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# Full atomistic simulations of normal and brittle bone collagen: molecular origin of brittle bone disease

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## ABSTRACT

Collagen constitutes one third of the human proteome, providing mechanical stability, elasticity and strength to organisms. Normal type I collagen is a heterotrimer and consists of two alpha-1 chains and one alpha-2 chain. A mouse model of the genetic brittle bone disease, *osteogenesis imperfect (oim)*, is characterized by a replacement of the alpha-2 chain by a alpha-1 chain, resulting in a homotrimer collagen molecule. In this study, we use molecular simulations to study the structural and mechanical differences between the heterotrimer and homotrimer collagen microfibrils. We find that the homotrimer microfibril has reduced mechanical property. Our results suggest that the *oim* microfibril is less dense compared to the normal microfibril as a result of local kink formations which explains the reduction of modulus of the *oim* microfibril. Our studies provide fundamental insight of the effect of the loss of alpha-2 chain at the molecular level and help understanding the molecular origin of the bone brittle disease at much larger length-scales.

## 1. INTRODUCTION

Collagenous tissues are hierarchical structures made of collagen molecules (**Fig. 1**) (Rainey, Wen et al. 2002, Fratzl 2008, Buehler and Yung 2009). Each collagen molecules consist of three chains forming into a triple helical structure. *Osteogenesis Imperfecta* (OI) is a heritable collagen-related pathology related to changes at the molecular level of type I collagen resulting in modifications of structure and mechanical competence throughout the hierarchy of bone, leading to extremely brittle bones. In the *oim* mouse, the most widely used animal model for OI, the tropocollagen is characterized by replacements of alpha-2(I) chains with alpha-1(I) chains resulting in the formation of homotrimer collagen molecules.

In this study, we perform full atomistic simulations to study the structural difference between wild-type and *oim* mouse type I collagen fibril.

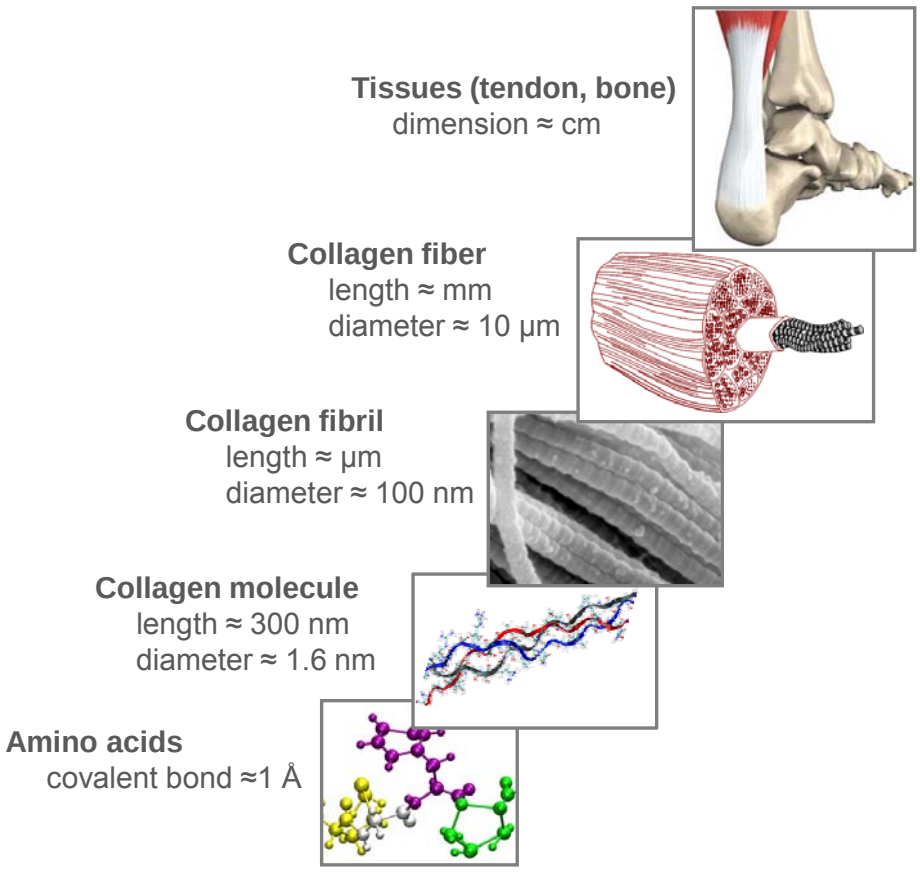


**Fig. 1:** Hierarchical collagen structure. Each collagen molecule is made of three peptide chains that form the 300 nm long triple helical collagen molecule. Collections of collagen molecules aggregate both in lateral and longitudinal directions to form fibrils. Fibrils in cornea are normally thin (≈30 nm) and uniform in diameter, while tissues such as tendon contain a wide-ranging distribution of diameters (100-500 nm). Fibrils are enriched by hydroxyapatite in bone tissue, which provide stiffness and compressive load resistance. In tendons and ligaments multiple fibrils make up collagen fiber, formed with the aid of proteoglycans. (Reprinted with permission from Gautieri, A., *et al*., *Hierarchical Structure and Nanomechanics of Collagen Microfibrils from the Atomistic Scale Up.* Nano Letters, 2011. Copyright 2011 American Chemical Society).

