**1.1 SOFT TISSUE IN HUMAN BODY**

In [anatomy](https://en.wikipedia.org/wiki/Anatomy), **soft tissue** includes the [tissues](https://en.wikipedia.org/wiki/Tissue_(biology)) that connect, support, or surround other structures and [organs](https://en.wikipedia.org/wiki/Organ_(anatomy)) of the body, not being [hard tissue](https://en.wikipedia.org/wiki/Hard_tissue) such as [bone](https://en.wikipedia.org/wiki/Osseous_tissue). Soft tissue includes [tendons](https://en.wikipedia.org/wiki/Tendon), [ligaments](https://en.wikipedia.org/wiki/Ligament), [fascia](https://en.wikipedia.org/wiki/Fascia), [skin](https://en.wikipedia.org/wiki/Skin), [fibrous tissues](https://en.wikipedia.org/wiki/Fibrous_connective_tissue), [fat](https://en.wikipedia.org/wiki/Fat), and [synovial membranes](https://en.wikipedia.org/wiki/Synovial_membrane) (which are [connective tissue](https://en.wikipedia.org/wiki/Connective_tissue)), and [muscles](https://en.wikipedia.org/wiki/Muscle), [nerves](https://en.wikipedia.org/wiki/Nerve) and [blood vessels](https://en.wikipedia.org/wiki/Blood_vessel) (which are not connective tissue).

It is sometimes defined by what it is not. Soft tissue has been defined as "nonepithelial, extraskeletal [mesenchyme](https://en.wikipedia.org/wiki/Mesenchyme) exclusive of the [reticuloendothelial](https://en.wikipedia.org/wiki/Reticuloendothelial) system and [glia](https://en.wikipedia.org/wiki/Glia)"

Human soft tissue is highly deformable, and its mechanical properties vary significantly from one person to another. Impact testing results showed that the stiffness and the damping resistance of a test subject’s tissue are correlated with the mass, velocity, and size of the striking object. Such properties may be useful for forensics investigation when contusions were induced. When a solid object impacts a human soft tissue, the energy of the impact will be absorbed by the tissues to reduce the effect of the impact or the pain level; subjects with more soft tissue thickness tended to absorb the impacts with less aversion.

Soft tissues have the potential to undergo large deformations and still return to the initial configuration when unloaded, i.e. they are hyperelastic materials, and their stress-strain curve is nonlinear. The soft tissues are also viscoelastic, incompressible and usually anisotropic. Some viscoelastic properties observable in soft tissues are: relaxation, creep and hysteresis. In order to describe the mechanical response of soft tissues, several methods have been used. These methods include: hyperelastic macroscopic models based on strain energy, mathematical fits where nonlinear constitutive equations are used, and structurally based models where the response of a linear elastic material is modified by its geometric characteristics.

**1.2 COLLAGEN AS A FIBROUS PROTEIN AND BASIC STRUCTURAL ELEMENT OF SOFT TISSUE MECHANICES (STM)**

Collagen is the main structural protein in the extracellular matrix in the various connective tissues in the body. Collagen consists of amino acids bound together to form a triple helix of elongated fibril known as a collagen helix. It is mostly found in fibrous tissues such as tendons, ligaments, and skin. Collagen is a type of protein fiber found abundantly throughout our body. It provides strength and cushioning to many different areas of the body, including the skin. More specifically, collagen is found in our various types of connective tissues such as cartilage, tendons, bones, and ligaments. If we could look closely at a collagen fiber, we'd see that its structure is similar to that of a rope. Each individual fiber of collagen is made up of many small fibers, called macrofibrils, all bound together. And all of the macrofibrils are themselves made up of even tinier fibers called microfibrils. This structure accounts for the strong nature of collagen. Like a rope, collagen has great tensile strength and can be pulled without breaking.



Image of a collagen under microscope

While collagen is a strong fiber, it's also very flexible. This allows certain parts of our body to move and change without damage. For example, pinch the skin on your arm and move it around. It's flexible, allowing for plenty of movement. When you let go, it goes right back to its normal state. This is due in part to the collagen found within the deeper layers of our skin.

Biomaterials play a pivotal role in field of tissue engineering. **Biomaterials** are those materials — be it natural or synthetic, alive or lifeless, and usually made of multiple components — that interact with biological systems. **Biomaterials** are often used in medical applications to augment or replace a natural function.

