IUSS
Sapere Aude
Istituto Universitario
di Studi Superiori
Pavia

MINI-COURSE

Mechanical modeling of soft biological tissues

LESSON 2

Multiscale modeling of aorta mechanics and damage mechanisms

Michele Marino

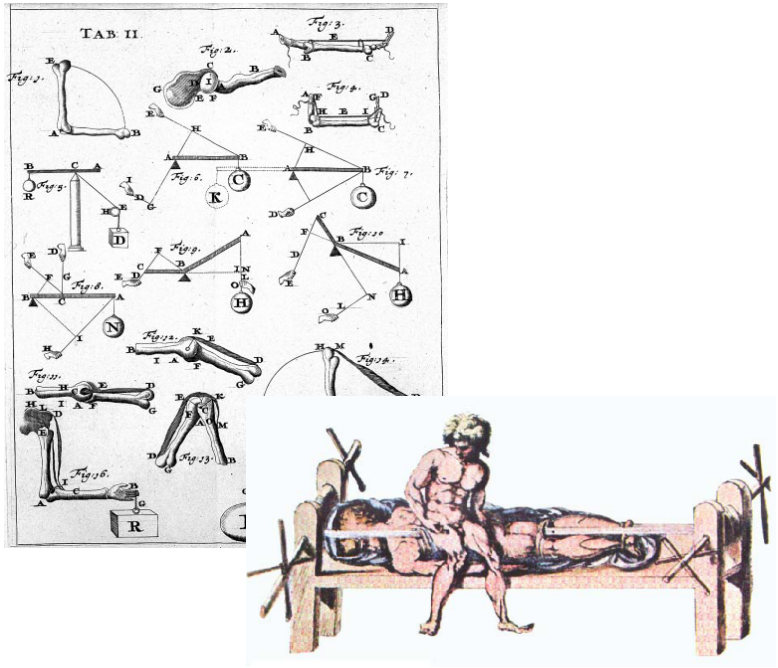
DICAr, Pavia, Italy
December 12th, 2013

Dicii
University of Rome "Tor Vergata"

Biomechanics?

"Biomechanics is the study of the structure and function of biological systems by means of the methods of mechanics"

