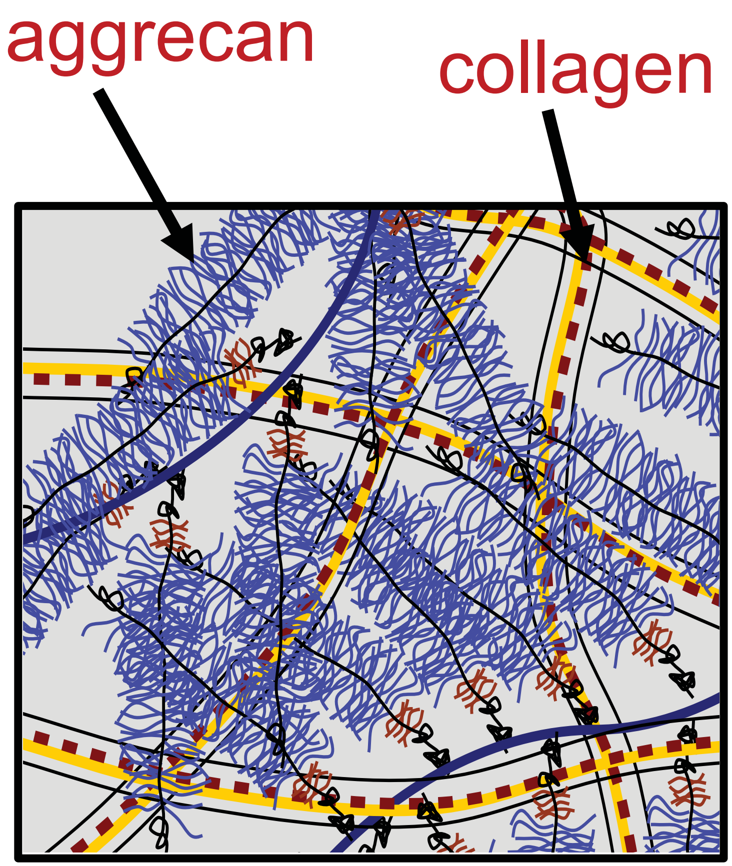
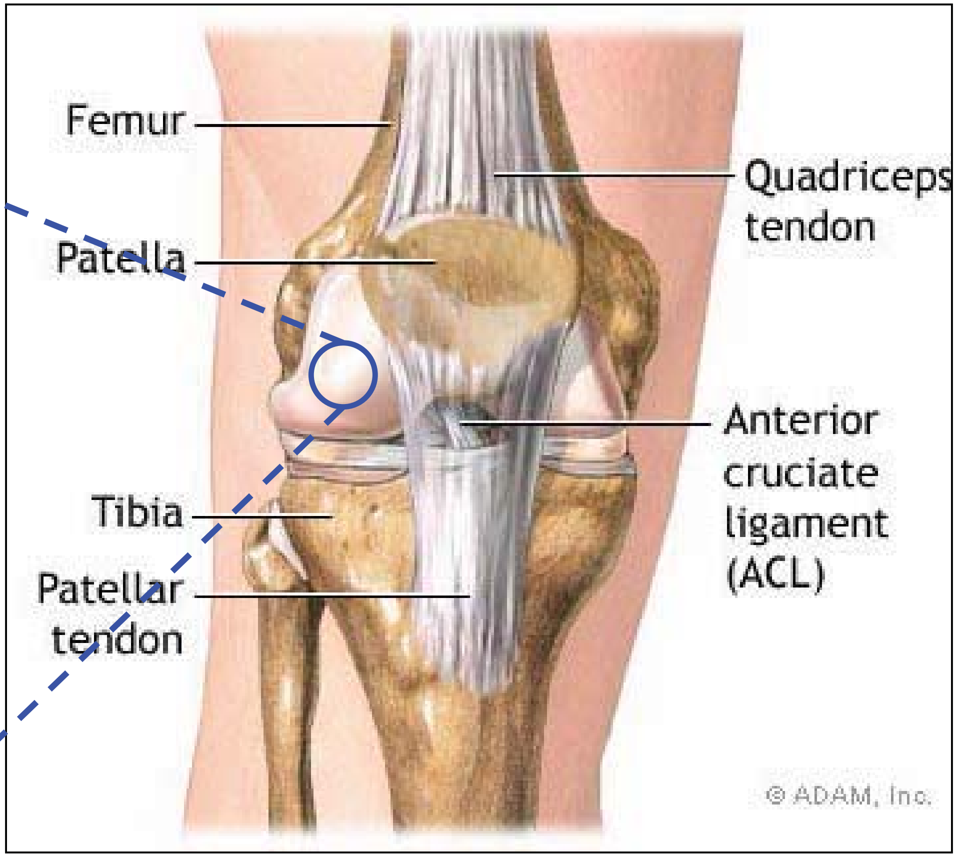
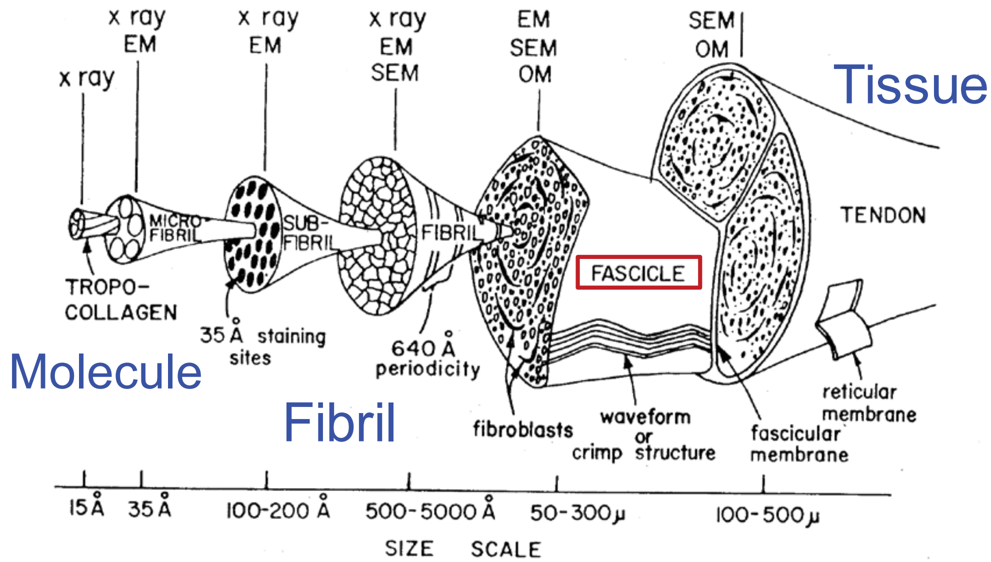
Aggrecan: Resists Compression (in tissues)

Collagen: Resists Tension (in tissues)

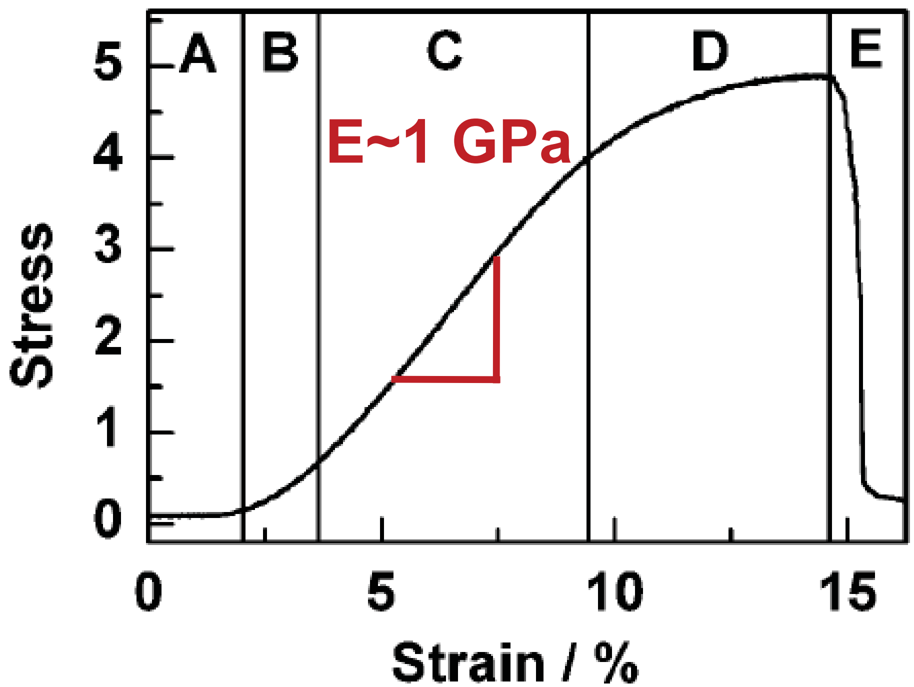




Tendon



Source: Kastelic, J., A. Galeski, and E. Baer. "The Multicomposite Structure of Tendon." *Connective Tissue Research* 6, no. 1 (1978): 11-23.



~Equilibrium

Stress vs strain curve of rat tail tendon:

(A-B) “Toe” region,

(C) ~linear region (~HILE)

(D) plateau,

(E) rupture of the tendon.

Courtesy of Elsevier, Inc., http://www.sciencedirect.com. Used with permission.
Source: Gutsmann, Thomas et al. "Force Spectroscopy of Collagen Fibers to Investigate their Mechanical Properties and Structural Organization." *Biophysical Journal* 86, no. 5 (2004): 3186-93.

- Need 2 independent measurements (2 moduli), to completely characterize an elastic tissue
- Every elastic modulus can then be expressed in terms of those 2 moduli

	bulk	Young's	Lamé #2	Shear	Poisson	Longitudinal
	$K =$	$E =$	$\lambda =$	$G =$	$\nu =$	$M =$ **H**
$(K,\, E)$	K	E	$\frac{3K(3K-E)}{9K-E}$	$\frac{3KE}{9K-E}$	$\frac{3K-E}{6K}$	$\frac{3K(3K+E)}{9K-E}$
$(K,\, \lambda)$	K	$\frac{9K(K-\lambda)}{3K-\lambda}$	λ	$\frac{3(K-\lambda)}{2}$	$\frac{\lambda}{3K-\lambda}$	$3K - 2\lambda$
$(K,\, G)$	K	$\frac{9KG}{3K+G}$	$K - \frac{2G}{3}$	G	$\frac{3K-2G}{2(3K+G)}$	$K + \frac{4G}{3}$
$(K,\, \nu)$	K	$3K(1 - 2\nu)$	$\frac{3K\nu}{1+\nu}$	$\frac{3K(1-2\nu)}{2(1+\nu)}$	ν	$\frac{3K(1-\nu)}{1+\nu}$
$(K,\, M)$	K	$\frac{9K(M-K)}{3K+M}$	$\frac{3K-M}{2}$	$\frac{3(M-K)}{4}$	$\frac{3K-M}{3K+M}$	M
$(E,\, \lambda)$	$\frac{E+3\lambda+R}{6}$	E	λ	$\frac{E-3\lambda+R}{4}$	$\frac{2\lambda}{E+\lambda+R}$	$\frac{E-\lambda+R}{2}$
$(E,\, G)$	$\frac{EG}{3(3G-E)}$	E	$\frac{G(E-2G)}{3G-E}$	G	$\frac{E}{2G} - 1$	$\frac{G(4G-E)}{3G-E}$
$(E,\, \nu)$	$\frac{E}{3(1-2\nu)}$	E	$\frac{E\nu}{(1+\nu)(1-2\nu)}$	$\frac{E}{2(1+\nu)}$	ν	$\frac{E(1-\nu)}{(1+\nu)(1-2\nu)}$
$(\lambda,\, G)$	$\lambda + \frac{2G}{3}$	$\frac{G(3\lambda+2G)}{\lambda+G}$	λ	G	$\frac{\lambda}{2(\lambda+G)}$	$\lambda + 2G$

Regulation of gene expression in intervertebral disc cells by low and high hydrostatic pressure

