz et al., 1993; Jameson et al., 1993). Of the two constituents in the extrafibrillar matrix (*i.e.* mineral crystals and organic interface), the mineral crystals are unlikely to directly contribute to the plastic deformation

of bone. Hence, we speculate that the organic interface makes a significant contribution to the plasticity and toughening of bone by allowing the mineral crystals to slide relative to each other (Buehler, 2007; Buehler et al., 2008; Ritchie et al., 2009).

To test this hypothesis, we proposed a two dimensional cohesive finite element (FE) model of the extrafibrillar matrix, as a hybrid nanocomposite of mineral crystals bound together by a thin organic interface. The mineral crystals and the organic interface were represented by Voronoi generated grains and cohesive interfacial zones respectively. Using this model, we simulated the mechanical behavior of the extrafibrillar matrix under different loading modes (tension vs. compression) and hydration status (wet vs. dry). In the model, newly defined traction-separation laws were introduced to mimic the interfacial behavior in the extrafibrillar matrix. The simulation results were compared with the experimental observations (*i.e.* microdamage formation and the *in-situ* mineral strain measured by synchrotron X-ray diffraction techniques) to verify the efficacy of the model in predicting the ultrastructural behavior of bone.

METHODS

Geometric model of the extrafibrillar matrix

For simplicity while ensuring reasonable accuracy, a two-dimensional (2-D) plane strain model of granular HA crystals bounded through a thin interface (Fig.1) was proposed in this study to mimic the extrafibrillar matrix in bone (Tai et al., 2006). Briefly, polygonal shaped mineral crystals were first generated using the Centroidal Voronoi tessellation method in a 2-D geometric model (Lin et al., 2014b). Then, a cohesive zone was created to represent the organic interface between the mineral crystals by recessing the edges of each grain cell in a parallel manner towards the centroid of the grain with a designated distance (Fig.1). Based on the previous convergence test of similar models (Evesque and Adjémian, 2002), a minimum of 100 grains were required for the proposed 2-D model to ensure consistent outcomes. In this study, roughly one hundred and forty four (144) grains were created in each representative model. In this study, the average grain size was set to be around 25nm , which is within the size range of mineral crystals reported in the literature (Qin et al., 2012). The thickness of organic interface was set to be $\delta_0 = 2\text{nm}$ throughout the model, which was selected based on the calculation from the estimated volume fraction of non-collagen proteins ($\sim 10\%$ by volume, in the extrafibrillar matrix) (Olszta et al., 2007; Sroga and Vashishth, 2012). Thus, the total dimension of representative model was $L_x \times L_y = 322\text{nm} \times 322\text{nm}$.

Cohesive zone model

In this study, the organic interface between the mineral crystals was modeled using a modified cohesive zone model derived from the Xu and Needleman's exponential cohesive model (Xu and Needleman, 1994). In this model, the traction-separation laws in normal and tangential direction are expressed as:

$$T_n = \begin{cases} \sigma_c \left(\frac{\Delta_n - \delta_0}{\delta_{dn} - \delta_0} \right) \exp(1) \exp \left(-\frac{\Delta_n - \delta_0}{\delta_{dn} - \delta_0} \right) & \Delta_n \leq \delta_{dn} \\ \sigma_c \left(\frac{\delta_{fn} - \Delta_n}{\delta_{fn} - \delta_{dn}} \right)^{p_n} & \Delta_n > \delta_{dn} \end{cases} \quad (1)$$

$$T_t = \begin{cases} \tau_c \sqrt{\exp(1)} \left(\frac{\Delta_t}{\delta_{dt}} \right) \exp \left(-\frac{\Delta_t^2}{2\delta_{dt}^2} \right) & |\Delta_t| \leq \delta_{dt} \\ \tau_c \frac{\Delta_t}{|\Delta_t|} \left(\frac{\delta_{ft} - |\Delta_t|}{\delta_{ft} - \delta_{dt}} \right)^{p_t} & |\Delta_t| > \delta_{dt} \end{cases} \quad (2)$$

where, T_n and T_t are traction force, σ_c and τ_c are the strength of the interface, δ_{dn} and δ_{dt} are the critical separation for initiation of interfacial damage, and δ_{fn} and δ_{ft} are the separation at failure in normal and tangential direction, respectively. δ_0 is the equilibrium position (zero separation) of the interfacial zone and $\exp(1) = 2.71828$. The shape parameters (p_n , p_t) are introduced in the model to characterize the damage progression at the interface. For instance, when $p_n = 0$ or $p_t = 0$, it represents the elastic perfectly plastic behavior in normal or tangential direction. For simplicity of analyses without losing critical information, p_n and p_t were set to be unity in this study, which represents a linear interfacial damage progression when the separation (Δ_n & Δ_t) exceeds the critical separation (δ_{dn} & δ_{dt}) in the normal and tangential direction, respectively.