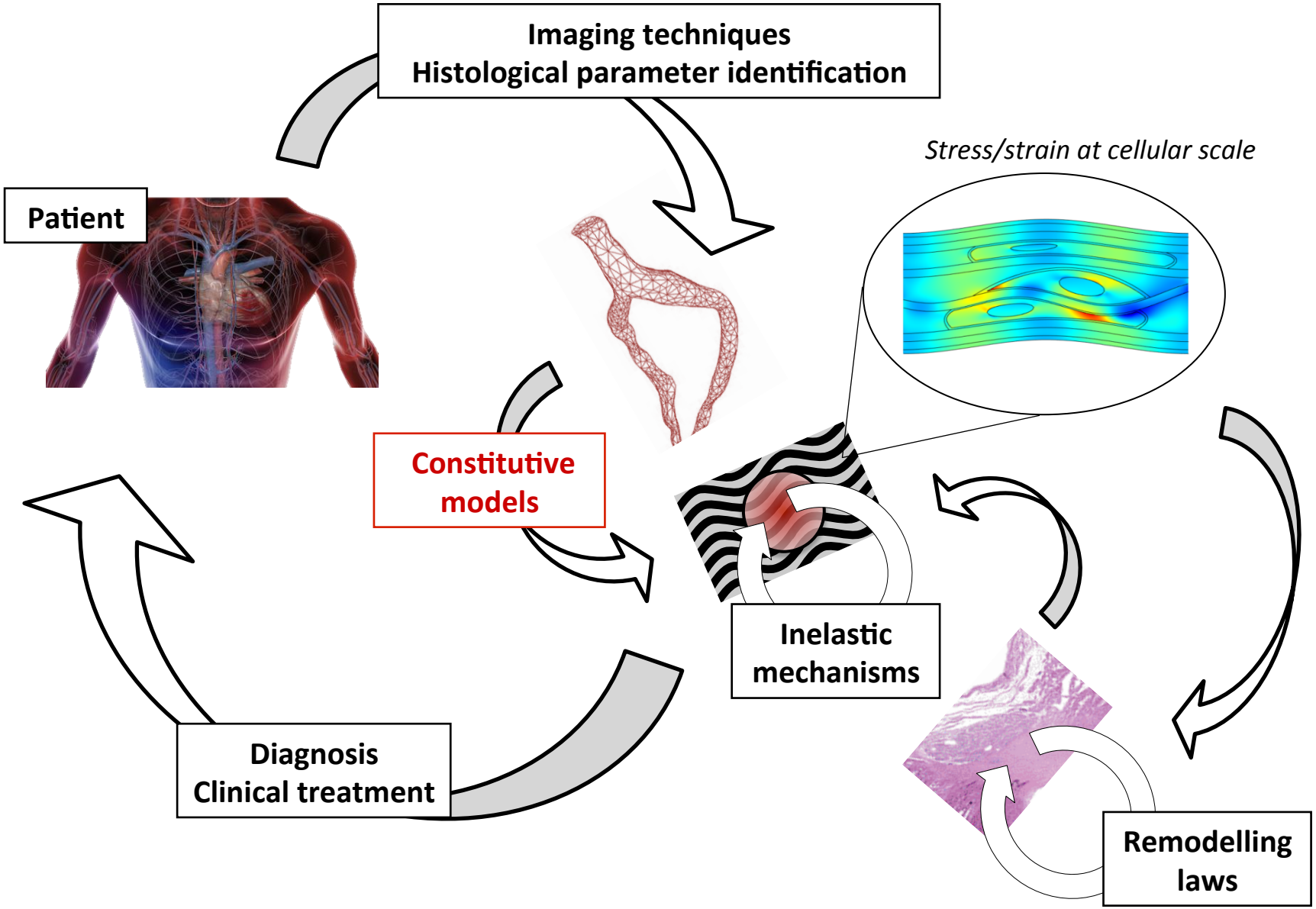
Herbert Hatze, University of Vienna, 1974



Models to predict the mechanics:

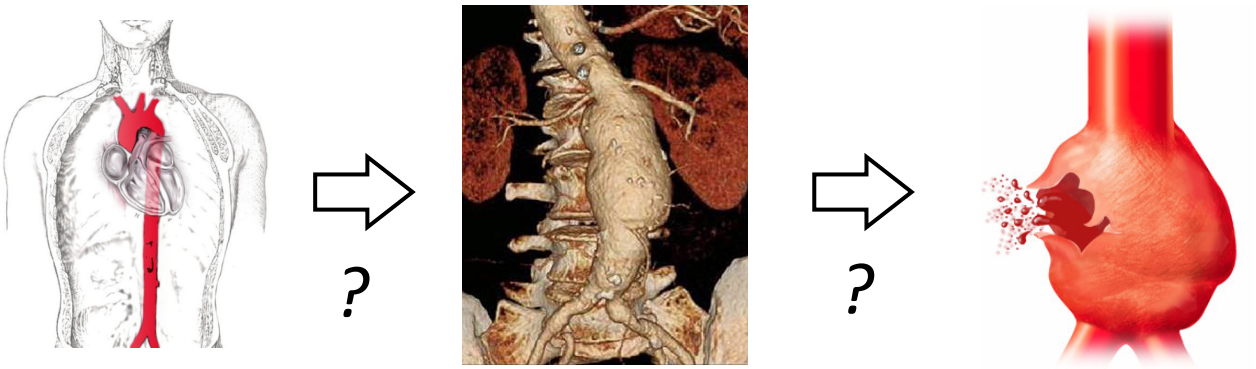
of biological structures

in biological structures


Imaging techniques
Histological parameter identification
Patient
Stress/strain at cellular scale
Constitutive models
Inelastic mechanisms
Remodelling laws
Diagnosis
Clinical treatment

Computer-Aided Diagnosis

The example of aneurysmal care



From ***Biomechanics and Pathobiology of Aortic Aneurysms***
by J.A. Phillippi, S. Pasta and D.A. Vorp

The **puzzle**:
"Our understanding of aortic diseases continues to advance as new partnerships between surgeons, biologists, engineers and mathematicians […]."