(Eur Spine J, 2006)

Cornelia Neidlinger-Wilke · Karin Würtz ·
Jill P. G. Urban · Wolfgang Börm · Markus Arand ·
Anita Ignatius · Hans-Joachim Wilke ·
Lutz E. Claes

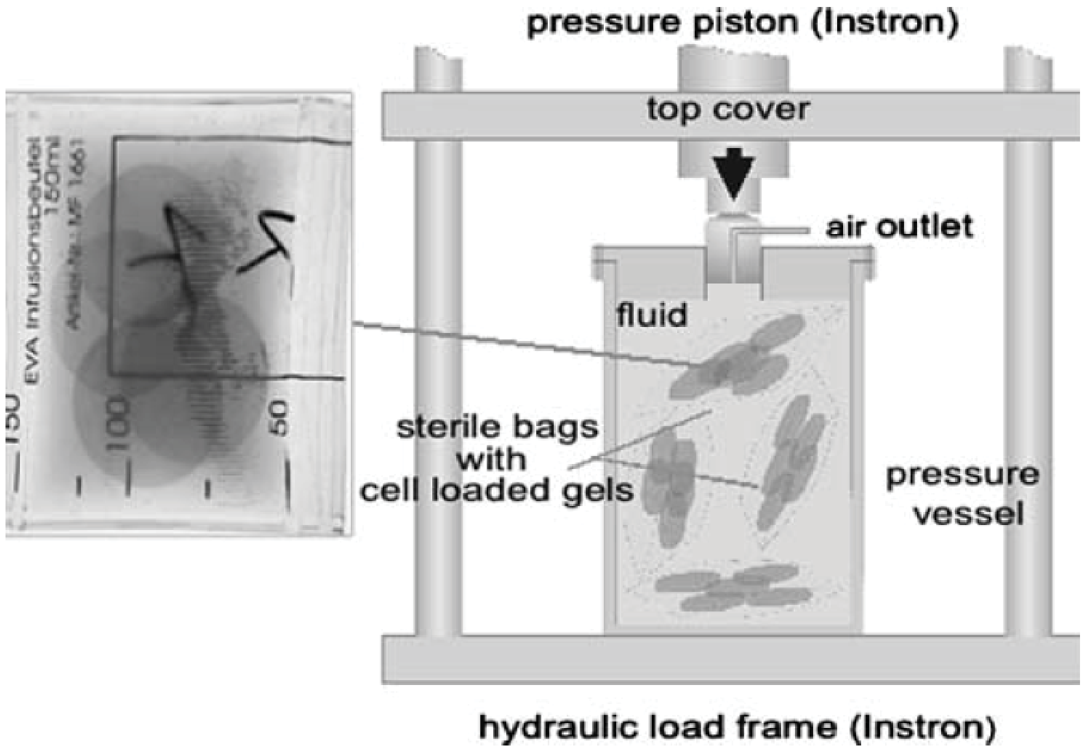
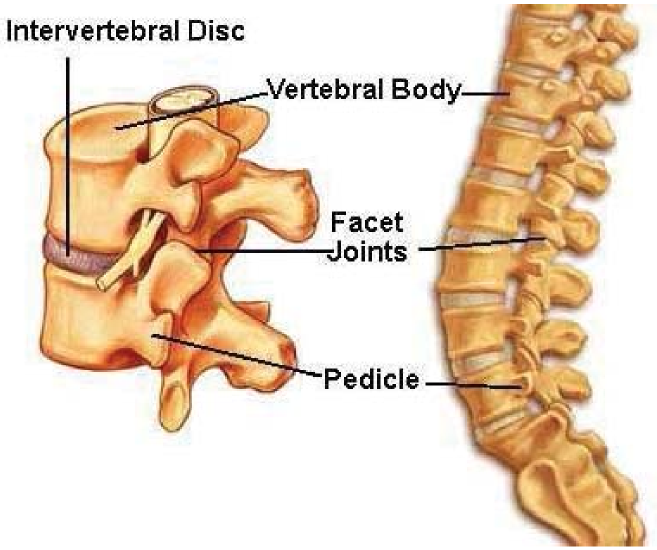


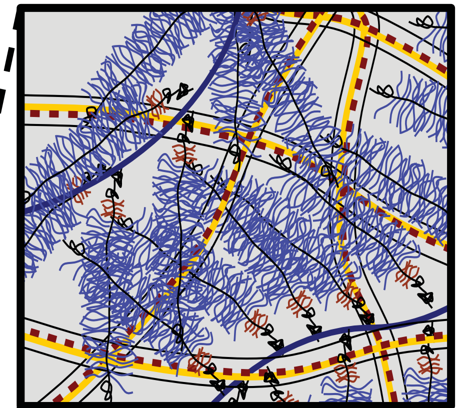
Fig. 1 Scheme of the stimulation device for the application of high hydrostatic pressure (2.5 MPa) and photo of a sterile bag with cell-seeded collagen gels

Source: Neidlinger-Wilke, Cornelia, et al. "Regulation of Gene Expression in Intervertebral Disc Cells by Low and High Hydrostatic Pressure." *European Spine Journal* 15, no. 3 (2006): 372-8.

Intervertebral Disc

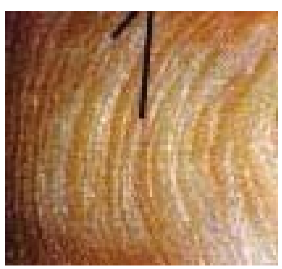
(Peter Roughley, Spine, 2004)

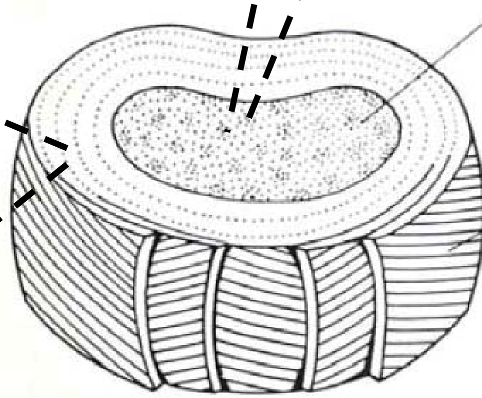




collagen II
aggrecan

col I,III



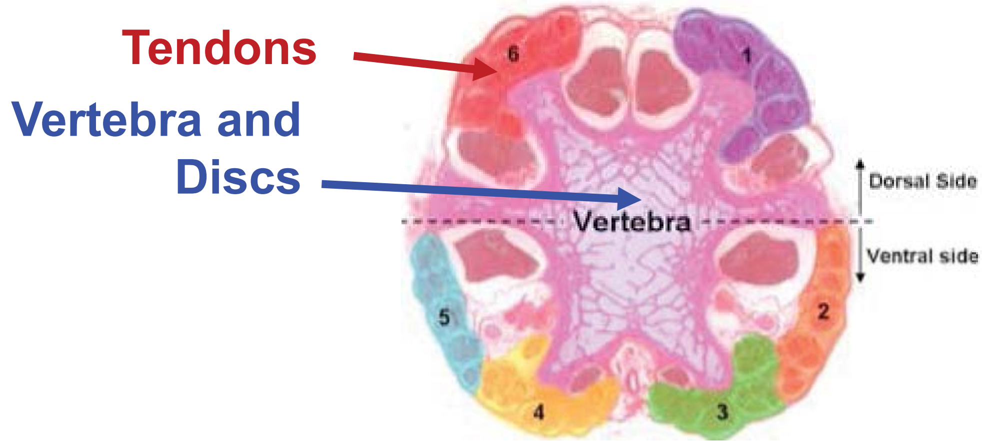


Nucleus **E ~1 MPa**

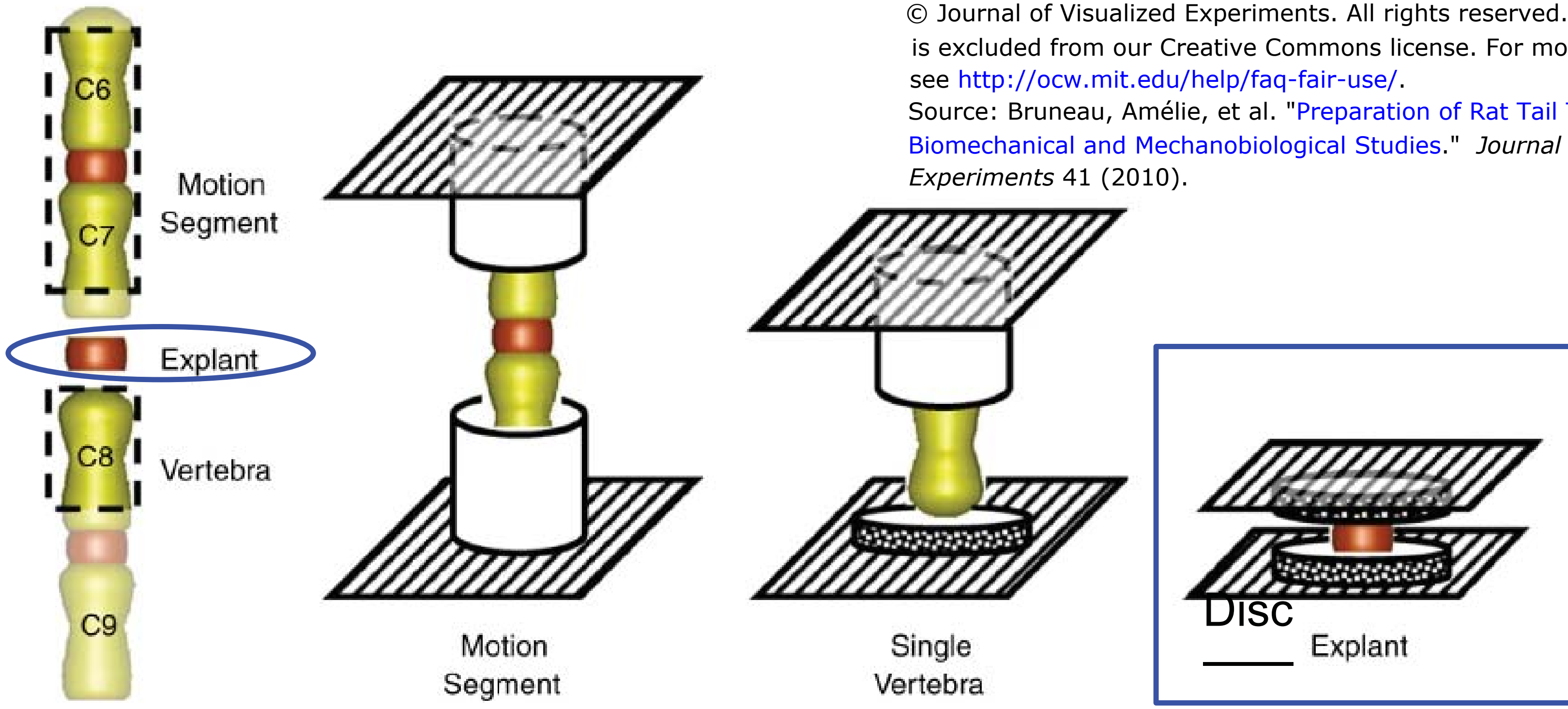
Annulus **E ~4 MPa**

Source: Roughley, Peter J. "Biology of Intervertebral Disc Aging and Degeneration: Involvement of the Extracellular Matrix." *Spine* 29, no. 23 (2004): 2691-9.

"Creep-Compression" of intervertebral disc (rat tail)



Source: Bruneau, Amélie, et al. "Preparation of Rat Tail Tendons for Biomechanical and Mechanobiological Studies." *Journal of Visualized Experiments* 41 (2010).