The stiffness of the interface is defined at the equilibrium position in the normal and tangential direction as:

$$\frac{dT_n}{d\Delta_n} = \sigma_c \exp(1) \left[\left(\frac{1}{\delta_{dn} - \delta_0} \right) \exp \left(-\frac{\Delta_n - \delta_0}{\delta_{dn} - \delta_0} \right) - \left(\frac{\Delta_n - \delta_0}{(\delta_{dn} - \delta_0)^2} \right) \exp \left(-\frac{\Delta_n - \delta_0}{\delta_{dn} - \delta_0} \right) \right] \Big|_{\Delta_n = \delta_0} = \frac{\sigma_c \exp(1)}{\delta_{dn} - \delta_0} \quad (3)$$

$$\frac{dT_t}{d\Delta_t} = \tau_c \sqrt{\exp(1)} \left[\frac{1}{\delta_{dt}} \exp \left(-\frac{\Delta_t^2}{2\delta_{dt}^2} \right) - \frac{\Delta_t^2}{\delta_{dt}^3} \exp \left(-\frac{\Delta_t^2}{2\delta_{dt}^2} \right) \right] \Big|_{\Delta_t = 0} = \frac{\tau_c \sqrt{\exp(1)}}{\delta_{dt}} \quad (4)$$

Eqs. (3) and (4) suggest that the value of $(\delta_{dn} - \delta_0)$ and δ_{dt} can be used to tune the interfacial stiffness in normal and tangential direction, respectively. Moreover, the normal and shear fracture energy of the interface could be defined, respectively, as the area under the traction-separation curves:

$$\mathcal{G}_n = \int_{\delta_0}^{\delta_{fn}} \mathbf{T} d\boldsymbol{\delta} \quad (5)$$

$$\varnothing_t = \int_0^{\delta_{ft}} \mathbf{T} d\boldsymbol{\delta} \quad (6)$$

Among all the model parameters (fracture energy, strength, critical separation and failure separation) of this cohesive zone model, there are only three independent parameters in each direction (*i.e.* normal or tangential). In this study, we selected the fracture energy ($\varnothing_n, \varnothing_t$), critical separation (δ_{dn}, δ_{dt}), and failure separation (δ_{fn}, δ_{ft}) as the independent model parameters, with the strength (σ_c, τ_c) being readily determined by the three independent parameters.

Cohesive finite element (FE) simulations

Finite element (FE) model—In the cohesive FE model, the mineral grains were meshed using linear triangular elements and the interface between the crystals was modeled as a cohesive zone, whereas the interfacial behaviors were determined by the traction-separation laws. All simulations were implemented using a custom-developed finite element package (Li et al., 2012; Lin et al., 2014a; Lin et al., 2015; Lin and Zeng, 2015; Zeng and Li, 2010, 2012). Uniaxial load (either tension or compression) was applied to the finite element model by assigning a uniform displacement on both the top and bottom edges of the model (Lin et al., 2014a), with the right and left side of the specimen kept unconstrained. In this study, two different test conditions were investigated. One set of simulations was performed to study the effect of loading modes (tension vs. compression) on the mechanical behavior of the extrafibrillar matrix. The other set was performed to examine the effect of interfacial hydration status on the mechanical behavior of the extrafibrillar matrix.

For each test condition, simulations were repeated on six sample models, which were generated using a Centroidal Voronoi tessellation (Lin et al., 2014b) based on a random distribution function in order to count for the possible effect of random variations in the shape and size distribution of grains within the model. To determine the optimum mesh size (*i.e.* 7.5nm), and the minimum sampling number (*i.e.* N=6), convergence tests were carried out until the peak mineral strain in the model became consistent.

