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Review Paper

The materials science of collagen

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ABSTRACT

Collagen is the principal biopolymer in the extracellular matrix of both vertebrates and invertebrates. It is produced in specialized cells (fibroblasts) and extracted into the body by a series of intra and extracellular steps. It is prevalent in connective tissues, and the arrangement of collagen determines the mechanical response. In biomineralized materials, its fraction and spatial distribution provide the necessary toughness and anisotropy. We review the structure of collagen, with emphasis on its hierarchical arrangement, and present constitutive equations that describe its mechanical response, classified into three groups: hyperelastic macroscopic models based on strain energy in which strain energy functions are developed; macroscopic mathematical fits with a nonlinear constitutive response; structurally and physically based models where a constitutive equation of a linear elastic material is modified by geometric characteristics. Viscoelasticity is incorporated into the existing constitutive models and the effect of hydration is discussed. We illustrate the importance of collagen with descriptions of its organization and properties in skin, fish scales, and bone, focusing on the findings of our group.

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1. Types of collagen and its ubiquity in nature

Collagen is a structural biological polymer of upmost importance. Over 200,000 articles have been written about collagen, divulging the intricacies of this biopolymer which is the key ingredient of connective tissues. It is prevalent in tendons, skin, blood vessels, cornea, and coordinates with minerals to make bones, teeth, fish scales, and cartilage. Collagen makes up to 30% of the mass of vertebrates and lays their structural framework. Due to its ubiquity and importance, collagen has been nicknamed the "steel of biological materials".

Collagen comes in many forms throughout nature. Each polypeptide molecule is a left-handed chain (Fig. 1a); three polypeptide molecules form a right handed triple helical structure (Fig. 1b). Each helical structure is called tropocollagen (Gelse et al., 2003). Each polypeptide chain (also called procollagen) contains a region characterized by a repeating amino acid motif: Gly-X-Y where Gly is a glycine and X or Y can be any amino acid. Glycine is at the core of the protein, while the X and Y amino acids are exposed at the surface.

The triple helical region is a major part of most collagens, but in some cases it can be only a minor part with other large non-collagenous domains of the molecule. In humans, there are 28 proteins known as collagens, as well as many other proteins which are considered part of the collagen superfamily. Collagens are classified into several general groups: fibrillar collagens, FACIT (Fibril Associated Collagens with Interrupted Triple Helices) and FACIT-like collagens, beaded filament collagens, basement membrane collagens, short chain collagens, transmembrane collagens, as well as some unclassified collagens. The most common form of collagen is type I, which is a fibrillar collagen (Hulmes, 2008). However, a brief description of the various classes is presented below.

1.1. *Fibrillar collagens*

Fibrillar collagens are characterized by a characteristic d-banding pattern, where a staggered collagen arrangement creates visible bands on the fibrils produced. Highly organized fibrils and fibers provide structural support throughout the body including in bones, skin, tendons, cartilage, dentin, blood vessels, nerves, intestines, and in the fibrous capsules of organs.

The structural hierarchy is illustrated in Fig. 1c. Hydrated collagen molecules of ~1.6 nm (Smith, 1968) diameter and ~299 nm length (as packed within fibrils) are staggered by integral multiples of ~67 nm, or one d-period (Orgel et al., 2011). The two-dimensional version of this is shown, but in three dimensions it becomes impossible to maintain equal staggering with all adjacent molecules (Smith, 1965). In order to maximize the number of quarter staggered molecules, Smith (1968) proposed a collagen filament composed of five molecules in cross-section where each molecule is staggered by one d-period. These five-molecule arrangements, called microfibrils, correspond to the observation of 2–3 nm diameter collagenous structures and is the only reasonable geometric arrangement to reflect these observations (Smith, 1968; Olsen, 1963). Each molecule is 4.46 d long, and a gap of 0.54 d (~36 nm) lies at the ends of non-overlapping molecules. There is also an overlap of 0.46 d, or 31 nm between adjacent molecules. The 0.54 d length empty period along with the 0.46 d overlap lead to the full 67 nm d-period. This overlapping pattern is called the quarter-staggered assembly (Vuorio and Decrombrugghe, 1990).

A full crystallographic description of type I fibrillar collagen supermolecular structure was presented by Orgel et al. (2006) and is shown in Fig. 2. The electron density map of Fig. 2a shows the collagen molecules forming a helicoid around the axis; the microfibril has a supermolecular right-

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