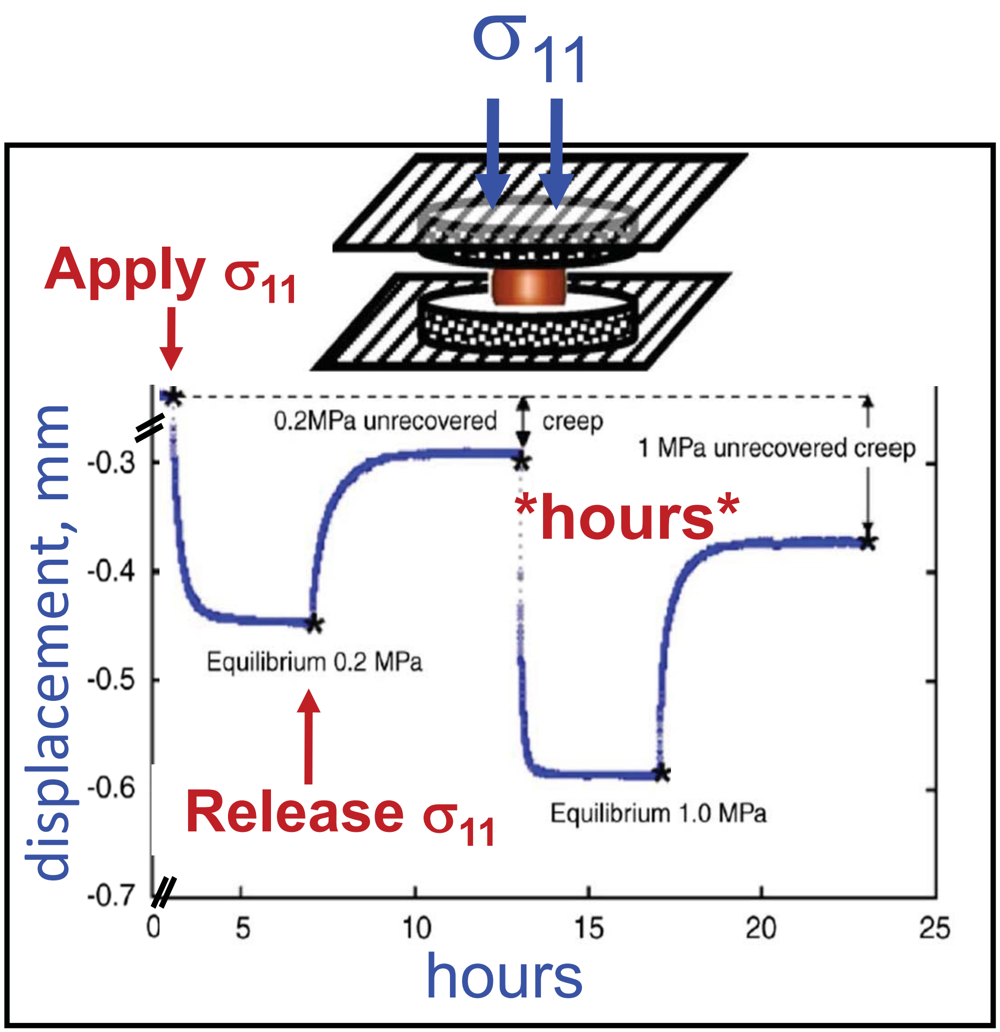


Source: MacLean, Jeffrey J. "Role of Endplates in Contributing to Compression Behaviors of Motion Segments and Intervertebral Discs." *-RXUQD0 RI %LRPHFKDQLFV* 40, no. 1 (2007): 55-63.

(MacLean+, J Biomechanics, 2007)

“Creep-Compression” of intervertebral disc (rat tail):

Apply <u>constant stress</u> (σ_{11}) and <u>measure displacement</u> (<u>strain</u>) vs time



Source: MacLean, Jeffrey J. "Role of Endplates in Contributing to Compression Behaviors of Motion Segments and Intervertebral Discs." *Journal of Biomechanics* 40, no. 1 (2007): 55-63.

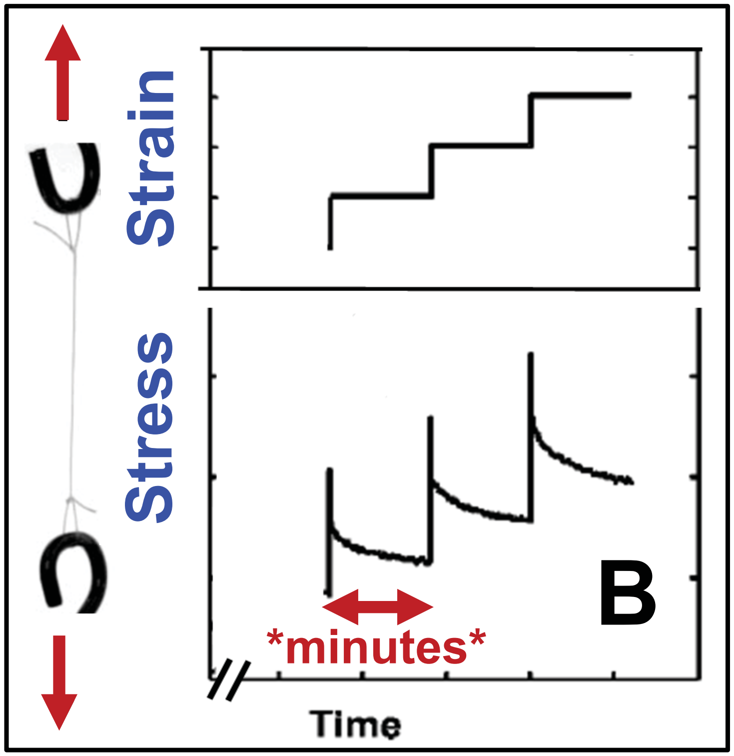
(MacLean+, J Biomechanics, 2007)

Influence of Decorin and Biglycan on Mechanical Properties of Multiple Tendons in Knockout Mice

"Stress Relaxation"

Apply step in strain (ε_{11}) and *measure stress vs time*

Mouse tendon fascicle



Tendon Hierarchy

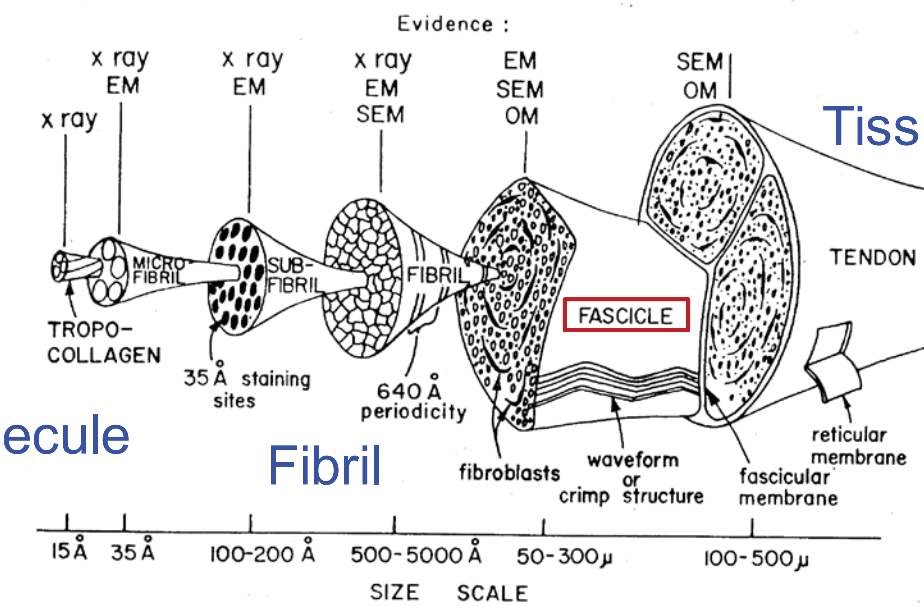


Figure 7.3:6 Hierarchy of structure of a tendon according to Kastelic et al. (1978). Reproduced by permission. Evidences are gathered from X ray, electron microscopy (EM), scanning electron microscopy (SEM), and optical microscopy (OM). (Y.C. Fung)

Source: Robinson, Paul S. et al. "Influence of Decorin and Biglycan on Mechanical Properties of Multiple Tendons in Knockout Mice." *Journal of Biomechanical engineering* 127, no. 1 (2005): 181-5.

Source: Kastelic, J., A. Galeski, and E. Baer. "The Multicomposite Structure of Tendon." *Connective Tissue Research* 6, no. 1 (1978): 11-23.

Robinson+, J Biomech Eng, 2005

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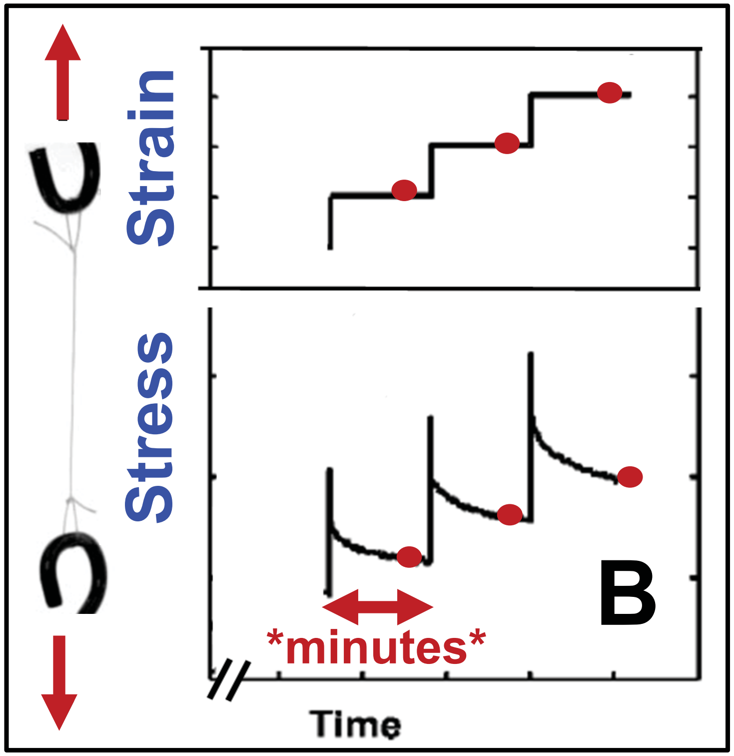

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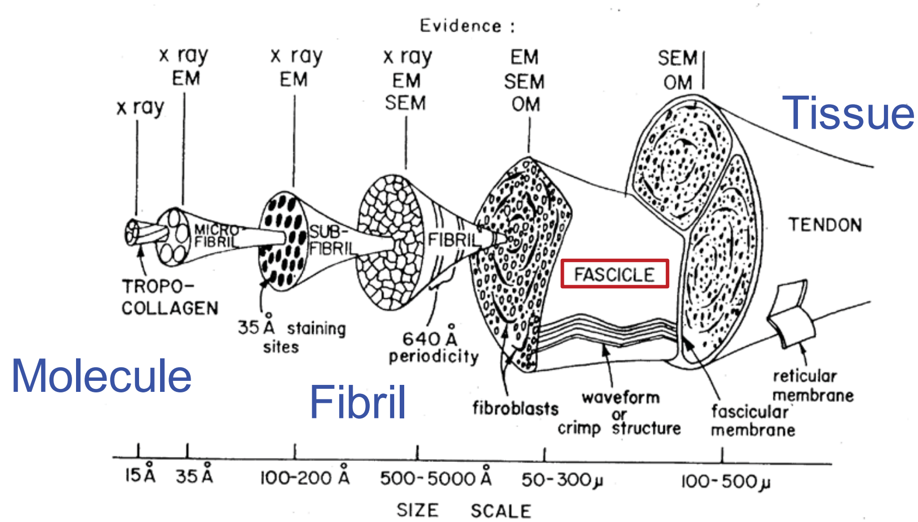

