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## DEFINING NASCENT BONE BY THE MOLECULAR NANOMECHANICS OF MINERALIZED COLLAGEN FIBRILS

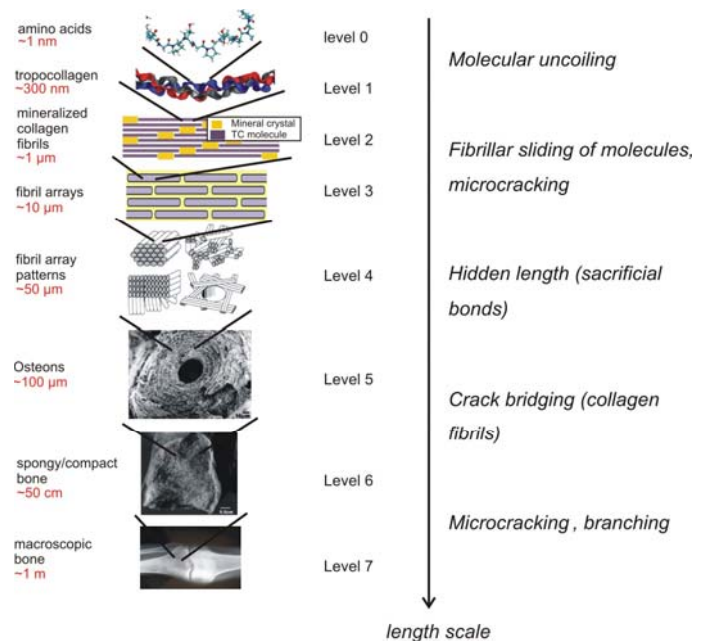
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### ABSTRACT

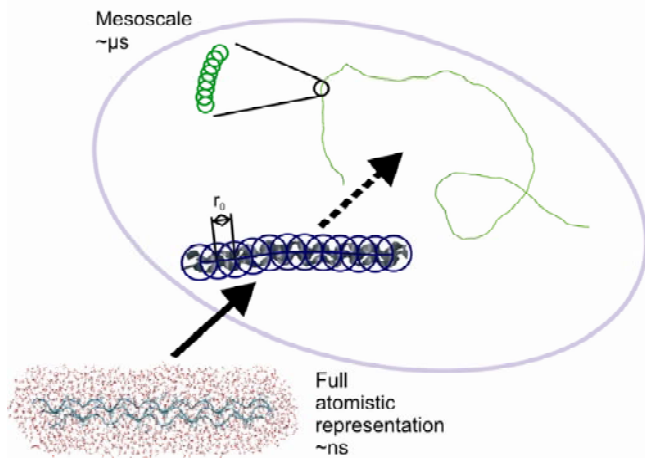
Here we focus on recent advances in understanding the deformation and fracture behavior of collagen, Nature's most abundant protein material and the basis for many biological composites including bone, dentin or cornea. We show that it is due to the basis of the collagen structure that leads to its high strength and ability to sustain large deformation, as relevant to its physiological role in tissues such as bone and muscle. Experiment has shown that collagen isolated from different sources of tissues universally displays a design that consists of tropocollagen molecules with lengths of approximately 300 nanometers. Using a combination of theoretical analyses and multi-scale modeling, we have discovered that the characteristic structure and characteristic dimensions of the collagen nanostructure is the key to the ability to take advantage of the nanoscale properties of individual tropocollagen molecules at larger scales, leading to a tough material at the micro- and mesoscale. This is achieved by arranging tropocollagen molecules into a staggered assembly at a specific optimal molecular length scale. During bone formation, nanoscale mineral particles precipitate at highly specific locations in the collagen structure. These mineralized collagen fibrils are highly conserved, nanostructural primary building blocks of bone. By direct molecular simulation of the bone's nanostructure, we show that it is due to the

characteristic nanostructure of mineralized collagen fibrils that leads to its high strength and ability to sustain large deformation, as relevant to its physiological role, creating a strong and tough material.