Computer-Aided Diagnosis

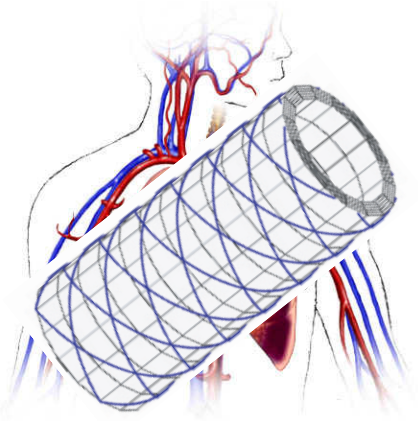
The example of aneurysmal care

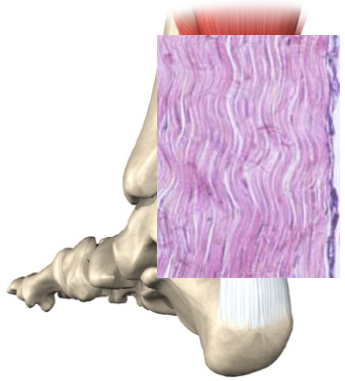
The **missing pieces**:

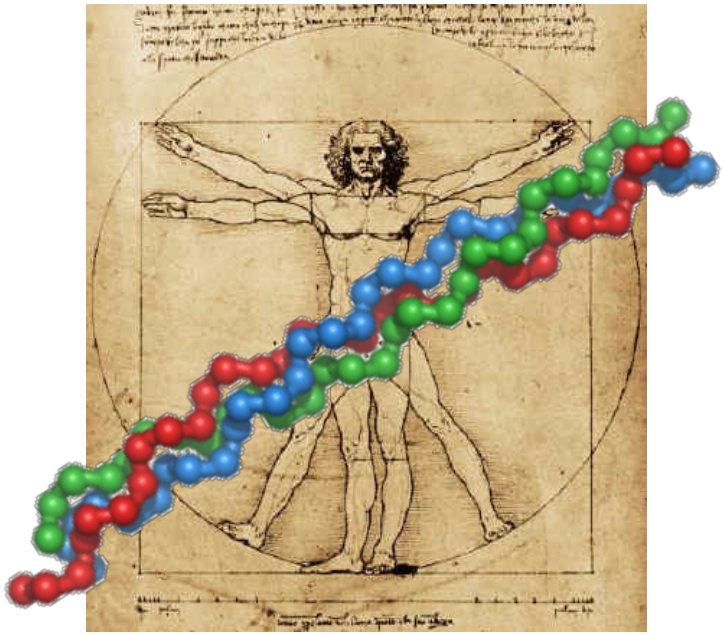
"[…] developing the enabling non-invasive technologies to measure wall stress and strain, refinement of the mathematical models and establishing links between the clinical manifestations and the biological mechanisms inciting them."