Material properties—In this study, two cases were investigated in the simulations. In *Case 1*, the models were loaded in either tension or compression to examine the mechanical response of extrafibrillar matrix under different loading modes. In *Case 2*, the effect of dehydration on the mechanical behavior of the extrafibrillar matrix was examined. The material properties of mineral crystals were chosen from the values reported in the literature: Young's modulus $E = 100\text{GPa}$, Poisson's ratio $\nu = 0.28$ (Siegmund et al., 2008), mineral density $\rho = 3,190\text{kg/m}^3$ (Haverty et al., 2005). The mechanical behavior of the organic interface was governed by traction-separation laws, which are uniquely defined by three independent parameters: *i.e.* fracture energy ($\varnothing_n, \varnothing_t$), critical separation (δ_{dn}, δ_{dt}), and failure separation (δ_{fn}, δ_{ft}). In this study, these parameters were estimated based on the experimental observations (Bayraktar et al., 2004; Currey, 2004; Fyhrie and Schaffler, 1994; Gupta et al., 2006; Keaveny et al., 1994; Kopperdahl and Keaveny, 1998; Mercer et al.,

2006; Pithioux et al., 2004; Samuel et al., 2016) and the information reported in the literature (Luo et al., 2011; Siegmund et al., 2008).

Case 1. Loading mode dependence: Of the three independent parameters for the interfacial zone model, the fracture energy in the opening mode (φ_n) was approximated as $0.04\text{J}/\text{m}^2$, assuming that the van der Waals type of interaction was dominant, whereas the fracture energy in the shear mode (φ_s) was estimated as $0.15\text{J}/\text{m}^2$, assuming that a hydrogen bond interaction was dominant. Since the mineral phase is much harder and stronger than the organic interface, the bulk deformation and the failure of the extrafibrillar matrix are most likely determined by the behavior of the organic interface. In this study, the parameters of traction-separation laws that govern the behavior of the interfacial zone were estimated assuming that the yield and failure strains in the model (*i.e.* yield and failure strains of the extrafibrillar matrix) were consistent with the global yield and failure strains measured experimentally in bone. Specifically, the critical displacement in the opening mode ($\delta_{dn} - \delta_0$) at the interface was set to be 0.15nm. This value was estimated approximately assuming that the tensile yield strain (*i.e.* initiation of interfacial damage) of the model was 0.5%, which was within the range of the tensile yield strain (0.36%–1.2%) of human bone reported in the literature (Bayraktar et al., 2004; Currey, 2004; Gupta et al., 2006). In compression, the deformation and failure of bone is dominated by the shear mode (George and Vashishth, 2005), which most likely occurs at the interfaces inside extrafibrillar matrix. Thus, the critical separation at the interface (δ_{ds}) in the shear mode was set to be 0.36nm, which was estimated assuming that the yield strain of the extrafibrillar model in compression was 1.4%, which was within the range of 0.75%~1.42% reported in the literature (Bayraktar et al., 2004; Keaveny et al., 1994; Kopperdahl and Keaveny, 1998). Similarly, the failure separation in the opening mode ($\delta_{fn} - \delta_0$) of 0.6nm was estimated assuming that the tensile failure strain of the model was about 2% (Pithioux et al., 2004), whereas the failure separation in the shear mode (δ_{fs}) was set to be 1.9nm assuming that the compressive failure strain of the model was 7.4%, which was within the range of the compressive failure strain (6%–15%) (Fyhrie and Schaffler, 1994; Mercer et al., 2006) (Table 1).

Case 2. Hydration status dependence: It is well known that dehydration makes bone stronger but more brittle (Akhtar et al., 2011; Samuel et al., 2016; Yan et al., 2008). A recent study indicated that bound water residing in very small ultrastructural space ($< 4\text{\AA}$) dominates the toughness of bone (Samuel et al., 2014). In this study, we assumed that the organic interface played the role in retaining the bound water in the extrafibrillar matrix. Thus, it could be reasonably deduced that the failure energy of the organic interface under wet condition would be much greater than that under the dehydrated condition. Hence, the failure energy of the dehydrated interface was assumed to be much less than those of hydrated ones. Specifically, the failure energy of dehydrated interfacial zone was selected as $0.02\text{J}/\text{m}^2$ for the opening mode (φ_n), and $0.06\text{J}/\text{m}^2$ for the shear mode (φ_s), respectively. Similarly, the critical displacement in the opening mode ($\delta_{dn} - \delta_0$) of 0.15nm was estimated, assuming that the tensile yield strain of the extrafibrillar model was 0.5%, whereas the critical separation in the shear mode (δ_{ds}) was determined as 0.36nm, assuming that the compressive yield strain of the model was 1.4% under compression. Finally, we assumed that the dehydrated interface would fail at the critical separation (δ_{dn} and δ_{ds}) without any

post-yield deterioration seen in the hydrated interface (Table 1). The curves of the traction-separation laws defined above are plotted in Fig.2.