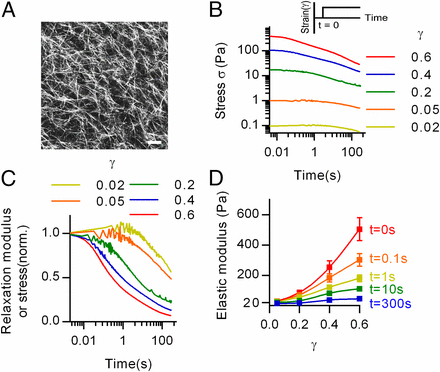
Collagen is the most widely distributed class of proteins in the human body. The use of collagen-based biomaterials in the field of tissue engineering applications has been intensively growing over the past decades. Multiple cross-linking methods were investigated and different combinations with other biopolymers were explored in order to improve tissue function. Collagen possesses a major advantage in being biodegradable, biocompatible, easily available and highly versatile. However, since collagen is a protein, it remains difficult to sterilize without alterations to its structure. This review presents a comprehensive overview of the various applications of collagen-based biomaterials developed for tissue engineering, aimed at providing a functional material for use in regenerative medicine from the laboratory bench to the patient bedside.

**1.3 STRESS-STRAIN RELATIONSHIP IN COLLAGEN BIOMATERIALS**

The extracellular matrix (ECM) is a complex assembly of structural proteins that provides physical support and biochemical signaling to cells in tissues. The mechanical properties of the ECM have been found to play a key role in regulating cell behaviors such as differentiation and malignancy. Gels formed from ECM protein biopolymers such as collagen or fibrin are commonly used for 3D cell culture models of tissue. One of the most striking features of these gels is that they exhibit nonlinear elasticity, undergoing strain stiffening. However, these gels are also viscoelastic and exhibit stress relaxation, with the resistance of the gel to a deformation relaxing over time. Recent studies have suggested that cells sense and respond to both nonlinear elasticity and viscoelasticity of ECM, yet little is known about the connection between nonlinear elasticity and viscoelasticity. Here, we report that, as strain is increased, not only do biopolymer gels stiffen but they also exhibit faster stress relaxation, reducing the timescale over which elastic energy is dissipated. This effect is not universal to all biological gels and is mediated through weak cross-links. Mechanistically, computational modeling and atomic force microscopy (AFM) indicate that strain-enhanced stress relaxation of collagen gels arises from force-dependent unbinding of weak bonds between collagen fibers. The broader effect of strain-enhanced stress relaxation is to rapidly diminish strain stiffening over time. These results reveal the interplay between nonlinear elasticity and viscoelasticity in collagen gels, and highlight the complexity of the ECM mechanics that are likely sensed through cellular mechanotransduction.

The composition and architecture of ECM is heterogeneous and varies with tissue type and location. One particularly important ECM protein is type Ι collagen, which is the most abundant ECM component and primarily determines the mechanics of connective tissue. Type 1 collagen self-assembles into fibers, and these fibers can form networks in vitro. Studies investigating the mechanical properties of collagen networks have revealed that these networks are nonlinearly elastic and exhibit strain stiffening, or an increase in the elasticity as the strain on the network is enhanced. This nonlinear elasticity is also a characteristic feature of fibrin gels, which serve as the major component of blood clots, as well as in reconstituted networks of intermediate filaments and cytoskeletal actin networks. These networks are all composed of semiflexible polymers or fibers, which are relatively rigid, so that the tangent to the contour of the polymer is correlated over long lengths, yet undergo substantial bending fluctuations due to thermal energy. Semiflexible polymers or fibers form networks at low volume fractions. Strain stiffening in these networks is thought to arise from either the entropic elasticity of single polymers resisting extension (entropic model) or from alignment of fibers in the direction of strain with a corresponding transition to a regime of elasticity dominated by fiber stretching at higher strains (nonentropic model) Although it has long been known that cells sense and respond to the elastic modulus of ECMs, recent work has indicated an impact of nonlinear elasticity as well. Studies have found that the nonlinear elasticity of ECM regulates modes of cell motility and differentiation of mesenchymal stem cells, alters how far cells are able to sense into the ECM , and enables long-range mechanical signaling between cells.

In addition to often displaying nonlinear elasticity, most biological gels are viscoelastic and exhibit a time-dependent elastic modulus. These gels undergo stress relaxation in response to an applied strain: the initial stress resisting an applied strain decreases over time due to reorganization processes that relax the stresses in the matrix. In the case of collagen gels typically used for in vitro studies, viscoelasticity and stress relaxation likely arise from unbinding of the weak interactions, such as hydrophobic and electrostatic forces, which hold the fibers in a network. Interestingly, recent studies have found that viscoelasticity in synthetic hydrogels used as cell culture substrates can influence cell behaviors such as spreading, proliferation, and differentiation . The nonlinear elasticity of collagen and fibrin is dependent on the history of applied strains, indicating an influence of viscoelasticity on nonlinear elasticity . Here, we directly investigate the coupling between viscoelasticity and nonlinear elasticity for various gels, and find that increased strain leads to faster stress relaxation in collagen and fibrin gels. In collagen gels, these results can be explained by force-dependent unbinding of cross-links, and indicate a mechanism whereby strain stiffening is rapidly dissipated.