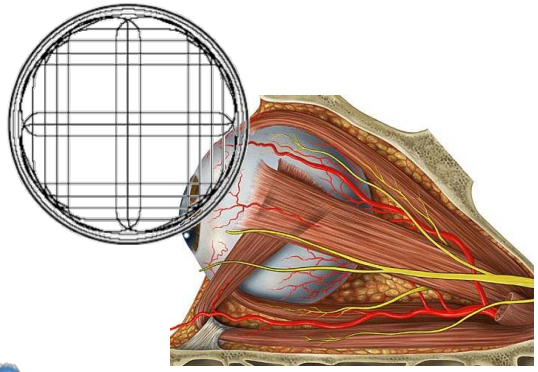
For an effective **patient-specific** simulation:

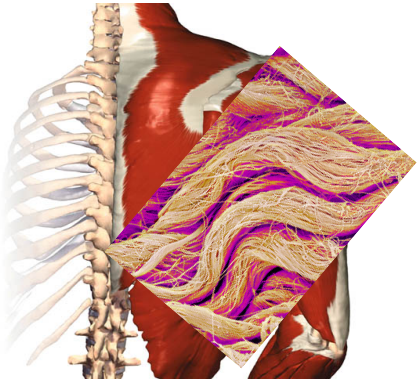
Constitutive modeling of biological tissues explicitly depending on actual histology, biological features and biochemical environment



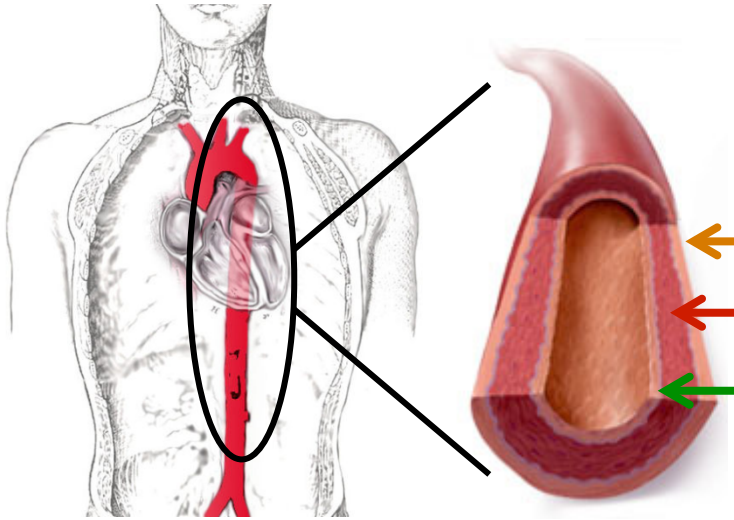








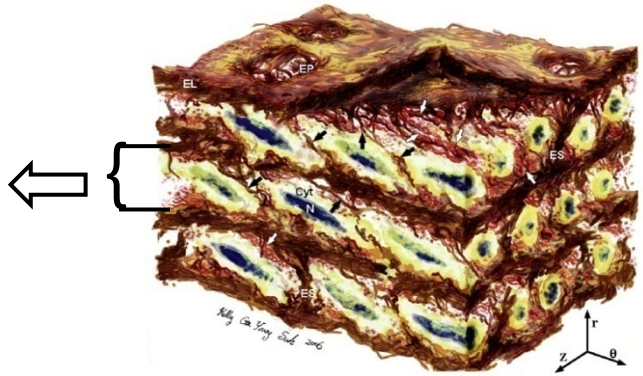
AORTA:



ADVENTITIA
MEDIA
INTIMA

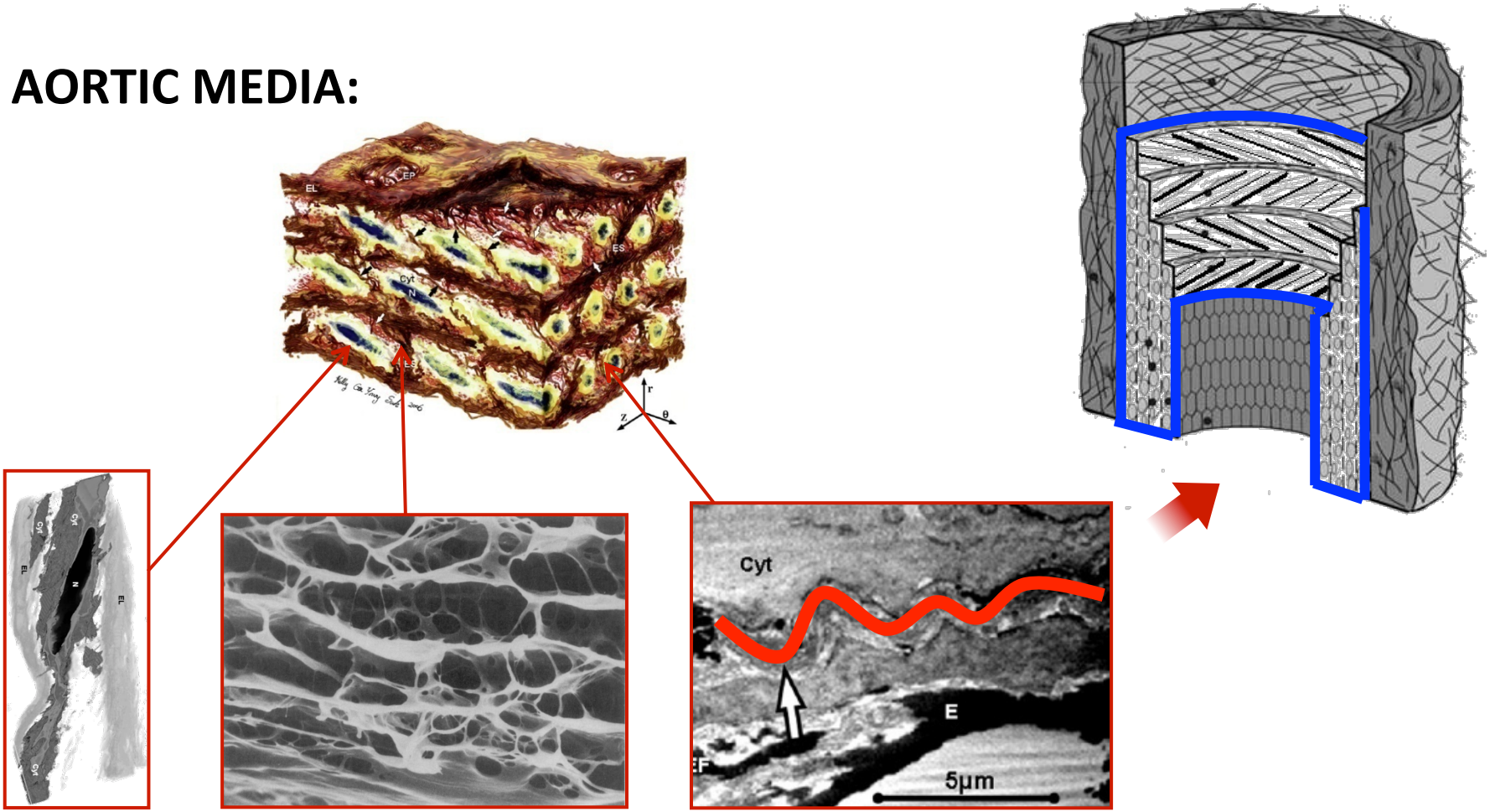
Medial Lamellar Unit
MLU

ELASTIN
CELLS
ELASTIN
COLLAGEN



M.K. O'Connell et al., The Three-dimensional Micro- and Nanostructure of the Aortic Medial Lamellar Unit Measured Using 3D Confocal and Electron Microscopy Imaging. *Matrix Biol.* 27, 2008

AORTIC MEDIA:



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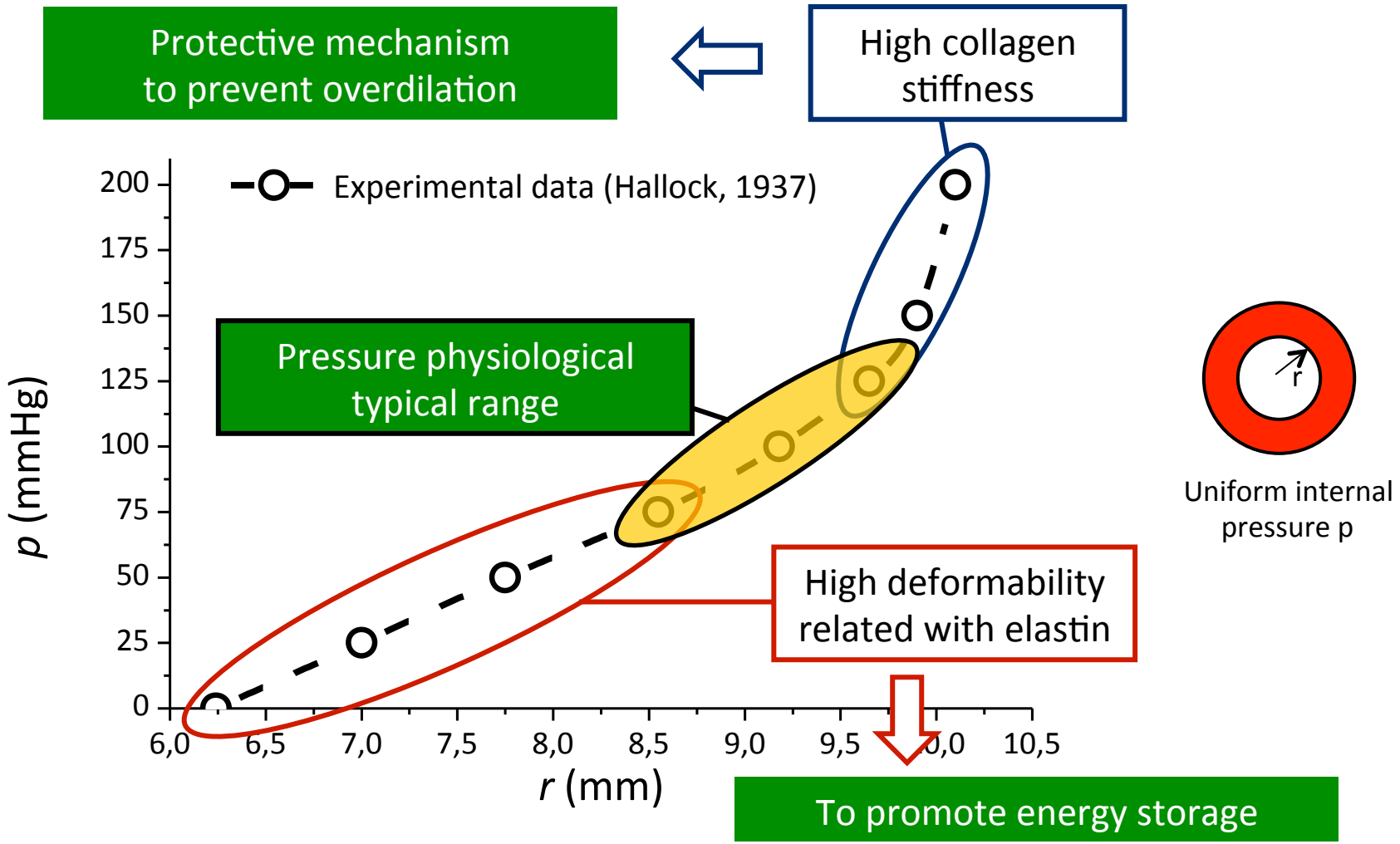
Protective mechanism
to prevent overdilation
High collagen
stiffness
Experimental data (Hallock, 1937)
Pressure physiological
typical range
High deformability
related with elastin
To promote energy storage
p (mmHg)
r (mm)
200
175
150
125
100
75
50
25
0
6,0
6,5
7,0
7,5
8,0
8,5
9,0
9,5
10,5
r
Uniform internal
pressure p