Data analysis

In this study, the progressive deformation and failure behavior of the extrafibrillar matrix were first plotted in terms of the snapshots of stress distribution and deformation/failure behaviors. Then, the average strains of mineral crystals obtained from different conditions (*i.e.* different loading modes and hydration status) were compiled as mean $\pm$ standard deviation and plotted with respect to the applied strain. Moreover, the internal mineral strain from simulation were compared with those obtained from the synchrotron X-ray diffraction measurements reported in the literature (Samuel et al., 2016).

RESULTS

Loading mode dependence

Deformation & failure pattern—Significant differences in the deformation and failure mode were observed when the extrafibrillar matrix model was subject to different loading modes (*i.e.* tension vs. compression) under wet condition (Fig.3 & Fig.5). The cohesive FE simulation results indicated that the damage and nano-cracks were always initiated at the interface perpendicular to the loading direction when the model was loaded in tension. In contrast, in compression shear bands were formed always along an inclined angle and intergranular cracks propagated *via* a relative sliding between the mineral crystals. For ease of observation, we plotted the normal stress (σ_{22}) distribution for the model loaded in tension to show the opening damage progression during the simulation (Fig.3), whereas the shear stress (σ_{12}) distribution in the model was plotted to exhibit the shear deformation and failure during the simulations (Fig.5).

In tension, it was observed that the damage always started at the interfaces perpendicular to the loading direction, showing the relaxation (or decrease) of normal stress σ_{22} in the crystals adjacent to the damaged interface zone. As the load increased, intergranular cracks nucleated, coalesced, and eventually traveled transversely through the specimen (Fig.3). These simulation results suggested that the opening mode was the dominant mode for the deformation and failure in tension.

In compression, however, the deformation was realized through the shear deformation along the organic interface between the mineral crystals. The simulation results indicated that shear bands (*i.e.* zone of shear stress concentration) were first formed in the model followed by sliding along the interfaces between mineral crystals. Finally, cracks propagated along an inclined angle (around 30° with respect to the loading direction) in the extrafibrillar matrix (Fig.5). These simulation results suggested that the deformation and failure of the model under compression was dominated by intergranular shear and sliding between the mineral crystals.

Stress-strain curve—The stress-strain curves were obtained for both tensile and compressive loading modes (Fig.7). Using the curves, the elastic moduli of the extrafibrillar matrix model were estimated around 27.0GPa under tension and 55.3GPa under

compression. In addition, the maximum stress was about 120MPa in tension and close to 600MPa in compression.

Internal mineral strain—The pre-yield curve of mineral strain vs. applied strain predicted in the cohesive FE simulations indicated a good agreement with the experimental observations in the synchrotron X-ray diffraction measurements in both loading models (Fig. 8). However, the yield strain in compression was greater than that in tension. In addition, the pre-yield curve of mineral strain vs. applied strain in tension was nonlinear, whereas the curve of mineral strain vs. applied strain in compression showed a relatively linear pattern.

In contrast, the post-yield curve of mineral strain vs. applied strain was significantly different from that observed in synchrotron X-ray diffraction measurements in bone under different loading modes. In tension, the mineral strain dropped at the onset of yielding and then gradually increased with increasing applied strain, whereas in compression, mineral strain was gradually decreased with increasing applied strain after yielding.

Effect of dehydration

Deformation & failure pattern—The simulation results exhibited that the hydration status did not impose significant effects on the deformation and failure patterns of the extrafibrillar matrix model in both loading modes. The dehydrated model showed similar opening mode damage and intergranular crack propagation perpendicular to the loading direction in tension (Fig.4), and the inclined intergranular crack propagation in compression (Fig.6). These simulation results are consistent with the experimental observations in dry bone (Kahler et al., 2003).

Stress-strain curve—Upon dehydration, the elastic moduli of the extrafibrillar matrix model were around 39.9GPa under tension and 65.1GPa under compression, which were slightly greater than those under hydrated conditions (Fig.7). However, the maximum stress of the model with dehydrated interfaces (*i.e.* 250MPa in tension and 900MPa in compression) was much greater than those observed under hydrated condition (*i.e.* 120MPa in tension and 600MPa in compression).