1. Confocal microscope image of a collagen gel using an overlay of images taken with confocal reflectance microscopy. (Scale bar: 25 µm.) (B) Stress relaxation tests on collagen with various strains. (Inset) A constant strain is applied during a stress relaxation test. (C) Normalized stress relaxation tests of collagen gels at different strains. In a stress relaxation test, the stress is directly proportional to the relaxation modulus. (D) Isochronal display of elastic modulus from the stress relaxation tests of different strains, showing the elastic modulus at each strain for the specific time points. Data are shown as mean ± SD; n = 5.

The purpose of the work described in this paper was to make a stress-strain curve for a collagen molecule and estimate Young's modulus of a molecule along the molecular axis. X-ray diffractometry was performed on bovine Achilles tendon in order to measure strain in the collagen molecule along the molecular axis as a response to a macroscopically applied force. By geometrical calculations and experiments, cross-sectional areas of a molecule and molecules in a tendon collagen fiber were determined. The applied force was translated to the stress and the stress-strain curve of the collagen molecule was constructed, which was found to be almost linear. Young's modulus of the molecule was determined to be slightly smaller than when determined by dynamic mechanical methods. The difference was considered to suggest the existence of a viscoelastic component within the molecule as well as the difference in the mechanical properties of collagen in different tissues. The expected viscoelasticity was speculated to be related to the hydrogen bond network in the collagen molecule.

**1.4 CARTILAGE AND ITS APPLICATIONS IN ARTICULATING JOINTS**

**Cartilage** is a resilient and smooth [elastic tissue](https://en.wikipedia.org/wiki/Elastic_fiber), a rubber-like padding that covers and protects the ends of long [bones](https://en.wikipedia.org/wiki/Bone) at the [joints](https://en.wikipedia.org/wiki/Joint), and is a structural component of the [rib cage](https://en.wikipedia.org/wiki/Rib_cage), the [ear](https://en.wikipedia.org/wiki/Ear), the [nose](https://en.wikipedia.org/wiki/Nose), the [bronchial tubes](https://en.wikipedia.org/wiki/Bronchus), the [intervertebral discs](https://en.wikipedia.org/wiki/Intervertebral_disc), and many other body components. It is not as hard and rigid as [bone](https://en.wikipedia.org/wiki/Bone), but it is much stiffer and much less flexible than [muscle](https://en.wikipedia.org/wiki/Muscle). The matrix of cartilage is made up of [glycosaminoglycans](https://en.wikipedia.org/wiki/Glycosaminoglycan), [proteoglycans](https://en.wikipedia.org/wiki/Proteoglycan), [collagen](https://en.wikipedia.org/wiki/Collagen) fibers and, sometimes, [elastin](https://en.wikipedia.org/wiki/Elastin). Because of its rigidity, cartilage often serves the purpose of holding tubes open in the body. Examples include the rings of the trachea, such as the [cricoid cartilage](https://en.wikipedia.org/wiki/Cricoid_cartilage) and [carina](https://en.wikipedia.org/wiki/Carina_of_trachea).

Cartilage is composed of specialized cells called [chondrocytes](https://en.wikipedia.org/wiki/Chondrocyte) that produce a large amount of collagenous [extracellular matrix](https://en.wikipedia.org/wiki/Extracellular_matrix), abundant [ground substance](https://en.wikipedia.org/wiki/Ground_substance) that is rich in [proteoglycan](https://en.wikipedia.org/wiki/Proteoglycan) and elastin fibers. Cartilage is classified in three types, [*elastic cartilage*](https://en.wikipedia.org/wiki/Elastic_cartilage), [*hyaline cartilage*](https://en.wikipedia.org/wiki/Hyaline_cartilage) and [*fibrocartilage*](https://en.wikipedia.org/wiki/Fibrocartilage), which differ in relative amounts of [collagen](https://en.wikipedia.org/wiki/Collagen) and proteoglycan. Cartilage does not contain [blood](https://en.wikipedia.org/wiki/Blood) vessels (it is avascular) or [nerves](https://en.wikipedia.org/wiki/Nerve) (it is aneural). Nutrition is supplied to the chondrocytes by [diffusion](https://en.wikipedia.org/wiki/Diffusion). The compression of the articular cartilage or flexion of the elastic cartilage generates fluid flow, which assists diffusion of nutrients to the chondrocytes. Compared to other connective tissues, cartilage has a very slow turnover of its extracellular matrix and does not repair.