		EVIDENCE	REFERENCE
NANO	Elastin stiffness	↗	Bruel, 1997
	Cross-link density	↗	Bailey, 2001
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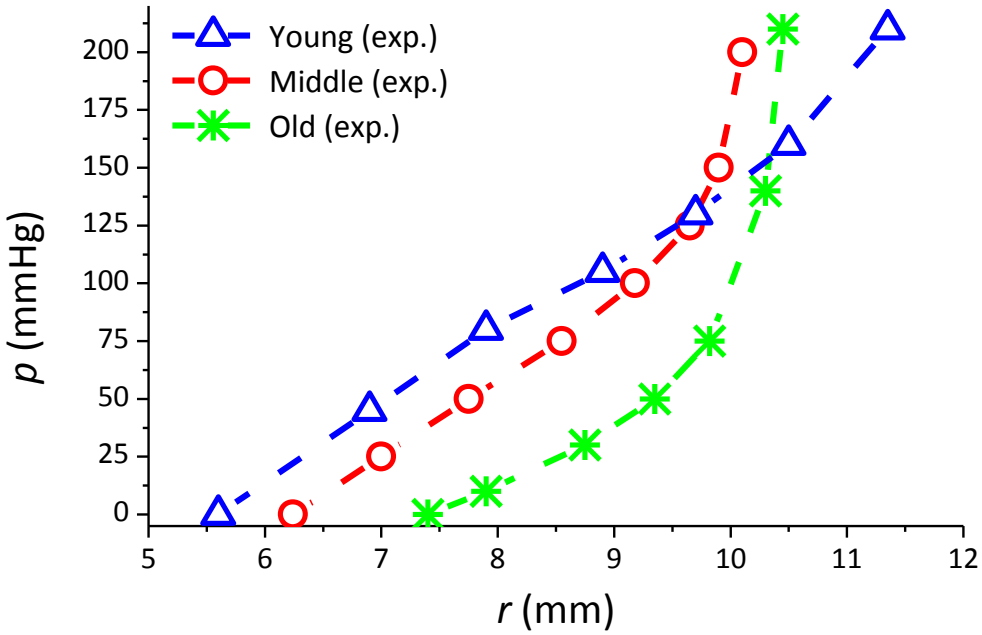
MACRO	Diameter at p=0	↗	Astrand, 2008
	Media thickness	↗	Astrand, 2008

Age-dependent histological alterations

… corresponding to relevant alterations in arterial mechanics

Correlation also between aortic dilation, aneurysm, rupture risk, etc. etc. and histo-chemical alterations
(Bruel et al., 1998; Carmo et al., 2002; Lindeman et al. 2010)



STATE OF THE ART

Two main approaches:

1) Phenomenological laws (Fung, 1973; Yin and Elliott, 2004)

2) Structural models: incorporate structure-based parameters

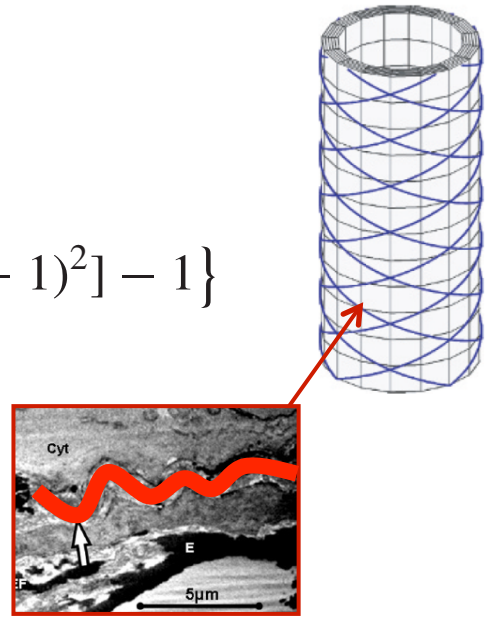
(Comninou and Yannas, 1976; Lanir, 1979; Freed and Doehring, 2005; Holzapfel et al., 2000, 2002)