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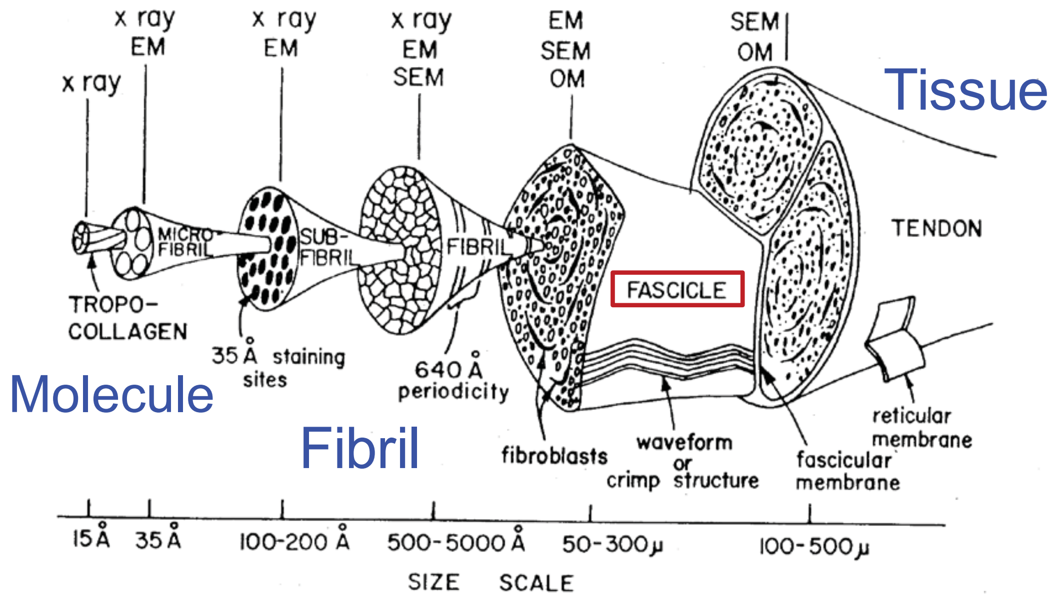
Robinson+, J Biomech Eng, 2005

Tendon



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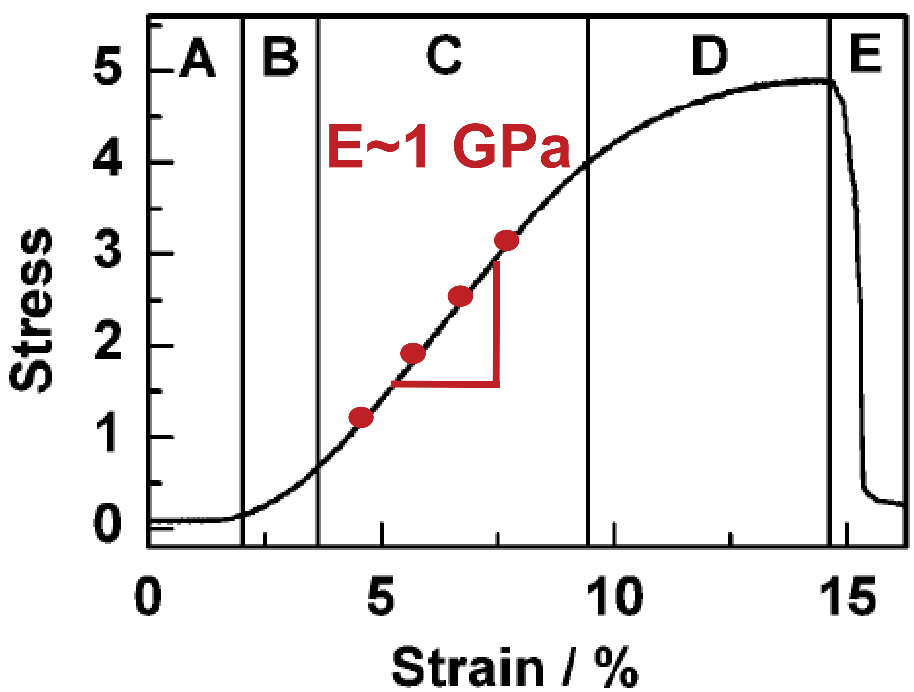


~Equilibrium

Stress vs strain curve of rat tail tendon:

(A-B) "Toe" region,

(C) ~linear region (~HILE)

(D) plateau,

(E) rupture of the tendon.

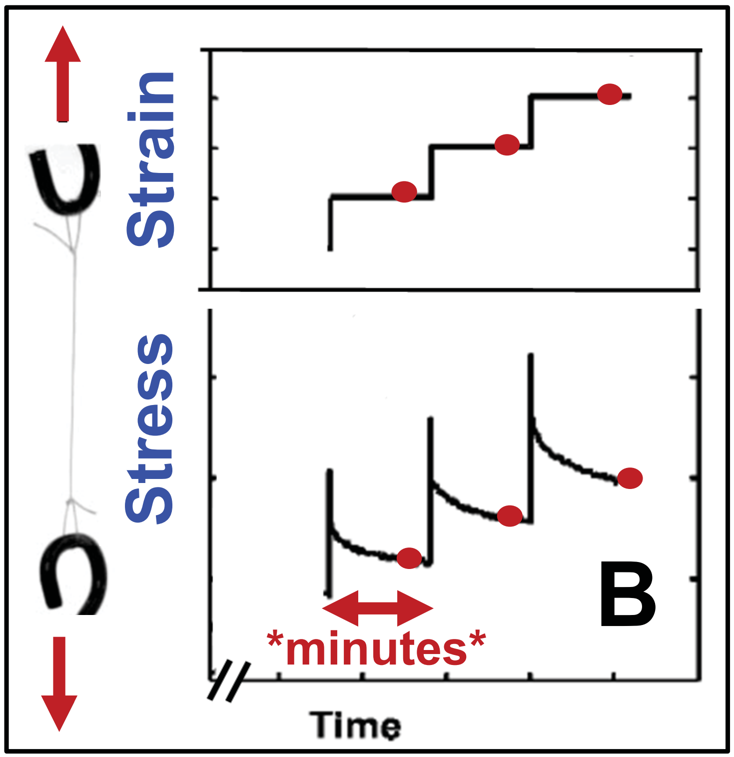
Source: Gutsmann, Thomas et al. "Force Spectroscopy of Collagen Fibers to Investigate their Mechanical Properties and Structural Organization." *Biophysical Journal* 86, no. 5 (2004): 3186-93.

Influence of Decorin and Biglycan on Mechanical Properties of Multiple Tendons in Knockout Mice

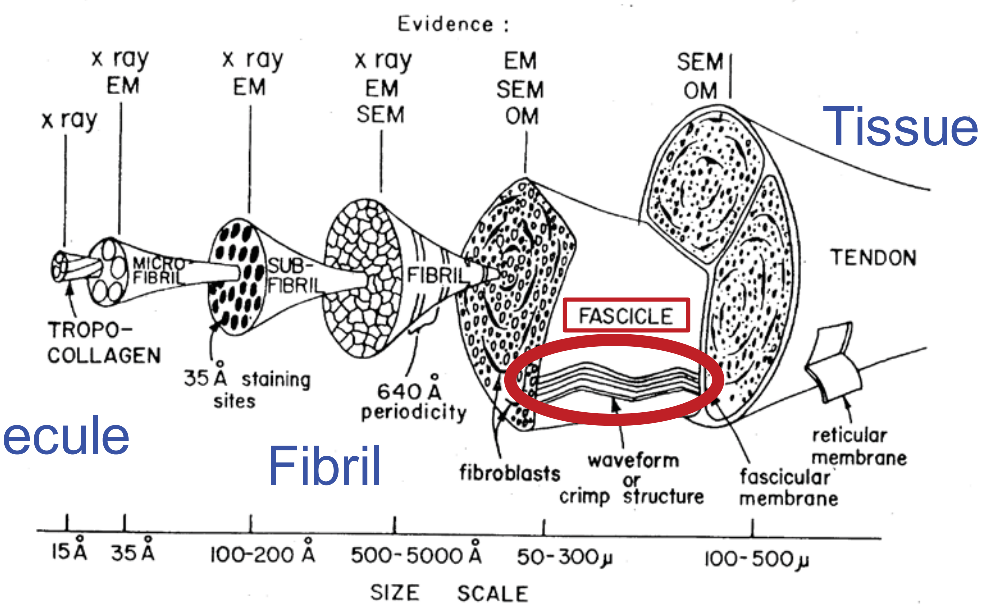
"Stress Relaxation"

Molecular- & Tissue-level Mechanisms??

Mouse tendon fascicle



Tendon Hierarchy



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Robinson+, J Biomech Eng, 2005

PROTEOGLYCAN SUPERFAMILY

- **ECM molecules with (1) Core protein, and (2) Glycosaminoglycan (GAG) chains**

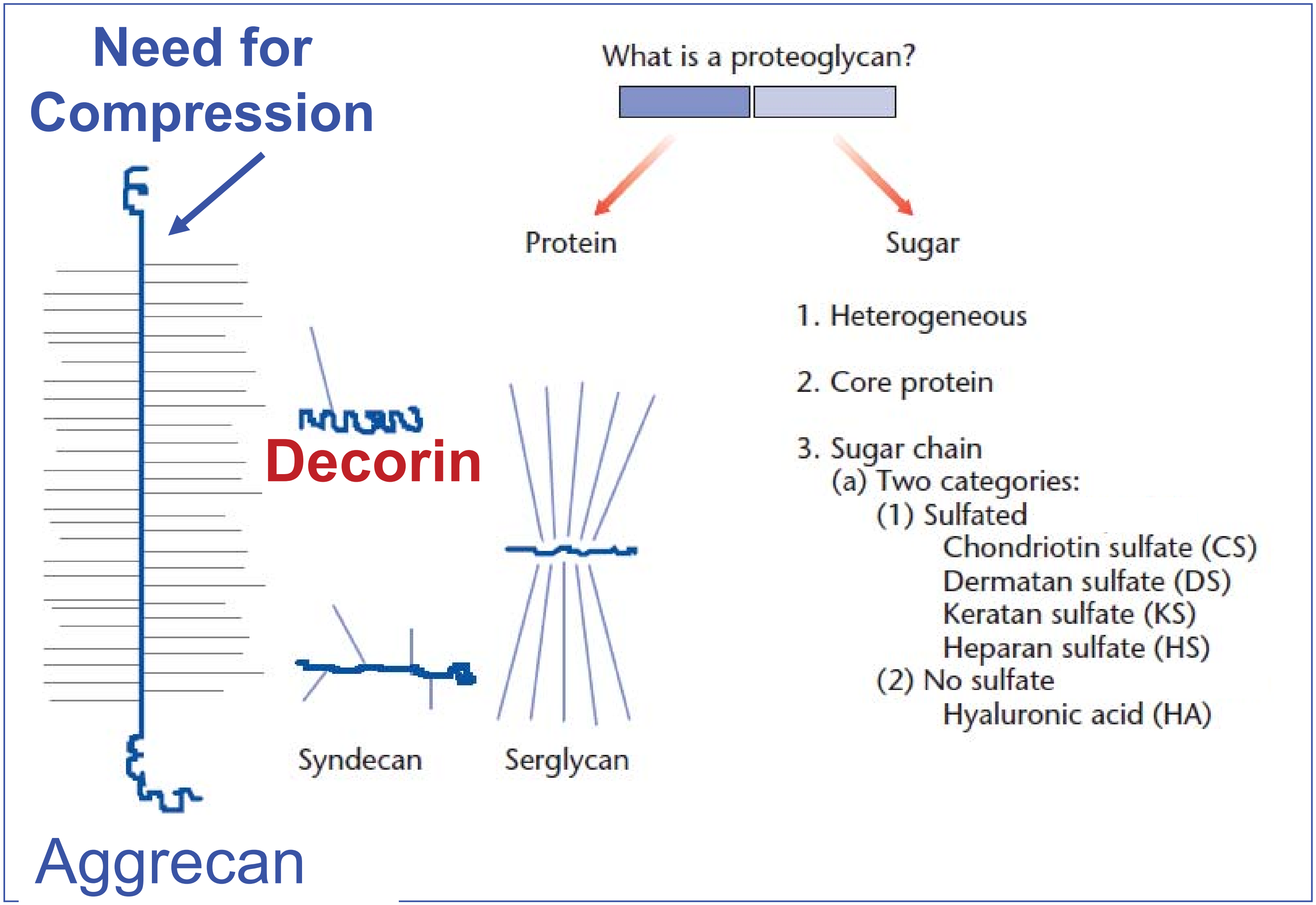
- **“Sub-families” include**

  - Extracellular • Large Aggregating (Aggrecan)
    • **Small Leucine-Rich PG (SLRPs)**
  - Cell Surface (e.g., glycocalyx HSPGs)

Proteoglycans

Encyclop Life Sci, 2009

Nancy B Schwartz, *University of Chicago, Illinois, USA*



Source: Schwartz, Nancy B. "Proteoglycans." eLS (2009).