The articular cartilage function is dependent on the molecular composition of the [extracellular matrix](https://en.wikipedia.org/wiki/Extracellular_matrix) (ECM). The ECM consists mainly of [proteoglycan](https://en.wikipedia.org/wiki/Proteoglycan) and [collagens](https://en.wikipedia.org/wiki/Collagen). The main proteoglycan in cartilage is aggrecan, which, as its name suggests, forms large aggregates with [hyaluronan](https://en.wikipedia.org/wiki/Hyaluronic_acid). These aggregates are negatively charged and hold water in the tissue. The collagen, mostly collagen type II, constrains the proteoglycans. The ECM responds to tensile and compressive forces that are experienced by the cartilage. Cartilage growth thus refers to the matrix deposition, but can also refer to both the growth and remodeling of the extracellular matrix. Due to the great stress on the patellofemoral joint during resisted knee extension, the articular cartilage of the patella is among the thickest in the human body.

## Function

### Mechanical properties

The mechanical properties of articular cartilage in load-bearing joints such as the [knee](https://en.wikipedia.org/wiki/Knee) and [hip](https://en.wikipedia.org/wiki/Hip) have been studied extensively at macro, micro, and nano-scales. These mechanical properties include the response of cartilage in frictional, compressive, shear and tensile loading. Cartilage is resilient and displays [viscoelastic](https://en.wikipedia.org/wiki/Viscoelasticity) properties.

### Frictional properties

[Lubricin](https://en.wikipedia.org/wiki/Proteoglycan_4), a [glycoprotein](https://en.wikipedia.org/wiki/Glycoprotein) abundant in cartilage and synovial fluid, plays a major role in bio-lubrication and wear protection of cartilage.

### Repair

Cartilage has limited repair capabilities: Because chondrocytes are bound in [lacunae](https://en.wikipedia.org/wiki/Lacuna_(histology)), they cannot migrate to damaged areas. Therefore, [cartilage damage](https://en.wikipedia.org/wiki/Articular_cartilage_damage) is difficult to heal. Also, because hyaline cartilage does not have a blood supply, the deposition of new matrix is slow. Damaged hyaline cartilage is usually replaced by fibrocartilage scar tissue. Over the last years, surgeons and scientists have elaborated a series of [cartilage repair procedures](https://en.wikipedia.org/wiki/Articular_cartilage_repair) that help to postpone the need for joint replacement.

[Biological engineering](https://en.wikipedia.org/wiki/Biological_engineering) techniques are being developed to generate new cartilage, using a cellular "scaffolding" material and [cultured cells](https://en.wikipedia.org/wiki/Autologous_chondrocyte_implantation) to grow artificial cartilage.

**1.5 MECHANICAL TESTING PROCEDURE FOR SOFT TISSUES**

This protocol or procedures follows the ethical guidelines of human research ethical committee guidelines on the use, storage, and disposal of human tissue. Human tissue samples can be excised from cadaveric bodies that have been consented for research purposes with relevant ethical approvals. Samples can also be discarded tissue from consented patients undergoing surgical procedures, with relevant ethical approval.

### 1. Preparation of Skin

* Prepare specimens by manually dissecting off the adipose tissue and the thin layer of deep dermis using a scalpel blade and forceps. This step is important to ensure consistency between samples.
* Cut the resulting sheet of split-thickness skin into a standardized sample size (e.g., 1 cm × 5 cm samples). Determine the specimen size based on the dimensions of the testing apparatus. If a tissue-engineered construct is also being tested, the specimen size should be appropriate for the material of interest. Dispose of scalpel blades in the appropriate sharps bins.
* To enable completion of the mechanical calculations, measure the thickness of the skin being tested using electronic calipers before and after mechanical testing.

### 2. Tensile Testing

NOTE: All materials testing machines should be calibrated according to the manufacturer's guidelines prior to testing.