**Figure 1.** Hierarchical multi-scale structure of bone, showing seven hierarchical levels, and their relation to the mechanisms of mechanical properties (inlays in level 4-7 bone reprinted with permission from Weiner et al. [1]). The left panel shows the characteristic structural features; the right panel indicates associated deformation and toughening (fracture resistance) mechanisms.

We present a thorough analysis of the molecular mechanisms of protein and mineral phases in deformation, and report discovery of a new fibrillar toughening mechanism that has major implications on the fracture mechanics of bone. Our studies of collagen and bone illustrate how hierarchical multi-scale modeling linking quantum chemistry with continuum fracture mechanics approaches can be used to develop predictive models of hierarchical protein materials. We conclude with a discussion of the significance of hierarchical multi-scale structures for the material properties and illustrate how these structures enable one to overcome some of the limitations of conventional materials design, combining disparate material properties such as strength and robustness.



**Figure 2.** Schematic showing developing of the coarse-grained molecular model from a full atomistic description, illustrating the procedure utilized in various studies discussed in this paper. The full atomistic representation of the triple helical tropocollagen structure is replaced by a collection of beads. The mesoscale model enables the treatment of ultra long tropocollagen molecules at time- and length scales not in reach by full-atomistic models.

## INTRODUCTION

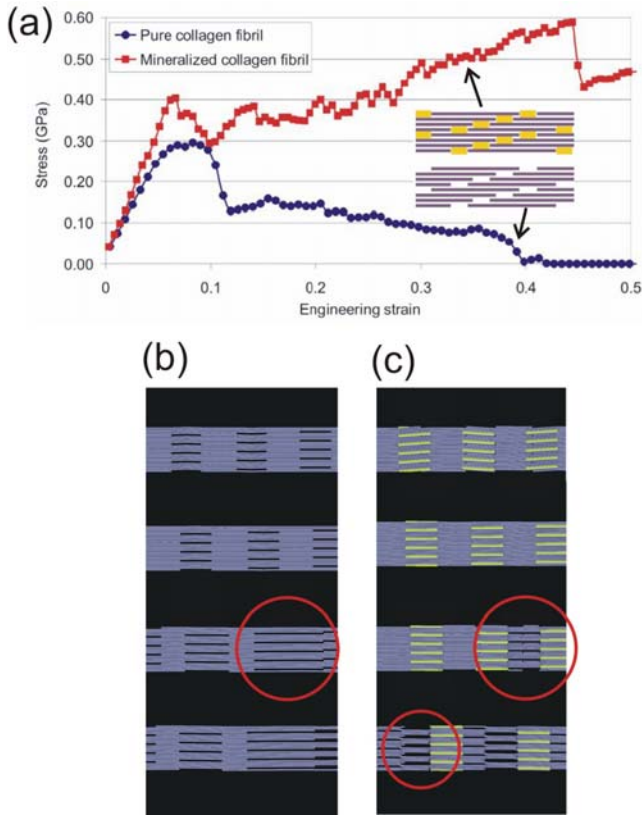
One of the most intriguing materials found in Nature is bone, a material composed out of assemblies of tropocollagen molecules and tiny hydroxyapatite crystals, forming an extremely tough, yet lightweight material [1-4]. Bone has evolved to provide structural support to a variety of organisms, and therefore, its mechanical properties are of great

physiological relevance. Figure 1 shows the hierarchical structure of bone, showing its seven hierarchical levels, and their relation to the mechanisms associated with mechanical deformation [1, 3]. It is noted that bone is a very complex biological material, and currently we are only at the beginning of understanding quantitatively how this material deforms, fails and breaks and what type of mechanisms operate at various structural length- and time-scales. However, the advent of multi-scale experiments and novel theoretical and computational tools now enables the analysis of bone as a “material” with rigorous physical science techniques and great advances in the understanding of bone are expected in the years to come (Figure 2).