## 2. FULL ATOMISTIC MODELS

In this work, full atomistic models of wild-type and *oim* collagen fibril are constructed to provide important insights into mechanical alterations at the fibril level due to pathologies such as OI, in this case allowing insights into the mechanisms behind altered macromechanical behaviour of *oim* tissue. **Fig. 2A** shows the collagen microfibril model which has a triclinic unit cell (*a*≈ 40.0 Å, *b*≈27.0 Å, *c*≈678 Å, α≈89.2°, β≈94.6°, γ≈105.6° (Orgel, Irving et al. 2006). The real sequences of type I alpha-1 and type I alpha-2 chains of mus musculus (wild type mouse) are used. The heterotrimer collagen microfibril model is built of two alpha-1 chains and one alpha-2 chain while the homotrimer collagen microfibril model is built of three alpha-1 chains. The sequences are adopted from NCBI protein database (http://www.ncbi.nlm.nih.gov/protein): AAH50014.1 for alpha-1 chain and NP_031769.2 for alpha-2 chain. In both collagen microfibril models, ions are added to neutralize the system. VMD is used to solvate both normal and *oim* microfibril models.

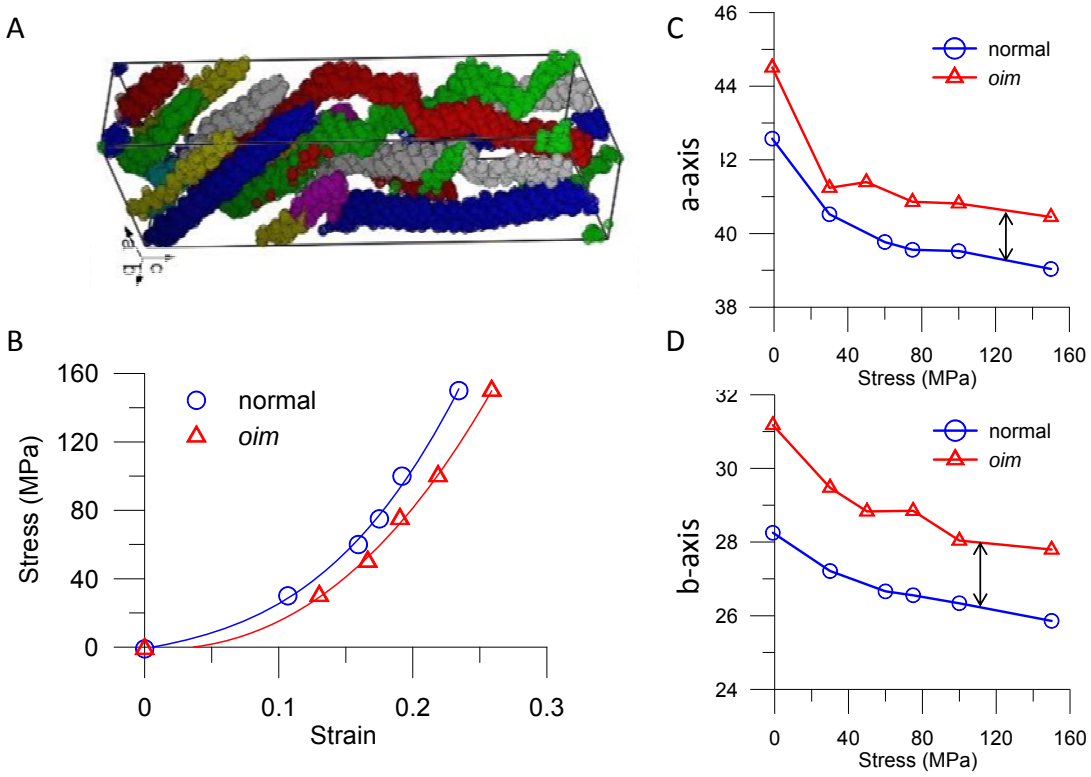


**Fig. 2: (**A) The collagen microfibril model is generated based on the *in situ* structure of full length collagen type I molecule, which has a triclinic unit cell (*a*≈ 40.0 Å, *b*≈27.0 Å, *c*≈678 Å, α≈89.2°, β≈94.6°, γ≈105.6°(Orgel, Irving et al. 2006). (B) Stress-strain curves of normal and *oim* collagen fibril. Atomistic simulations reveal that *oim* collagen fibril has larger lateral spacing ((C) and (D)).

## 3. TENSILE MECHANICAL TESTS of TYPE I COLLAGEN MICROFIBRILS

Different tensile stress levels are applied to study the mechanical response. **Fig. 2B** shows the stress-strain curves of normal and *oim* collagen microfibril. The modulus (along *c*-axis direction of the microfibril model) of *oim* microfibril is smaller when compared to normal (heterotrimer) collagen microfibrils. Atomistic simulations reveal that *oim* collagen fibril has larger lateral spacing (**Fig. 2C and D**). Our results suggest that the replacement of alpha-2 chain with alpha-1 chain in type I collagen molecule induces the formation of local kinks and therefore increases the lateral spacing between *oim* collagen molecules when forming into a fibril. The larger lateral spacing indicates that *oim* collagen molecule is packing loosely in the lateral directions. Interestingly, no significant difference between the *D*-period of normal and *oim* collagen fibril is found while the *oim* microfibril has larger gap/overlap ratio compared with normal microfibril.

### References

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