* Test skin samples in uniaxial tension using a materials testing machine at room temperature (22 °C).
* Orientate the skin samples in the same direction for all samples (e.g., perpendicular or in-line with Langer Lines (topological lines drawn on a map of the human body and referring to the natural orientation of collagen fibers in the dermis).
* Immobilize the sample between two clamps (a commercial jig), one affixed to a 98.07 N load cell and the other to an immovable base plate. The resulting area between the clamps tested in uniaxial tension should be 1 cm x 4 cm .NOTE: A commercial jig was utilized to avoid non-uniform gripping and damage to the sample before testing. The sample is fixed to a "finger-tight" tightness.
* Cover the sample area (after placement in the apparatus) on both sides with petroleum jelly to prevent specimen desiccation.
* Program the tensile loading and relaxation testing regime into the software as a list of actions, as follows: Zero Load | Zero Position | Find Contact (Tensile loading) | Wait (Relaxation).
* Start the test with the software program. Load the sample under tension to 29.42 N at 1 mm/s. Use a rate and load that does not cause failure of the skin (e.g., 29.42 N at 1 mm/s).
* After the 29.42 N-load is reached, allow the tissue to relax for 1.5 h, a time-point at which there is minimal change in relaxation behavior, controlled by the computer software. Note: The displacement is held constant during the relaxation phase, not the load.
* Calculate elastic and viscoelastic properties as per the analysis section guidelines. The mechanical properties investigated will represent the average properties of the split-thickness skin constituents (epidermis and dermis). Note: There is no defined tare load, as it is clear from the raw data when deformation is occurring and thus, only these data points are included.

### 3. Preparation of Cartilage

* Remove the skin and fascia from the cartilage specimen using a scalpel blade and forceps.
* Divide the cartilage specimens into a standardized sample size (e.g., 1.5-cm blocks) using a scalpel blade and forceps. For all samples, use a semicircular-shaped indenter that has a diameter and thickness at least 8 times greater than the size of the cartilage sample. This ratio ensures that the indenter is not affected by any edge effects from specimen preparation. Dispose of scalpel blades in the appropriate sharps bins.
* To enable completion of the mechanical calculations, measure the thickness of the cartilage to be loaded using electronic calipers before and after mechanical testing.

### 4. Compressive Indentation Testing

* Compress the cartilage samples using a materials testing machine in a hydrated environment at room temperature. Cover the cartilage sample with phosphate-buffered saline (PBS) prior to and during compression testing to ensure that the sample is hydrated. NOTE: PBS does not exactly match the physiological environment, but it allows both the materials and the tissues to be compared equally.
* Orientate the cartilage sample so the surface is perpendicular to the indenter. This allows the compression to be uniaxial and limits any shear loading.
* Program the compressive loading and relaxation testing regime into the software as a list of actions, as follows: Zero Load | Zero Position | Find Contact (Compressive loading) | Wait (Relaxation).
* Start the test using the software program. Load the sample under compression to 2.94 N at 1 mm/s. NOTE: This was determined to be a non-destructive load that is sensitive enough to identify both elastic and viscoelastic properties of cartilage15.
* After the 2.94-N limit is reached, allow the cartilage to relax for 15 min, a time-point at which there is minimal change in relaxation behavior, using the computer software

### 5. Calculation of Young's Elastic Modulus for Indentation and Tensile Testing

* Collect the raw data including time (s), displacement (mm), and load (N) from the materials testing device.
* Calculate the stress (MPa) and strain (%) using the formulas . NOTE: If a hemispherical indenter was used during compression testing, dividing the force by the cross-sectional area gives the nominal (average) stress, but not the peak stress.
* Use a linear scatter plot to plot the stress MPa (y-axis) against the strain (x-axis). Determine the linear curve fit. The linear curve fit is equal to y = mx + b with a respective R value. NOTE: All data points are included to achieve a minimum R value >0.98. The m value is the slope, which corresponds to the modulus of stress over strain, indicating compressive resistance or resistance to tension in MPa (i.e., Young's Modulus). If the R value is not >0.98, then the assumption of characterizing linear viscoelastic behavior is invalid.
* To identify the viscoelastic properties in which fluid flow from exposure to deformation has reached equilibrium, the ratio of stress over time over the last 200 s of mechanical testing and the final stress level at the end of the experiment are calculated. NOTE: With increasing time, the stress level will decrease (relax) as fluid flow reaches equilibrium. A fast stress-relaxation response indicates that it is difficult to maintain high stresses within the sample.

### 6. Relaxation Properties

* Plot stress in MPa (y-axis) against time in s (x-axis) on a linear scatter plot.
* Determine a linear curve fit to calculate the rate of relaxation. The linear curve fit is equal to y = mx + b with a respective value of the last 200 s. The m value is the rate of relaxation.
* Include all data points to obtain a minimum R value >0.98. The final stress (MPa) at 1.5 h for skin and 15 min for cartilage is the final absolute relaxation value.

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