The basic building blocks of bone are collagen protein filaments and hydroxyapatite mineral crystals, which form so-called level 1 bone. These two constituents form the major structural ingredients in bone, together with a few non-collagenous proteins. The smallest scale hierarchical features of bone include the protein phase composed of tropocollagen molecules, collagen fibrils as well as mineralized collagen fibrils, referred to as level 2 bone. The collagen phase provides elasticity and the ability to dissipate energy under mechanical deformation.

Here we carry out molecular dynamics simulations of bone nanoplasticity, based on a molecular based coarse-grained model (for details see [5]). In this model, tropocollagen molecules are described as chains of beads (Figure 2). The molecules are arranged in the characteristic staggered array as shown in Figure 1, and small mineral platelets are added in the void region of the fibrils. Figure 3 shows the results of this nanomechanical analysis of bone deformation, along with structural mechanistic details of the associated deformation mechanisms. This result was obtained by a combination of molecular dynamics simulation and theoretical analysis, where it has been shown that the characteristic nanostructure of mineralized collagen fibrils is vital for its high strength and its ability to sustain large deformation, as relevant to the

physiological role of bone, creating a strong and tough material.



**Figure 3.** (a) Computational result of the stress-strain response of a mineralized versus unmineralized collagen fibril, revealing the significant effect the presence of mineral crystals in collagen fibril has on the mechanical response [5]. (b) Snapshots of the deformation mechanisms of collagen fibrils, and (c) and mineral collagen fibrils. Slip initiates at the interface between mineral particles and tropocollagen molecules. Repeated occurrence of slip reduces the density, leading to formation of nano-scale voids.

Figure 3(a) plots the stress-strain response of a pure collagen fibril compared with that of a mineralized collagen fibril, under tensile loading, for tensile strains up to 50%. The stress-strain responses for both structures are qualitatively and quantitatively different, indicating that precipitation of hydroxyapatite crystals during bone formation significantly alters the material response. The mineralized collagen fibril features a larger strength and much increased energy dissipation under deformation. Plastic deformation starts at approximately 6.7% tensile strain for the mineralized

fibril, whereas it occurs at approximately 5% tissue strain in the case of a pure collagen fibril. Further, the mineralized collagen fibril shows significant softening at larger strains, with a characteristic saw tooth shaped stress-strain curve due to repeated intermolecular slip. The mineralized fibril features a higher stiffness than the pure collagen fibril. Figures 3(b-c) show snapshots of the molecular geometry under increasing tensile load, clearly showing the deformation mechanism of intermolecular slip. Fibrillar yield is characterized by intermolecular slip (see red circle highlighting a local area of repeated molecular slip). Slip leads to formation of regions with lower material density, as can be seen in the images.

## DISCUSSION AND CONCLUSION

The analysis of the molecular mechanisms of protein and mineral phases under large deformation of mineralized collagen fibrils revealed a fibrillar toughening mechanism that leads to a manifold increase of energy dissipation compared to fibrils without mineral phase. This fibrillar toughening mechanism increases the resistance to fracture by forming large local yield regions around crack-like defects, a mechanism that protects the integrity of the entire structure by allowing for localized failure. As a consequence, mineralized collagen fibrils are able to tolerate micro-cracks on the order of several hundred micrometers size without causing any macroscopic failure of the tissue, which may be essential to enable bone remodeling. The analysis proves that adding nanoscopic small platelets to collagen fibrils increases their Young's modulus, yield strength as well as their fracture strength. It is found that mineralized collagen fibrils have a Young's modulus of 6.23 GPa (versus 4.59 GPa for the collagen fibril), yield at a tensile strain of 6.7% (versus 5% for the collagen fibril) and feature a fracture stress of 0.6 GPa (versus 0.3 GPa for the collagen fibril). Other deformation and fracture mechanisms exist in bone at larger hierarchical levels, including the breaking of sacrificial bonds between mineralized fibrils, the formation of microcracks, crack bridging (via collagen fibrils

arranged orthogonal to the crack), and the formation of larger plastic zones around crack tips that contribute to an increase in bone's overall toughness [3, 6-8]. Future studies could be focused on an analysis of genetic disease mechanisms, such as in osteogenesis imperfecta [9].

#### ACKNOWLEDGMENTS

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