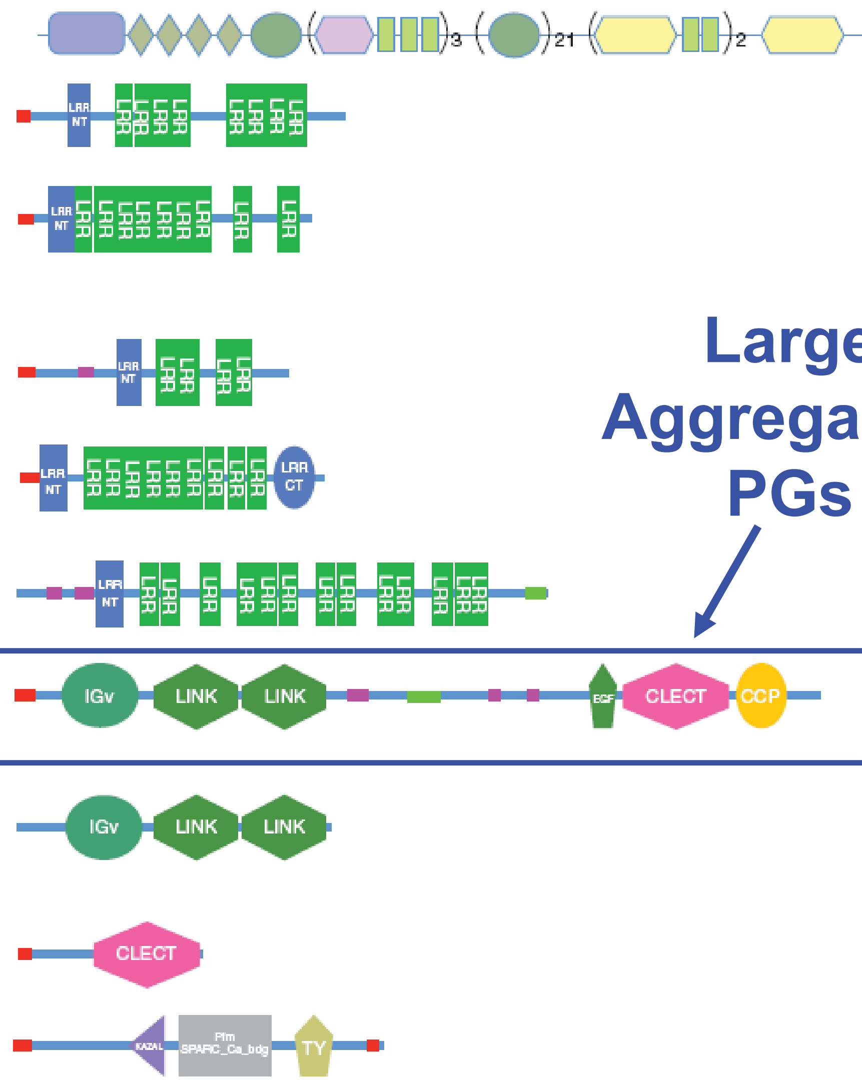
Table 1. Extracellular matrix proteoglycans (Proteoglycan Superfamily)

(36 - 42 or more)

GENE NAME	COMMON NAME(S)	DOMAINS	GAGs
HSPG2	heparan sulfate proteoglycan 2/**perlecan**	complex	HS/CS
ASPN	asporin	LRR	maybe none
BGN	**biglycan**	LRR	CS/DS
DCN	decorin	LRR	CS/DS
FMOD	fibromodulin	LRR	KS
KERA	keratocan	LRR	KS
LUM	**lumican**	LRR	KS
OMD	osteomodulin/osteoadherin	LRR	KS
PRELP	PRELP/prolargin (pro/arg-end/leu-rich repeat protein)	LRR	KS ??
EPYC	**epiphycan**	LRR	CS/DS
OGN	osteoglycin/mimecan	LRR	KS
OPTC	opticin	LRR	??
CHAD	**chondroadherin**	LRR	maybe none
CHADL	chondroadherin-like	LRR	maybe none
NYX	nyctalopin (probably GPI-linked)	LRR	maybe none
NEPNP	nephrocan (pseudogene in human)	LRR	
PODN	**podocan**	LRR	maybe none
PODNL1	podocan-like 1	LRR	maybe none
ACAN	aggrecan	LINK/CLEC/CCP	CS/KS
BCAN	**brevican**	LINK/CLEC/CCP	CS
NCAN	neurocan	LINK/CLEC/CCP	CS
VCAN	versican	LINK/CLEC/CCP	CS/DS
HAPLN1	**hyaluronan and proteoglycan link protein 1**	LINK	
HAPLN2	hyaluronan and proteoglycan link protein 2	LINK	
HAPLN3	hyaluronan and proteoglycan link protein 3	LINK	
HAPLN4	hyaluronan and proteoglycan link protein 4	LINK	
PRG2	proteoglycan 2, bone marrow PG	CLEC	
PRG3	**proteoglycan 3**	CLEC	
SPOCK1	testican 1	SPARC, Kazal, TY	CS/KS
SPOCK2	testican 2	SPARC, Kazal, TY	CS/KS
SPOCK3	testican 3	SPARC, Kazal, TY	CS/KS
PRG4	proteoglycan 4/lubricin	SO/HX	maybe none
SRGN	serglycin	serglycin	HS/CS
IMPG1	interphotoreceptor matrix proteoglycan 1	SEA domain	CS
IMPG2	interphotoreceptor matrix proteoglycan 2	SEA domain	CS
ESM1	endocan/endothelial cell-specific molecule 1	IB domain	CS/DS

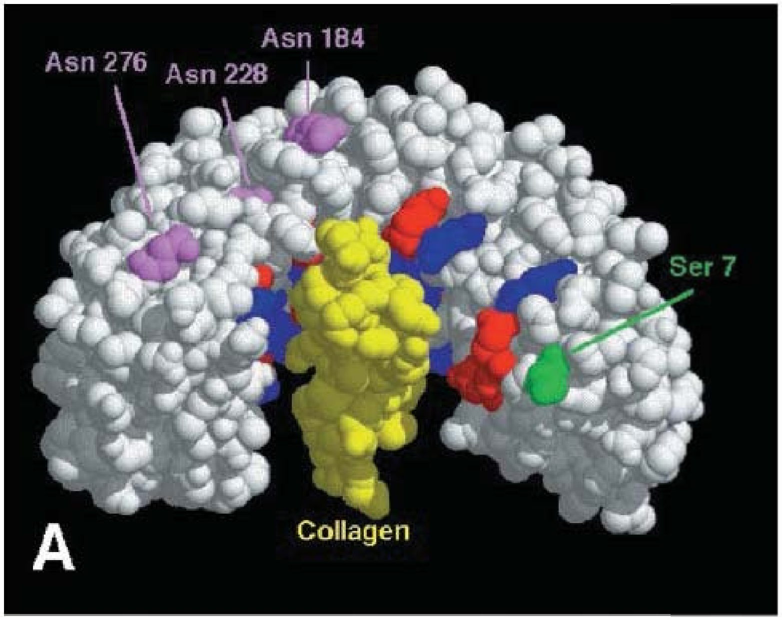
SLRPS

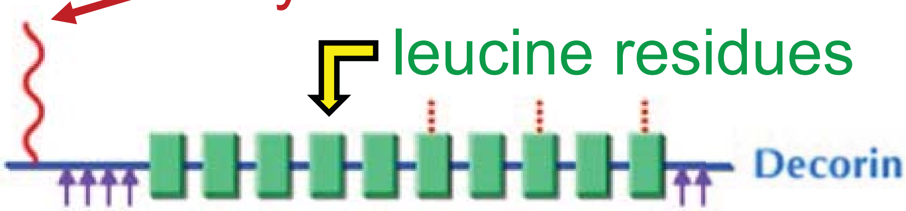
Large Aggregating PGs

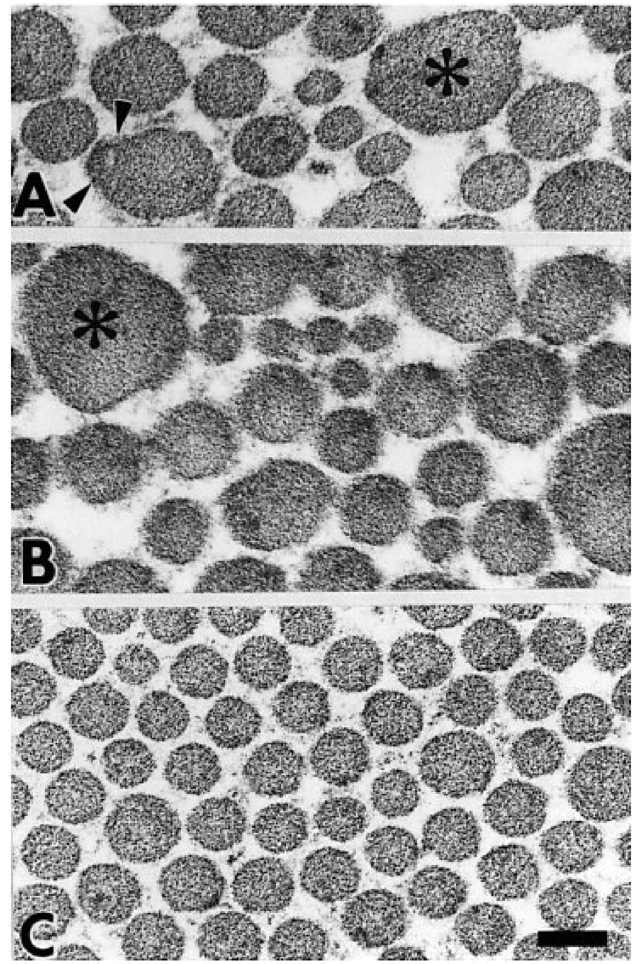


Source: Hynes, Richard O., and Alexandra Naba. "Overview of the Matrisome—An Inventory of Extracellular Matrix Constituents and Functions." &R0G 6SULQJ +DUERU 3HUVSHFWLYHV LQ %LRORJ\ 4, no. 1 (2012): a004903.

