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Research Paper

Investigation of mechanisms of viscoelastic behavior of collagen molecule

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ABSTRACT

Unique mechanical properties of collagen molecule make it one of the most important and abundant proteins in animals. Many tissues such as connective tissues rely on these properties to function properly. In the past decade, molecular dynamics (MD) simulations have been used extensively to study the mechanical behavior of molecules. For collagen, MD simulations were primarily used to determine its elastic properties. In this study, constant force steered MD simulations were used to perform creep tests on collagen molecule segments. The mechanical behavior of the segments, with lengths of approximately 20 (1X), 38 (2X), 74 (4X), and 290 nm (16X), was characterized using a quasi-linear model to describe the observed viscoelastic responses. To investigate the mechanisms of the viscoelastic behavior, hydrogen bonds (H-bonds) rupture/formation time history of the segments were analyzed and it was shown that the formation growth rate of H-bonds in the system is correlated with the creep growth rate of the segment ($\beta = 2.41\beta_H$). In addition, a linear relationship between H-bonds formation growth rate and the length of the segment was quantified. Based on these findings, a general viscoelastic model was developed and verified here, using the smallest segment as a building block, the viscoelastic properties of larger segments could be predicted. In addition, the effect of temperature control methods on the mechanical properties were studied, and it was shown that application of Langevin Dynamics had adverse effect on these properties while the Lowe-Anderson method was shown to be more appropriate for this application. This study provides information that is essential for multi-scale modeling of collagen fibrils using a bottom-up approach.

1. Introduction

Development of constitutive models for connective tissues has been a primary focus in biomechanics. The approaches used for this purpose have been mostly phenomenological and consider the tissue as a continuum with macroscopic mechanical models that are often nonlinear, rate dependent and may include directional dependence. Understanding the mechanical characteristics of collagen molecule would provide a basis to investigate the micromechanics of connective

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tissues. This knowledge, in turn, can be used to study the effect of mutation or disease of collagen on tissue mechanical properties, or to determine initiation of micro-failure due to trauma among other applications. While several microstructural elements may interact within connective tissues, collagen, the main protein in their extracellular matrix (ECM), is believed to largely determine their structural integrity (Silver et al., 2006).

Organization into a complex hierarchical structure is an important factor for the mechanical function of collagen. The first level of collagen structural hierarchy, Tropocollagen is a triple-helix protein with an approximate length of 290 nm and a diameter of about 1.5 nm. This superhelix is comprised of three polypeptide left-handed chains (α chain). The common characteristic of each of these chains is a continuous amino acid motif (Gly – X – Y) repeat, where X and Y are mostly proline and hydroxyproline, but can also be any amino acid. Tropocollagens have a distinctive cross-striation with a periodicity of 67 nm and five of them organize into a micro-fibril. Micro-fibrils wind together to form a fibril (Shoulders and Raines, 2009).

In addition to experimental studies that report elastic (Sasaki and Odajima, 1996; Shen et al., 2011, 2008; Svensson et al., 2010a; Van der Rijt et al., 2006; Wenger et al., 2007) and viscoelastic properties (Sun et al., 2002; Svensson et al., 2010b) of collagen at the fibrillar scale, computational models at the molecular scale have recently become possible by the improvements in computational methods and resources. In several studies, the elastic properties of collagen molecule have been characterized using molecular dynamics (MD) simulations (Bhowmik et al., 2009; Buehler, 2006a, 2006b, 2008; Gautieri et al., 2010, 2008; Pradhan et al., 2011). The shear interaction between collagen molecules in a model microfibril (Gautieri et al., 2012a) and the intermolecular slip mechanism between two collagen molecule (Gautieri et al., 2009) were also investigated using MD simulations. The viscoelastic behavior of collagen was primarily studied in a series of papers by Gautieri et al. (2013), (2012b), (Vesentini et al., 2013) in which fully solvated (wet) and dry collagen segments with length of 20 nm were examined using constant force steered molecular dynamics (SMD) simulations. The results were fitted using a linear Kelvin–Voigt (KV) viscoelastic model. It was further shown that the higher number of intramolecular H-bonds in the dry segment resulted in a higher Young's modulus in comparison with the wet segment. The H-bonds that the solvated collagen molecule formed with the surrounding water molecules were found to be the underlying mechanism for the viscous behavior.

This study is a first step in our bottom-up approach for characterizing the constitutive behavior of collagen fibrils. Since the mechanical behavior of collagenous tissues is generally nonlinear viscoelastic (Fung, 1993), the main objective of this study was to test the hypothesis that this nonlinear behavior starts at the molecular scale. A series of SMD creep tests were performed to characterize nonlinear viscoelastic constitutive models of collagen homotrimer molecule segments with different lengths. It was also hypothesized that a quantitative relationship can be established between

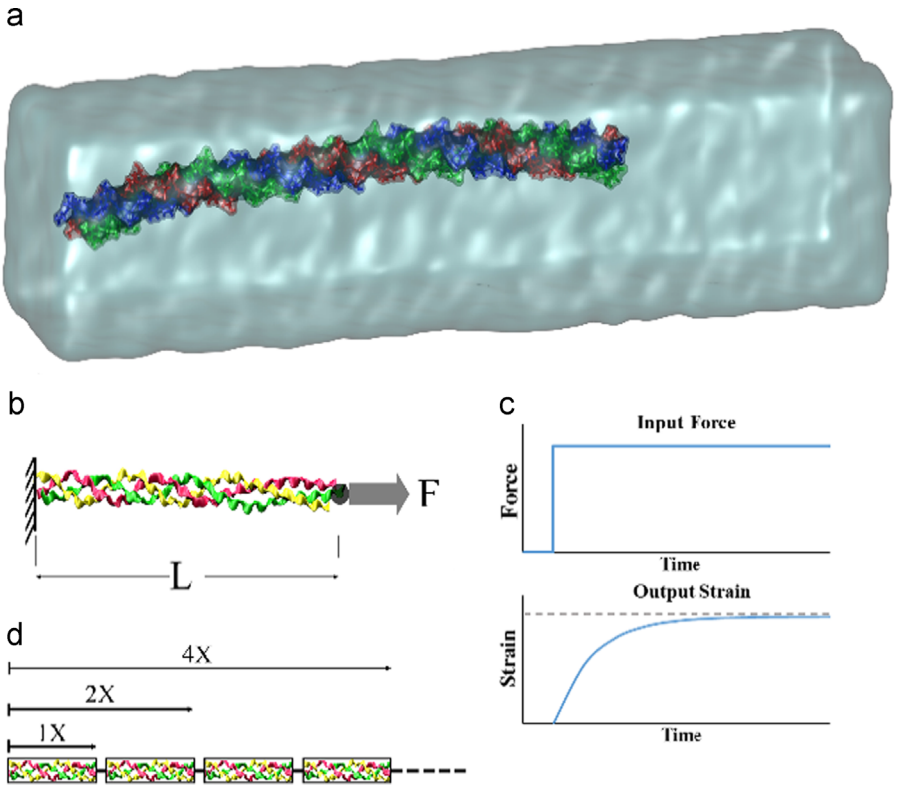

Fig. 1 – Schematic of collagen molecule creep test. (a) Equilibrated 1X segment solvated in water box, (b) a constant force is applied to one end of the molecule while the other end is fixed, (c) the applied force on the molecule is the input and measured increase of strain over time is the output of the system and (d) representation of larger segments of collagen molecule constructed from a series of 1X segments as the building block.