Molecular and Mesoscale Mechanisms of Osteogenesis Imperfecta Disease

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MOLECULAR AND MESOSCALE MECHANISMS OF OSTEOGENESIS IMPERFECTA DISEASE

Sebastien Uzel[1,2,†] and Markus J. Buehler[1,*]

[1] Laboratory for Atomistic and Molecular Mechanics
Department of Civil and Environmental Engineering
[2] Department of Mechanical Engineering
Massachusetts Institute of Technology
Cambridge, MA, 02139, USA

[†] Presenting author
* Corresponding author, mbuehler@MIT.EDU

INTRODUCTION

Collagen is a crucial structural protein material, formed through a hierarchical assembly of tropocollagen molecules, arranged in collagen fibrils that constitute the basis for larger-scale fibrils and fibers. Osteogenesis imperfecta is a genetic disorder in collagen characterized by mechanically weakened tendon, fragile bones, skeletal deformities and in severe cases prenatal death. Even though many studies have attempted to associate specific mutation types with phenotypic severity, the mechanisms by which a single point mutation influences the mechanical behavior of tissues at multiple length-scales remain unknown. In this study, we report a series of systematic molecular scale based bottom-up computational experiments focused on pure collagenous tissue, carried out using atomistic-level molecular dynamics (MD), adaptive Poisson-Boltzmann solver (APBS) calculations, and a mesoscale molecular model of collagen fibrils.

RESULTS

We investigate eight 30-amino-acid-long tropocollagen segments, created using the triple-helical collagen building script tool (THeBuScr) and solvated in a water box. Each peptide structure is $[(GPO)_5\text{-}(\mathbf{X}PO)\text{-}(GPO)_4]_3$, where the **X** position is occupied by glycine, alanine, serine, cysteine, arginine, valine, glutamic acid, or aspartic acid. The molecular dynamics simulations are performed with the GROMACS code and the GROMOS96 43a1 force field. The stretching is carried out by using steered molecular dynamics (SMD) at a velocity of 1 m.s^{-1} after proper equilibration.

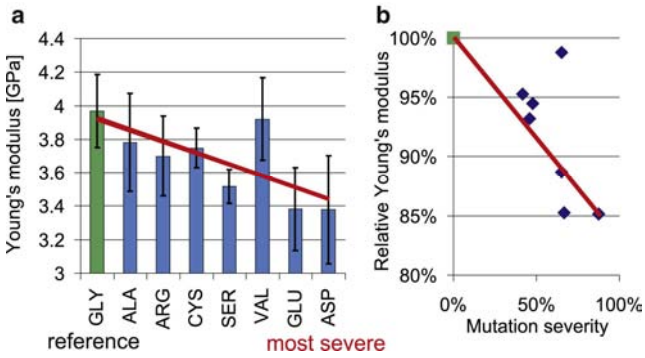

Figure 1. Reduction of Young's modulus of a single tropocollagen molecule, as a function of the (*a*) glycine replacement and as a function of (*b*) OI severity

At the molecular level, the stretching simulations reveal a softening effect of the mutation on the tropocollagen molecules (Fig. 1). The effect of mutation at the intermolecular level was measured by determining the intermolecular energy landscape (Fig. 2a). The results show that the mutations have a deleterious effect by increasing the intermolecular equilibrium spacing and reducing the adhesion energy (Fig 2b,c). It can also be observed on both Fig. 1 and 2 that the effect on the softening and the reduction of intermolecular interaction increases with the severity of the mutation.

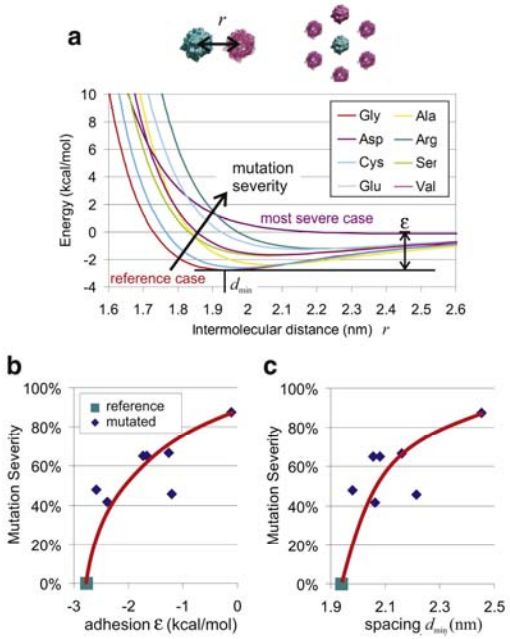

Figure 2. Influence of OI mutations on the mechanical properties of a collagen fibril, leading to a significant reduction of mechanical strength and yield strain, in the case of highly cross-linked or cross-link deficient fibrils.