Decorin & Collagen Fibrillogenesis







SKIN decorin KO

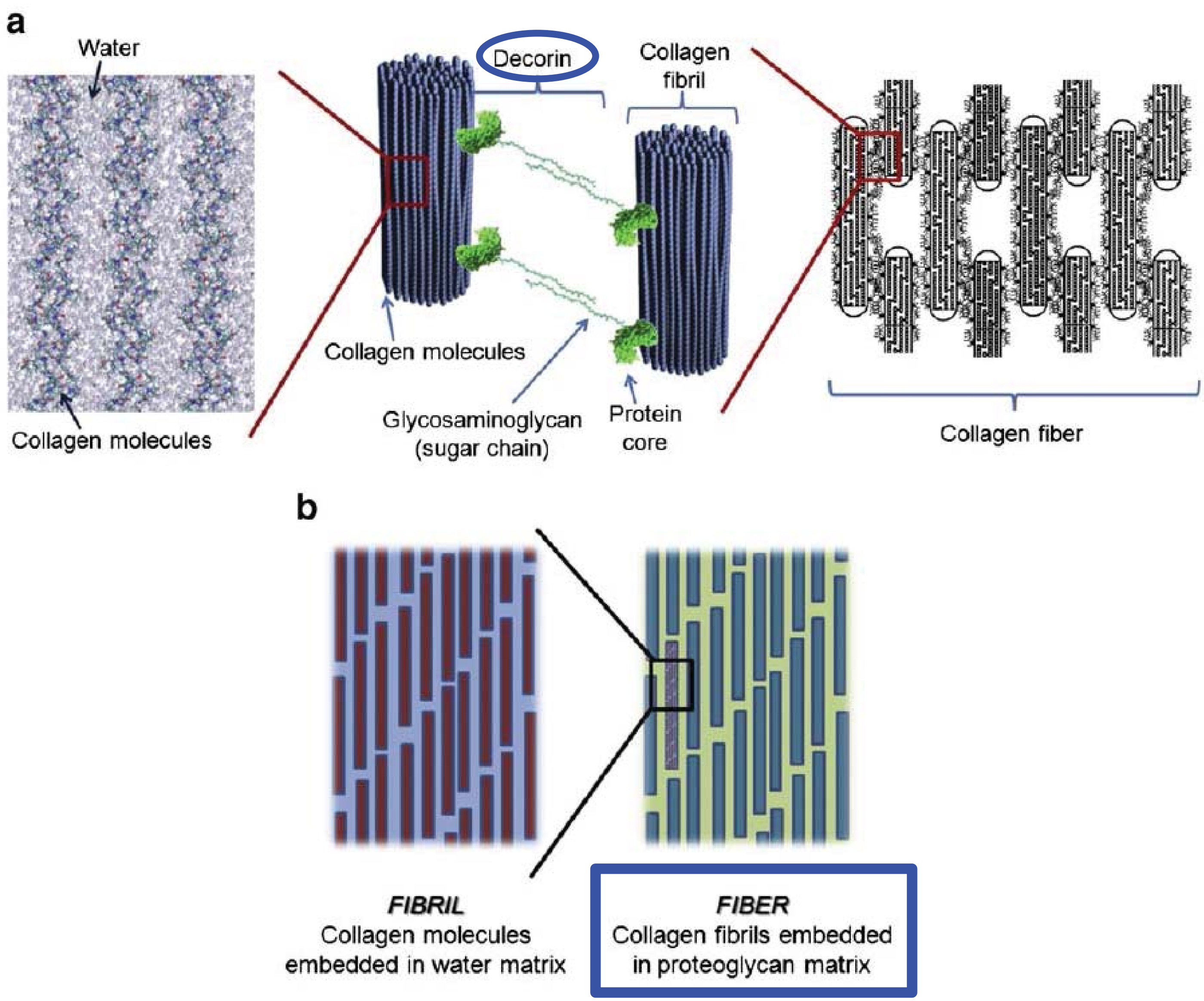
decorin KO

Normal (WT)

Example of Small-Leucine-Rich Proteoglycans

Figure 4 Ultrastructural appearance of dermal collagen from the skin of decorin null (*A* and *B*) and wild-type (*C*) mice. Notice the larger and irregular cross-sectional profiles in the decorin null collagen fibers (*asterisks*) with evidence of lateral fusion (*A*, *arrowheads*). Bar: 90 nm.

(Iozzo +, Normal and decorin null mice, J Biol Chem 1999)



Source: Gautieri, Alfonso et al. "Viscoelastic Properties of Model Segments of Collagen Molecules." *Matrix Biology* 31, no. 2 (2012): 141-9.

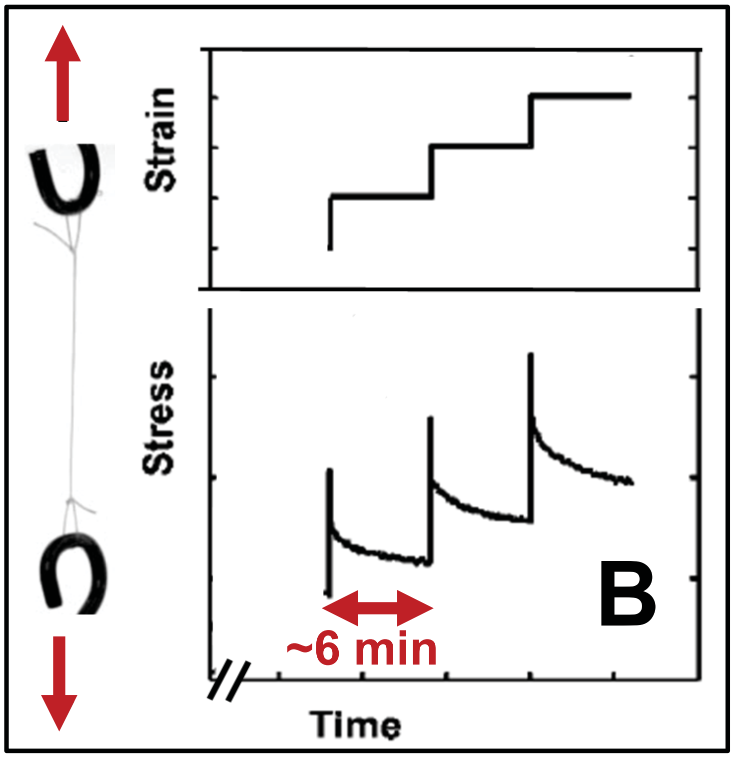
Gauteri, Buehler et al., Matrix Biology, 31:141-9, 2012

Influence of Decorin and Biglycan on Mechanical Properties of Multiple Tendons in Knockout Mice

"Stress Relaxation"

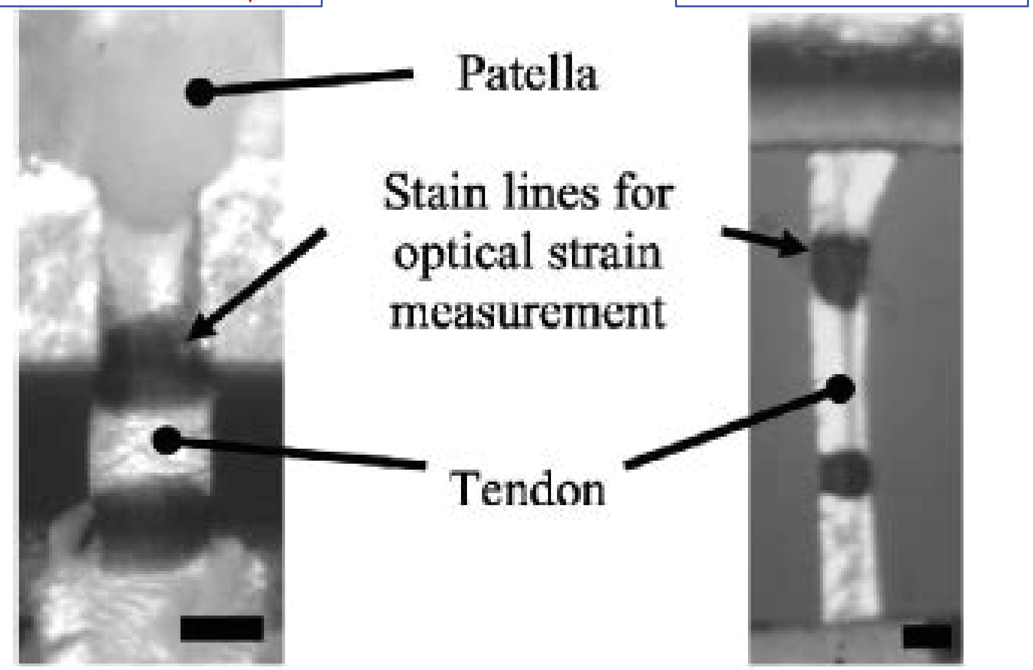
Apply step in strain (ε_{11}) and *measure stress vs time*

Mouse tendon fascicle



decorin k/o
Modulus ↓

Biglycan k/o
Modulus ↑



Patellar (left) and flexor digitorum longus (right)

Source: Robinson, Paul S., et al. "Influence of Decorin and Biglycan on Mechanical Properties of Multiple Tendons in Knockout Mice." *Journal of Biomechanical Engineering* 127, no. 1 (2005): 181-5.

Robinson+, J Biomech Eng, 2005

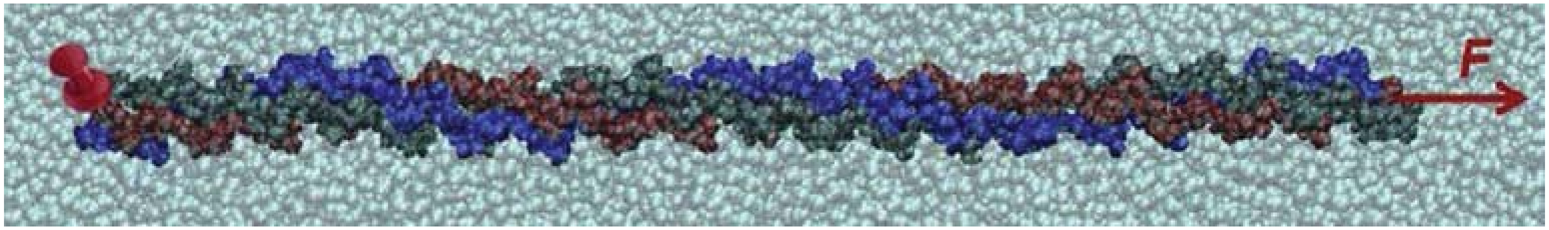
“Lumped Element” Viscoelastic Models

Matrix Biology, March 2012, 31:141-9

Viscoelastic properties of model segments of collagen molecules

Alfonso Gautieri [a,b], Simone Vesentini [b], Alberto Redaelli [b], Markus J. Buehler [a,c,*]

- ….a deep understanding of the relationship between molecular structure and mechanical properties remains elusive, hindered by the complex hierarchical structure of collagen-based tissues…
- Although extensive studies of viscoelastic properties have been pursued at the macroscopic (fiber/tissue) level, fewer investigations have been performed at the smaller scales, including collagen molecules and fibrils.
- Here, using atomistic modeling, we perform **"in silico" creep tests** of a collagen-like peptide…..**relate time-dependence to molecular structure**



Source: Gautieri, Alfonso et al. "Viscoelastic Properties of Model Segments of Collagen Molecules." *Matrix Biology* 31, no. 2 (2012): 141-9.