Internal mineral strain—Considerable differences in mineral strain vs. applied strain are observed between hydrated and dehydrated interfaces (Fig.8). The mineral strains (ϵ_m) with dry organic interface were larger than that of specimens with wet organic interface and showed little post-yield deformation. The slopes of mineral strain vs. applied strain are steeper when interface is dry. Under tension, the mineral strain almost immediately dropped to zero with dry interface after yield point. Under compression, the mineral strain drops very sharply after yielding point with dry interface.

DISCUSSION

In this study, the extrafibrillar matrix in bone was modeled as a hybrid composite of granular mineral crystals interconnected *via* an organic interface using a novel cohesive finite element method. Under different loading modes and hydration conditions, the mechanical behavior of the extrafibrillar matrix was simulated to compare with the experimental observations of

the ultrastructural behavior of bone from microdamage histomorphometry and synchrotron X-ray diffraction measurements reported in the literature (Deymier-Black et al., 2012; Dong et al., 2011; Giri et al., 2012; Gupta et al., 2005; Samuel et al., 2016; Schaffler et al., 1994). The simulation results matched very well with the experimental observations, thus providing important insights into the underlying mechanisms of bone deformation and failure at the ultrastructural levels.

It has been known that the loading-mode dependence of bone mechanical behavior is manifested across all the hierarchies of the tissue (*i.e.* from bulk to ultrastructure) and originates most likely at the ultrastructural level (Li et al., 2013; Mirzaali et al., 2015; Nyman et al., 2009; Samuel et al., 2016). At the bulk tissue level, the stress-strain curve of bone in compression shows a strain softening behavior in the post-yield deformation and allows for larger plastic deformation and higher yield and failure strains compared with those in tension. In contrast, the stress-strain curve of bone in tension exhibits a strain hardening behavior after yielding. At the microstructural level, shear induced “cross-hatches” formation is the major failure mode of bone in compression, whereas the diffuse damage formation is the major failure mode in tension (Ebacher et al., 2007; Poundarik et al., 2012; Schaffler et al., 1994). At the ultrastructure level, the *in situ* deformation of mineral crystals also exhibits a loading-mode dependent behavior (Samuel et al., 2016).

The simulation results of the extrafibrillar matrix model reveal that both deformation and failure in tension are most likely dominated by the opening mode at the intergranular interface perpendicular to the loading direction (Figs. 3 & 4), whereas the damage progression in compression is controlled by the intergranular shear or sliding along the interface between the mineral crystals (Figs. 5 & 6). In fact, the two distinct deformation and failure patterns in tension and compression are consistent with bulk failure patterns reported in the literature (Ebacher et al., 2007; Fazzalari et al., 1998; Taylor et al., 2007). Specifically, the diffuse damage of bone observed in tension (Parsamian and Norman, 2001) is composed of numerous nano-cracks at ultrastructural levels of bone. The intergranular cracks formed in the extrafibrillar matrix as predicted in this study may actually be the source of nano-cracks observed in the diffuse damage. A recent observation of nanoscopic dilatation bands formed in the extrafibrillar matrix also supports the speculation (Poundarik et al., 2012).

In contrast, “cross-hatch” cracks are formed mainly in bulk tissue of bone under compression and always aligned with an angle between 30–40° with respect to the loading direction as observed in the experiments (Ebacher et al., 2007). Similarly, the simulation results of this study indicate that the shear-induced intergranular damage and cracks are formed in a typical inclination angle of about 30° with respect to the loading direction (Fig. 5). This result suggests that the intergranular sliding at the interface between the mineral crystals in the extrafibrillar matrix may be the ultrastructural origin of bulk bone failure in compression. In fact, such intergranular sliding actually accommodates much larger deformation of bone in compression compared with tension.

In addition, the pre-yield deformation of mineral crystals predicted using the extrafibrillar matrix model is very similar to that observed in synchrotron X-ray diffraction measurements, suggesting that the extrafibrillar matrix plays a major role in the pre-yield

deformation of bone. It is not surprising because the extrafibrillar matrix is mainly composed of mineral crystals (~90%), thereby making it significantly stiffer than the mineralized collagen fibrils, which contains only 20–40% of mineral crystals (Fratzl et al., 2004; Hang and Barber, 2011; Nudelman et al., 2010). Recent experimental studies have shown that the elastic modulus of mineralized collagen fibrils is in the range of 1–3GPa (Hang and Barber, 2011; Nair et al., 2013), whereas the elastic modulus of the extrafibrillar matrix predicted in this study is between 27.0–39.9GPa in tension and 55.3–065.1GPa in compression. Such a great difference in the elastic modulus would make the extrafibrillar matrix carry a major portion of the load in the pre-yield deformation, thus dominating the bulk pre-yield behavior of bone.