The mesoscale model of collagen fibrils is identical to that reported in [4,5] , with modifications to reflect changes in the segment's stiffness and intermolecular interactions observed in the most severe case of OI mutation.

We find that the presence of mutations leads to a significant change in the mechanical response of collagen fibrils. Fig. 3a shows a loss in strength of more than 35% in a cross-link free fibril. The loss of strength is even greater in a cross-linked fibril (reduction of 50%). Fig. 3b shows how the presence of a mutation at the end of a molecule effects its mechanical response, in the case of a cross-linked fibril.

These strength reductions find an explanation in the fact the maximum shear stress along the molecule in the mutated case is much higher than in the non-mutated case (between 40 and 70% higher, depending in the content of cross-link) (Fig. 3c).

DISCUSSION

We have identified three major effects of OI mutations on the mechanical properties of collagenous tissues at ultra-small scales. First, at the single molecule level, where molecular softening occurs as the disease severity increases. Second, at the intermolecular level, where mutations lead to a weakening of intermolecular adhesion and increase of intermolecular equilibrium spacing as disease severity increases, leading to a reduction in likelihood of cross-link formation. Third, at the collagen fibril level, where OI mutations lead to reduction in strength through a change in the stress distribution within fibrils. Our work shows that microscopic events involving only tens to hundreds of atoms can trigger tissue failure with potentially system wide catastrophic consequences. Future work could be focused on other genetic diseases associated with collagen, such as Alport's syndrome [6].

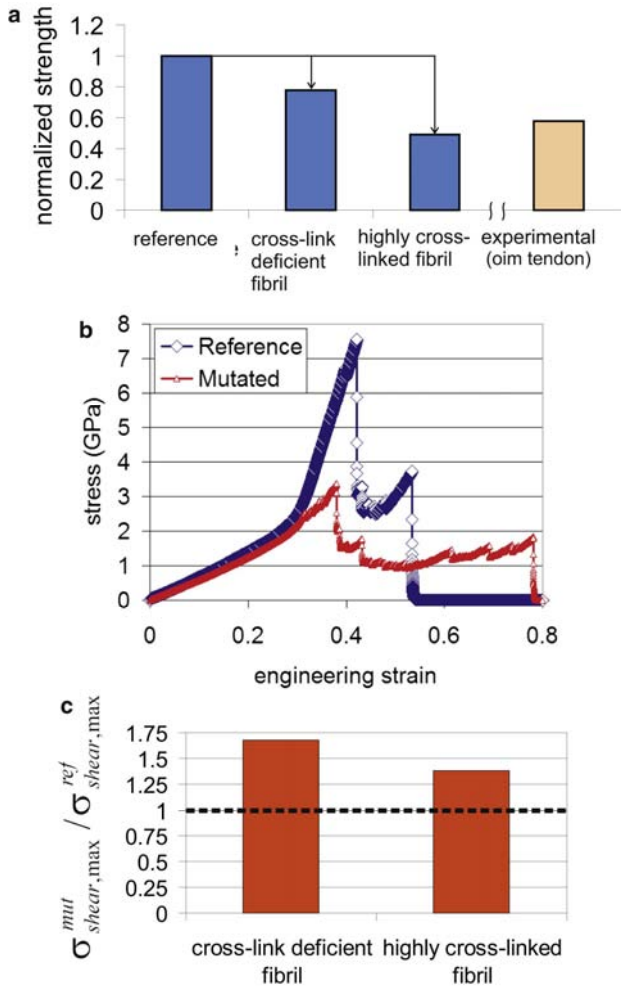

Figure 3. Influence of OI mutations on the mechanical properties of a collagen fibril, leading to a significant reduction of mechanical strength and yield strain, in the case of highly cross-linked or cross-link deficient fibrils.

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