"In silico" creep test of a segment of a collagen molecule

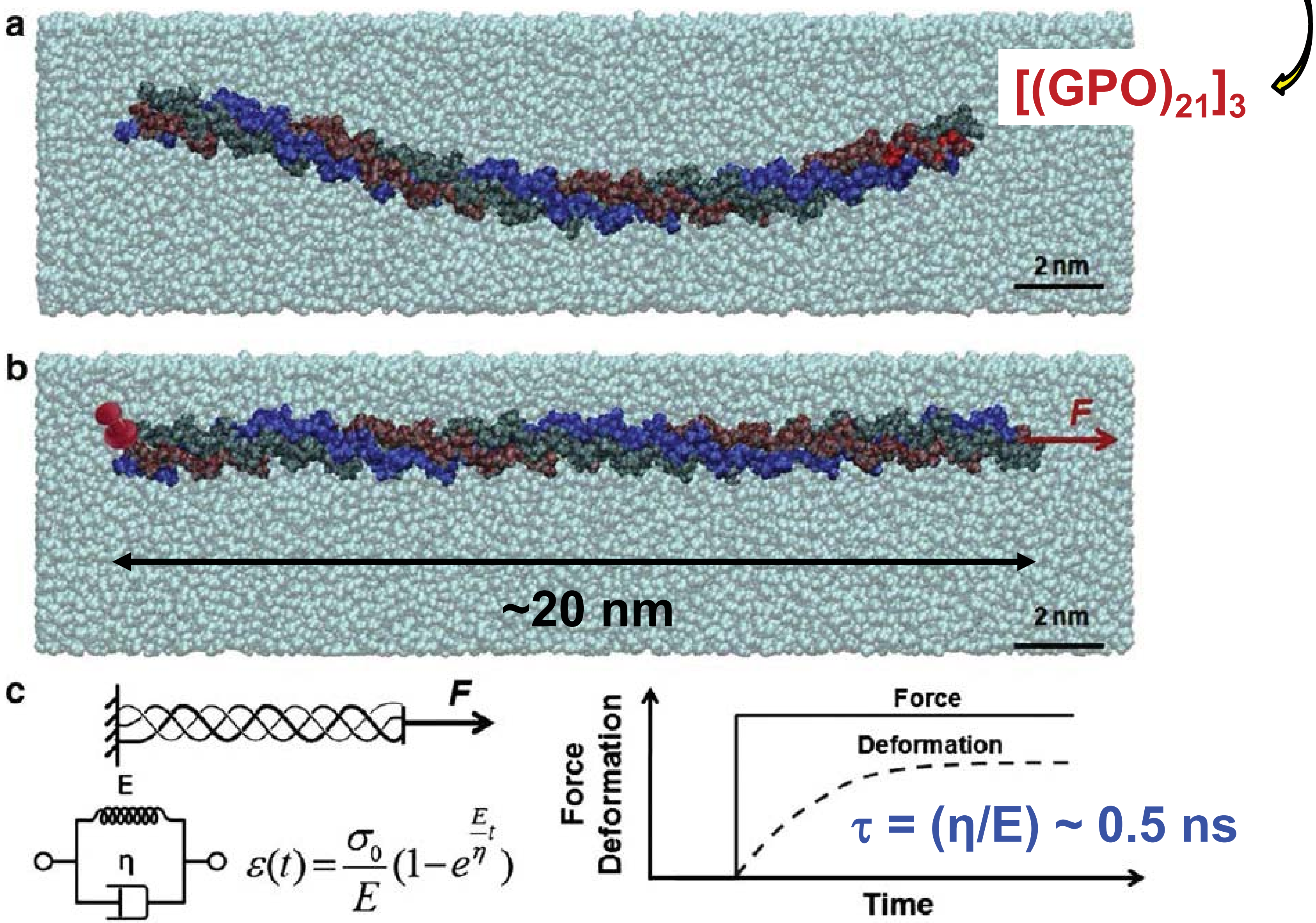
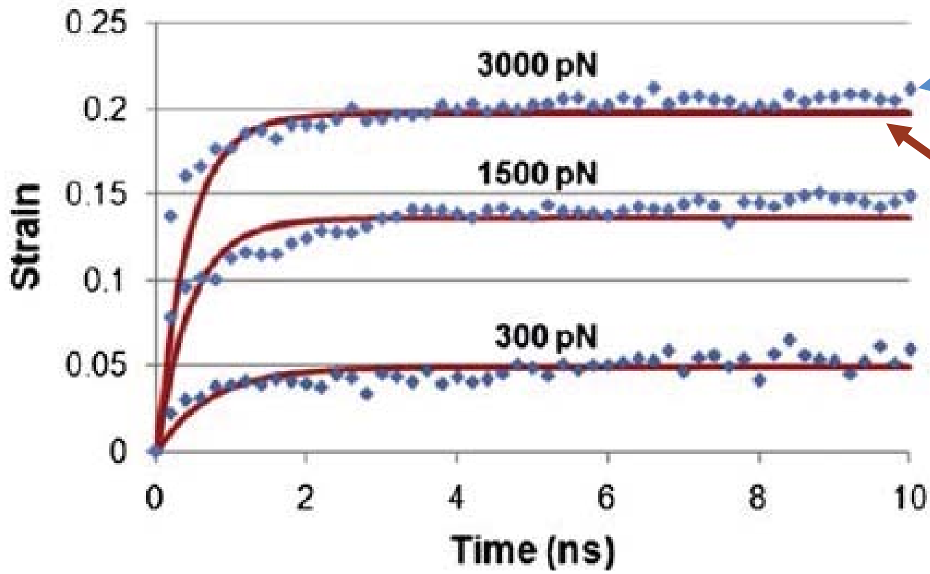


Fig. 1. Snapshots of the collagen peptide in water box. Panel a shows the conformation of the full atomistic model of a $[(GPO)_{21}]_3$ collagen peptide solvated in water box and equilibrated for 30 ns. After equilibration the molecule is subjected to virtual creep tests: one end of the collagen peptide is held fixed, whereas the other end is pulled with constant force (from 300 pN to 3000 pN) until end-to-end distance reaches equilibrium (Panel b). Panel c shows a schematic of the creep test; a constant force is applied instantaneously to the molecule and its response (deformation over time) is monitored. The mechanical response of collagen molecule is modeled using a KV model, from which molecular Young's modulus (E) and viscosity (η) are calculated.

Source: Gautieri, Alfonso et al. "Viscoelastic Properties of Model Segments of Collagen Molecules." *Matrix Biology* 31, no. 2 (2012): 141-9.



"In Silico Experiment"

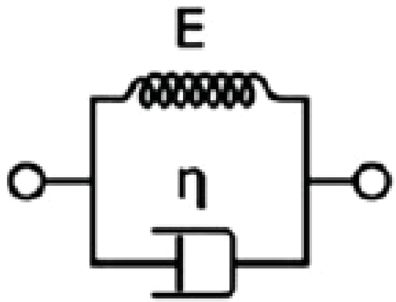
Spring-dashpot curve-fit

constant force "Steered Molecular Dynamics) (MSD) simulations…

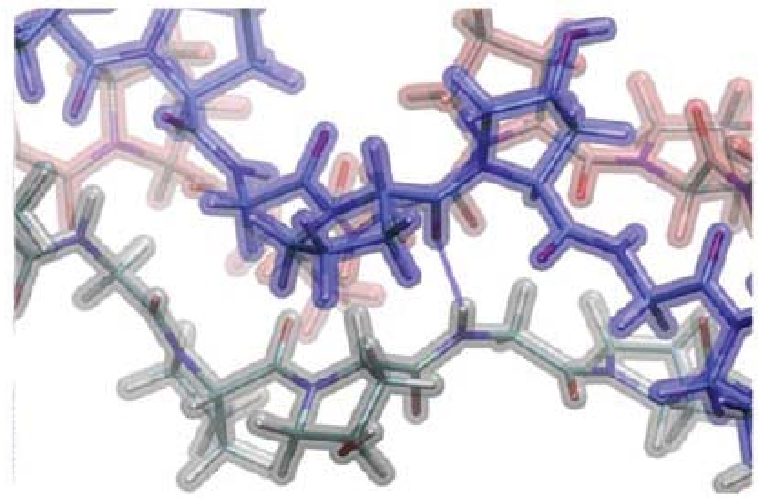
Source: Vesentini, Simone, et al. "Nanomechanics of Collagen Microfibrils." *Muscles, Ligaments and Tendons Journal* 3, no. 1 (2013): 23.

Fig. 2. Single molecule creep test. Mechanical response of solvated collagen molecule to creep tests for three cases with increasing value of external force. Dots represent the experimental data, whereas curves represent the fitted curves using a Kelvin–Voigt model.

$$\tau = (\eta/E) \sim 0.5 \text{ ns}$$

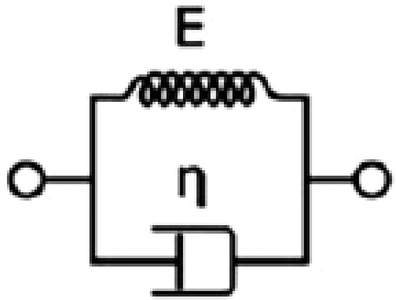


$$\varepsilon(t)=\frac{\sigma_0}{E}\left(1-e^{\frac{E}{\eta}t}\right)$$

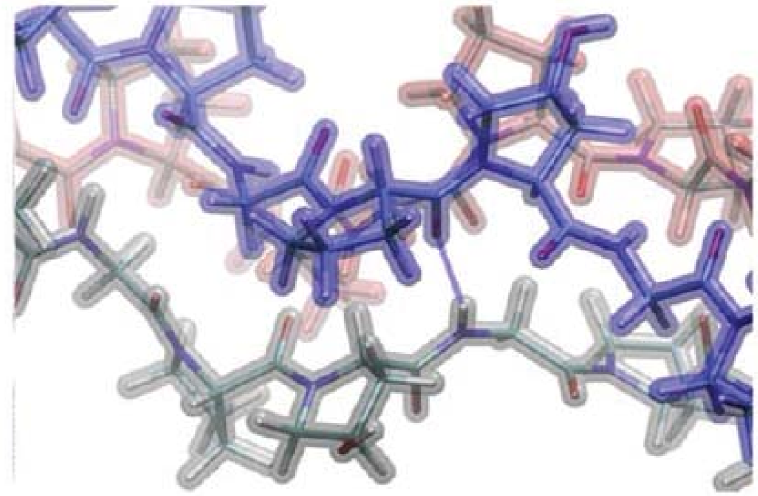


We use the KV model to fit the extension-time curves since this model is the most basic viscoelastic mechanical model available and it provides an excellent fit to the measured mechanical response. It

Source: Vesentini, Simone, et al. "Nanomechanics of Collagen Microfibrils." *Muscles, Ligaments and Tendons Journal* 3, no. 1 (2013): 23.



$$\varepsilon(t)=\frac{\sigma_0}{E}(1-e^{\frac{E}{\eta}t})$$



Source: Vesentini, Simone, et al. "Nanomechanics of Collagen Microfibrils." *Muscles, Ligaments and Tendons Journal* 3, no. 1 (2013): 23.

We use the KV model to fit the extension-time curves since this model is the most basic viscoelastic mechanical model available and it provides an excellent fit to the measured mechanical response. It is of great interest to discuss whether the two elements of the KV model, i.e. the purely elastic spring and the purely viscous dashpot, have an actual physical meaning. A likely explanation would be that the elastic spring corresponds to the protein backbone, while the damping effect could be attributed to the interchain H-bonds. The backbone deformation include dihedral, angle and bond deformation, which are terms expressed by harmonic (or similar) functions in the molecular dynamics force field, and thus result in an elastic response to stretching. On the other hand, the viscous behavior may be due to the breaking and reforming of H-bonds, in particular H-bonds between the three collagen chains.