Moreover, the simulation results indicate that the yield strain of the model in compression is much greater than that in tension, which matches very well with the experimental results obtained in the synchrotron X-ray diffraction measurements (Fig.8). This difference can be explained based on the distinct deformation and failure modes of the extrafibrillar matrix under tension and compression. The deformation and failure of the extrafibrillar matrix in tension is dominated by the opening mode, whereas the deformation and failure in compression is mainly manifested in the shear mode at the interface between mineral crystals. Since the shear mode deformation may accommodate much greater deformation until interfacial failure than the opening mode, the yield strain would be greater under compression than under tension.

However, the post yield predictions from the extrafibrillar matrix model do not match the experimental observations very well. One of the reasons is that the model predictions only represent the deformation of the extrafibrillar matrix, whereas the synchrotron X-ray diffraction measurements represent the combined contribution of mineral crystals in both mineralized fibrils and extrafibrillar matrix. It is presumable that damage progression and failure of the extrafibrillar matrix is responsible for the initiation of yielding of bone. After yielding, mineralized collagen fibrils would be more involved in load bearing since the damaged extrafibrillar matrix loses its ability to carry load. For instance, the experimental results show that the mineral strain in bulk bone tissue drops after yielding but increases gradually with increasing applied strain (Fig.8a). Since the extrafibrillar matrix loses its load bearing capacity quickly after yielding, the load is transferred to the adjacent mineralized collagen fibrils. As the deformation of the fibrils increases, the load to the mineral crystals in the fibrils increases as well, which explains the gradual increase of the post-yield mineral strain observed in the experiments (Fig.8).

It is also noted from the simulation results that the hydration dependence of the mechanical properties of the extrafibrillar matrix is most likely dominated by the behavior of the organic interface in the matrix. Several researchers have shown that bone behaves like a brittle material in the absence of water (Akhtar et al., 2011; Samuel et al., 2016; Yan et al., 2008). Recent synchrotron experiments also indicate that the mechanical behavior of the mineral phase is influenced by the hydration status at the ultrastructural level (Samuel et al., 2016). Similarly, another recent study shows that water residing only in the ultrastructural spaces penetrable by molecules smaller than 4Å actually dominates the bulk behavior of bone (Samuel et al., 2014). These results suggest that the role of water as a plasticizer is most

likely manifested at the ultrastructural level. In this study, we assumed that the hydration status influences the behavior of the organic interface in the extrafibrillar matrix. To avoid arbitrary assignments of model parameters required by the traction-separation law of the cohesive interfacial zone, we selected the parameters based on the bulk behavior of bone experimentally observed by assuming that the strain of extrafibrillar matrix is consistent with the bulk strain applied to bone. The cohesive FE simulations demonstrate that a tough interface would allow relatively ductile deformation of the model as observed in wet bone, whereas a brittle interface would lead to a brittle deformation as observed in dry bone. Based on the simulation results it can be postulated that the hydration status of the organic interface may be one of the root causes of the hydration induced plasticity in bone.

There are several limitations associated with this study. First, a two dimensional (2-D) model was used in this study, which may not be fully representative of three dimensional (3-D) cases. Since the deformation of bone mineral crystals are axisymmetric with respect to the long axis of bone (Giri et al. 2012), thus a 2-D plane strain model is presumably sufficient in capturing the dominant deformation characteristics of the extrafibrillar matrix. Second, crystal shape/size generated by Voronoi tessellation in the model may not perfectly match those in real bone specimens. However, given the granular nature of the extrafibrillar mineral crystals observed in previous studies (Tai et al., 2006; McNally et al., 2012), we believe the Voronoi generated grains are appropriate representations of the extrafibrillar mineral crystals. Grain size can play a role in dictating the extrafibrillar matrix mechanical properties by altering the grain to organic interface ratio. Third, the organic interface properties are estimated based on the experimental observations and related information reported in the literatures, which could be used only for qualitative analysis. Finally, only the extrafibrillar matrix is considered in the current model, which is merely representative of the localized behavior of lamellae in bone. Nonetheless, the results of this study indicate that the proposed cohesive FE model is still able to capture the major behavior of bone at ultrastructural levels, which may give rise to the insights on the contribution of the extrafibrillar matrix to the bulk mechanical responses of bone.