"In silico" creep test of a segment of a collagen molecule

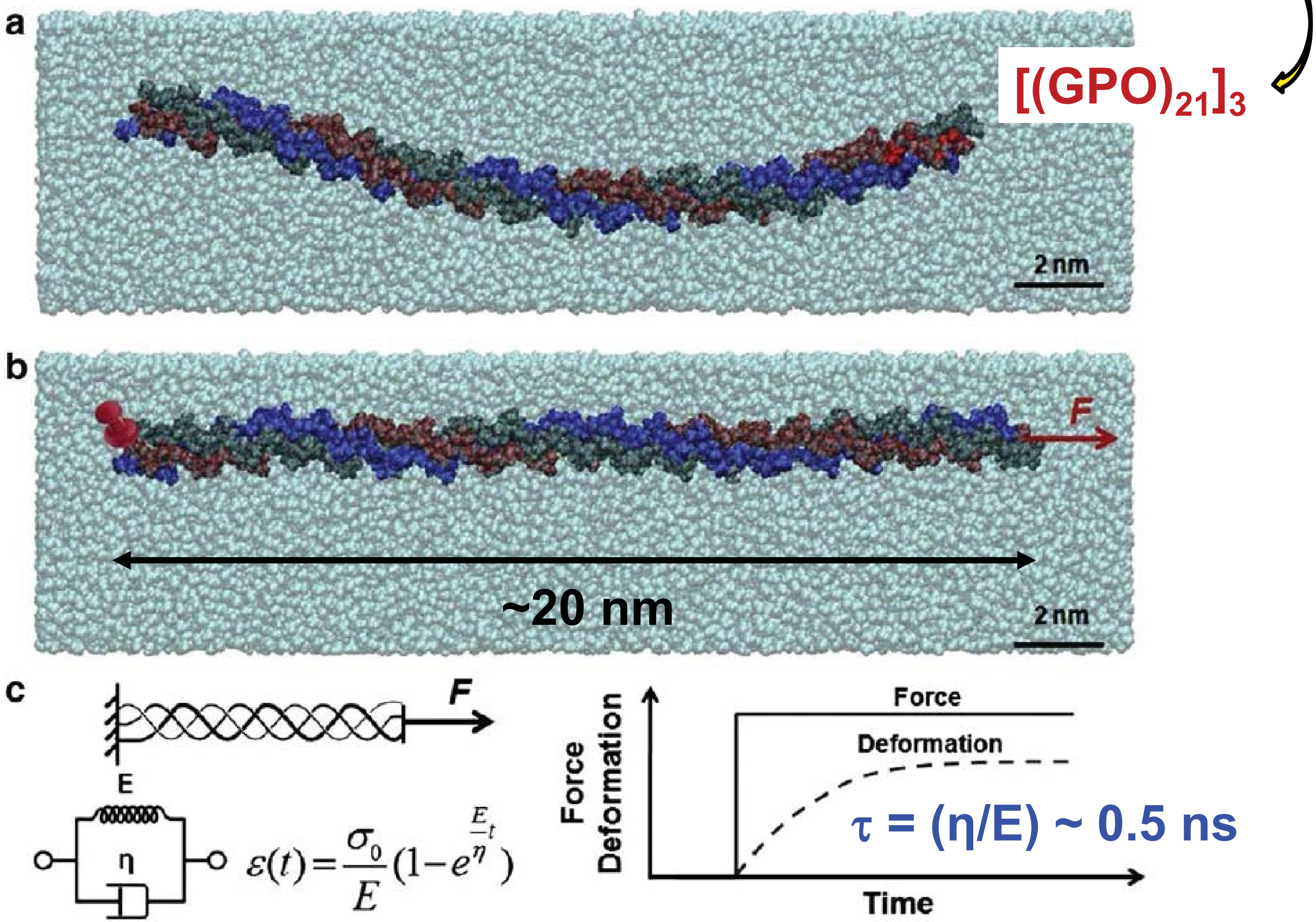


Fig. 1. Snapshots of the collagen peptide in water box. Panel a shows the conformation of the full atomistic model of a $[(GPO)_{21}]_3$ collagen peptide solvated in water box and equilibrated for 30 ns. After equilibration the molecule is subjected to virtual creep tests: one end of the collagen peptide is held fixed, whereas the other end is pulled with constant force (from 300 pN to 3000 pN) until end-to-end distance reaches equilibrium (Panel b). Panel c shows a schematic of the creep test; a constant force is applied instantaneously to the molecule and its response (deformation over time) is monitored. The mechanical response of collagen molecule is modeled using a KV model, from which molecular Young's modulus (E) and viscosity (η) are calculated.

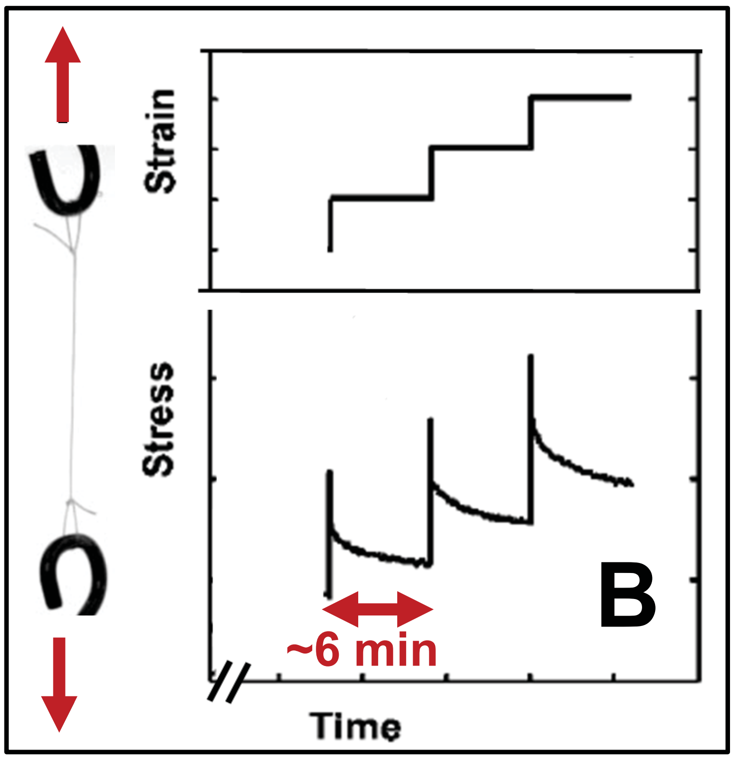
Source: Gautieri, Alfonso et al. "Viscoelastic Properties of Model Segments of Collagen Molecules." *Matrix Biology* 31, no. 2 (2012): 141-9.

Influence of Decorin and Biglycan on Mechanical Properties of Multiple Tendons in Knockout Mice

"Stress Relaxation"

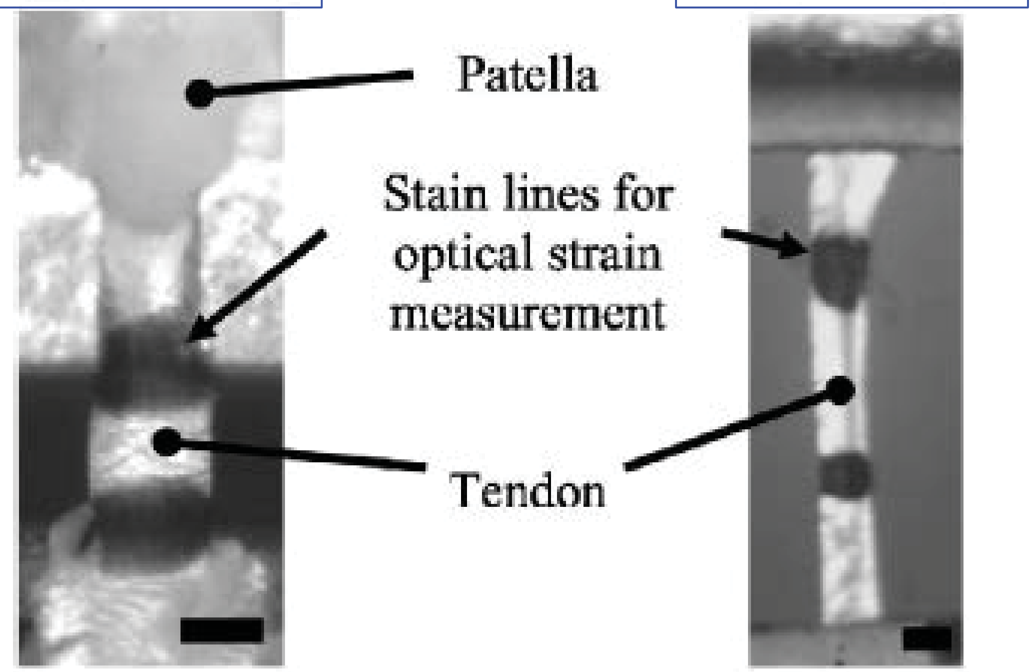
Apply constant strain (ε_{11}) and measure stress vs time

Mouse tendon fascicle



decorin k/o
Modulus

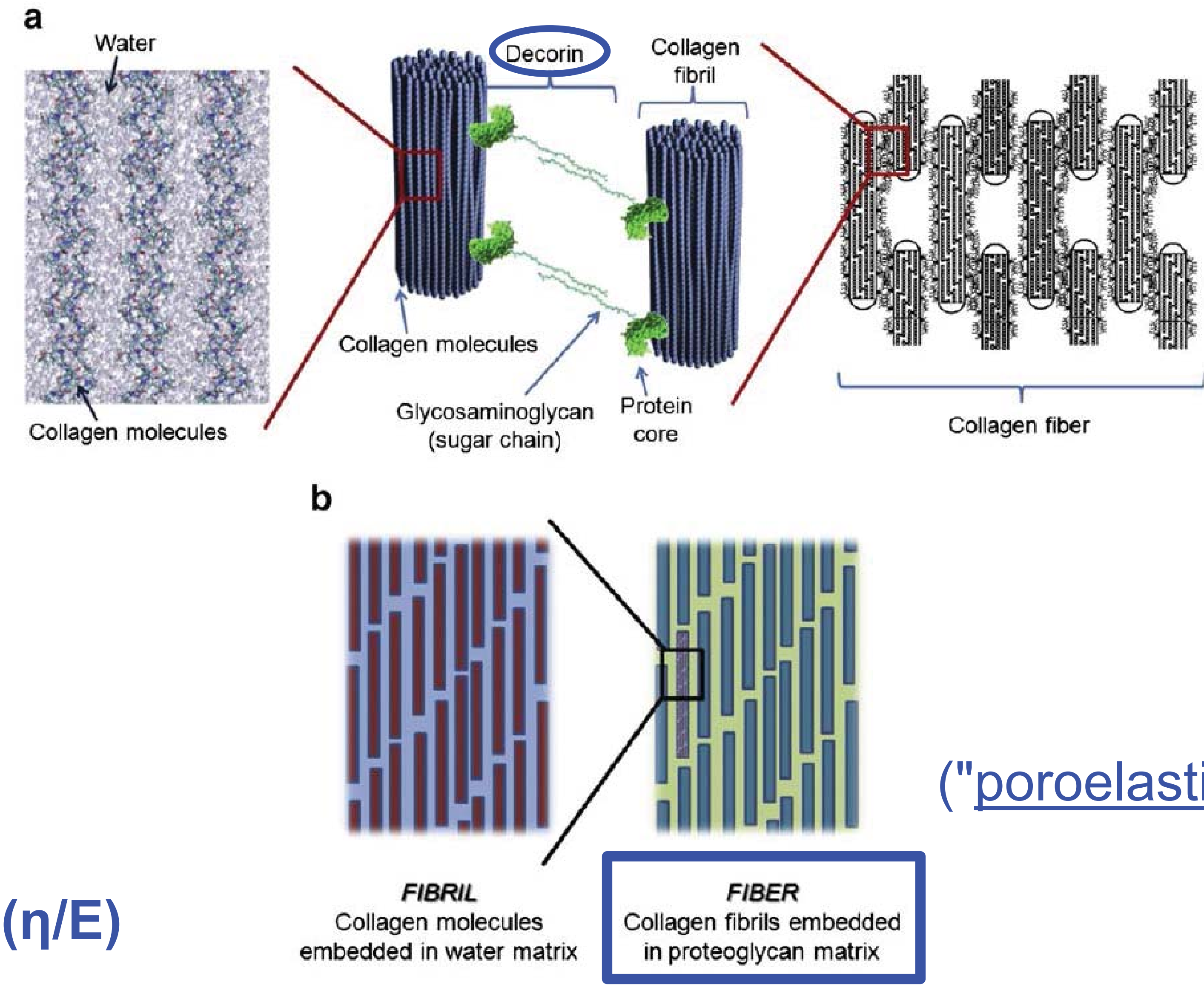
Biglycan k/o
Modulus ↑



Patellar (left) and flexor digitorum longus (right)

Source: Robinson, Paul S., et al. "Influence of Decorin and Biglycan on Mechanical Properties of Multiple Tendons in Knockout Mice." *Journal of Biomechanical Engineering* 127, no. 1 (2005): 181-5.

Robinson+, J Biomech Eng, 2005



("poroelasticity")

$\tau = (\eta / E)$

- ......the viscous behavior of fibrils and fibers involves additional mechanisms, such as molecular sliding between collagen molecules within the fibril or effects of relaxation of larger **volumes of solvent**

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20.310J / 3.053J / 6.024J / 2.797J Molecular, Cellular, and Tissue Biomechanics
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