CONCLUSIONS

In this study, we used a cohesive finite element model to study the mechanical behavior of the extrafibrillar matrix in bone. The simulation results provide new insights into the ultrastructural mechanical behavior of bone: (1) the failure mode of bone may be directly related to the behavior of the organic interface in the extrafibrillar matrix; (2) the pre-yield deformation of bone is most likely dominated by the mechanical behavior of the extrafibrillar matrix; (3) the loading mode dependence of the mechanical behavior of bone is manifested in the distinct deformation mode of the organic interface; namely, intergranular sliding in compression and intergranular opening in tension; and (4) the hydration status of the organic interface in the extrafibrillar matrix may contribute to the plasticity of bone.

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Fig. 1.

Schematic representation of the two dimensional (2-D) model of the extrafibrillar matrix in bone lamellae. The interfacial cohesive zone was generated by recessing the outline of the original Voronoi cells (dash black line) to form the outline of the mineral grain (solid red line) with the interfacial cohesive zone between the grains.

Fig. 2.

The traction-separation relationships of interfacial cohesive zone with respect to dry and wet conditions in (a) normal and (b) shear mode.

Fig. 3.

Snapshots of normal stress distribution in the loading direction (σ_{22}) for wet bone in tension:

(a) $\epsilon_b = 0.59\%$ (crack initiation), (b) $\epsilon_b = 0.61\%$ (crack nucleation) (c) $\epsilon_b = 0.64\%$ (crack coalescence), (d) $\epsilon_b = 1.24\%$ (complete failure)

Fig. 4.

Snapshots of normal stress distribution in the loading direction (σ_{22}) for dry bone in tension:

(a) $\epsilon_B=0.64\%$ (crack initiation), (b) $\epsilon_B=0.65\%$ (crack nucleation) (c) $\epsilon_B=0.66\%$ (crack coalescence), (d) $\epsilon_B=0.81\%$ (complete failure)

Fig. 5.

Snapshots of shear stress distribution (σ_{12}) for wet bone in compression: (a) $\epsilon_b = 1.2\%$, (b) $\epsilon_b = 1.3\%$ (shear band formed in an inclined angle with respect to the loading direction), (c) $\epsilon_b = 1.33\%$ (crack propagation in an inclined angle with respect to the loading direction), (d) $\epsilon_b = 2.48\%$ (complete failure)

Fig. 6.

Snapshots of shear stress distribution (σ_{12}) for wet bone in compression: (a) $\epsilon_b = 1.47\%$, (b) $\epsilon_b = 1.50\%$ (shear band formed in an inclined angle with respect to the loading direction), (c) $\epsilon_b = 1.57\%$ (crack propagation in an inclined angle with respect to the loading direction), (d) $\epsilon_b = 1.93\%$ (complete failure)

Fig. 7.

Stress-strain relationships predicted using the cohesive FE model. The moduli of the extrafibrillar matrix of wet bone predicted from the simulations were around 27.0GPa under tension and 55.3GPa under compression. For dry interface, the moduli of the extrafibrillar matrix predicted from the simulations were around 39.9GPa under tension and 65.1GPa under compression. Such a high value of the modulus would make the extrafibrillar matrix carry the most of load in the pre-yield deformation, thus dominating the bulk pre-yield behavior of bone

Fig. 8.

Comparison between the results of mineral strain predicted using the cohesive FE model and obtained from synchrotron X-ray experiments (Samuel et al., 2016). The mineral strain showed a linear trend in compression, but nonlinear pattern in tension before yield point. The mineral strain showed a greater value in compression compared to tension. The mineral strain dropped very fast with dry interface in both tension and compression after yield point.

Table 1

Parameters of the traction-separation law used in the cohesive FE simulations

	Wet	Dry
$\Psi_n(J/nr^2)$	0.04	0.02
$(\delta_{dn} - \delta_0)(nm)$	0.15	0.15
$(\delta_{fn} - \delta_0)(nm)$	0.6	0.15
p_n	1.0	-
$\Psi_t(J/nr^2)$	0.15	0.06
$\delta_{dt}(nm)$	0.36	0.36
$\delta_{ft}(nm)$	1.9	0.36
p_t	1.0	-