$$\overline{\Psi}(\bar{I}_1, \bar{I}_4, \bar{I}_6) = \overline{\Psi}_{\mathrm{g}}(\bar{I}_1) + \overline{\Psi}_{\mathrm{f}}(\bar{I}_4, \bar{I}_6)$$

$$\Psi_{\mathrm{g}}(\bar{I}_1) = \frac{c}{2}(\bar{I}_1 - 3) \qquad \overline{\Psi}_{\mathrm{f}}(\bar{I}_4, \bar{I}_6) = \frac{k_1}{2k_2} \sum_{i=4,6} \{\exp[k_2(\bar{I}_i - 1)^2] - 1\}$$

$$\bar{I}_4 = \mathbf{C} : \mathbf{A}_1 \qquad \bar{I}_6 = \mathbf{C} : \mathbf{A}_2$$

$$\mathbf{A}_1 = \mathbf{M} \otimes \mathbf{M} \qquad \mathbf{A}_2 = \mathbf{M}' \otimes \mathbf{M}'$$



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(Comninou and Yannas, 1976; Lanir, 1979; Freed and Doehring, 2005; Holzapfel et al., 2000, 2002)

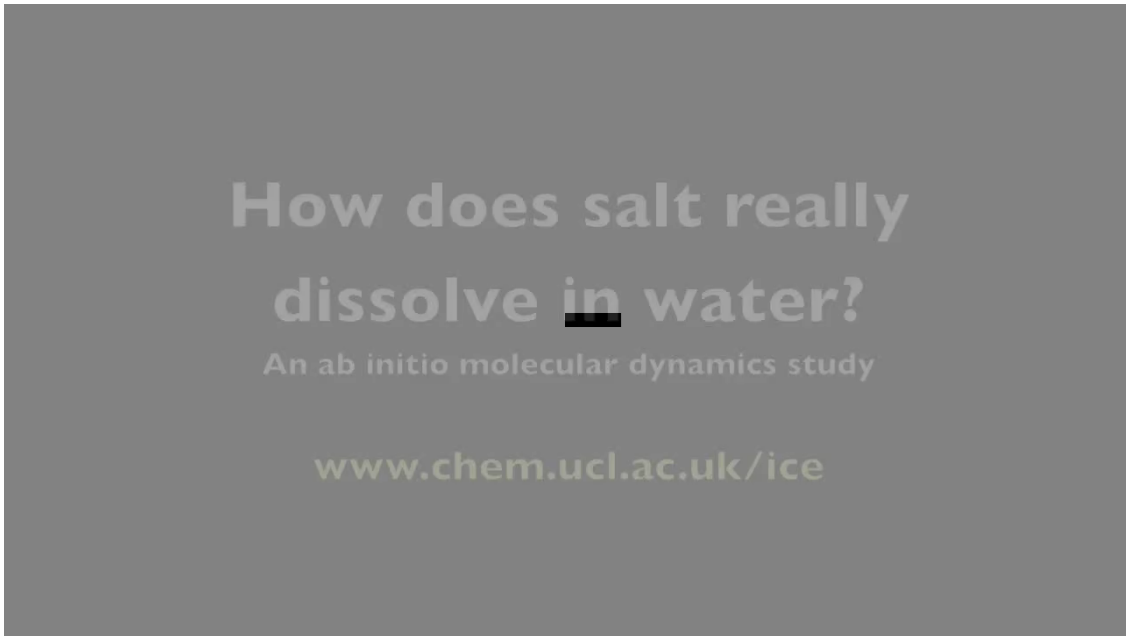
The **microscale** is the lowest scale explicitly modeled only in terms of collagen orientation

$$\overline{\Psi}_{\mathrm{f}}(\bar{I}_4, \bar{I}_6) = \frac{k_1}{2k_2} \sum_{i=4,6} \left\{ \exp[k_2(\bar{I}_i - 1)^2] - 1 \right\}$$

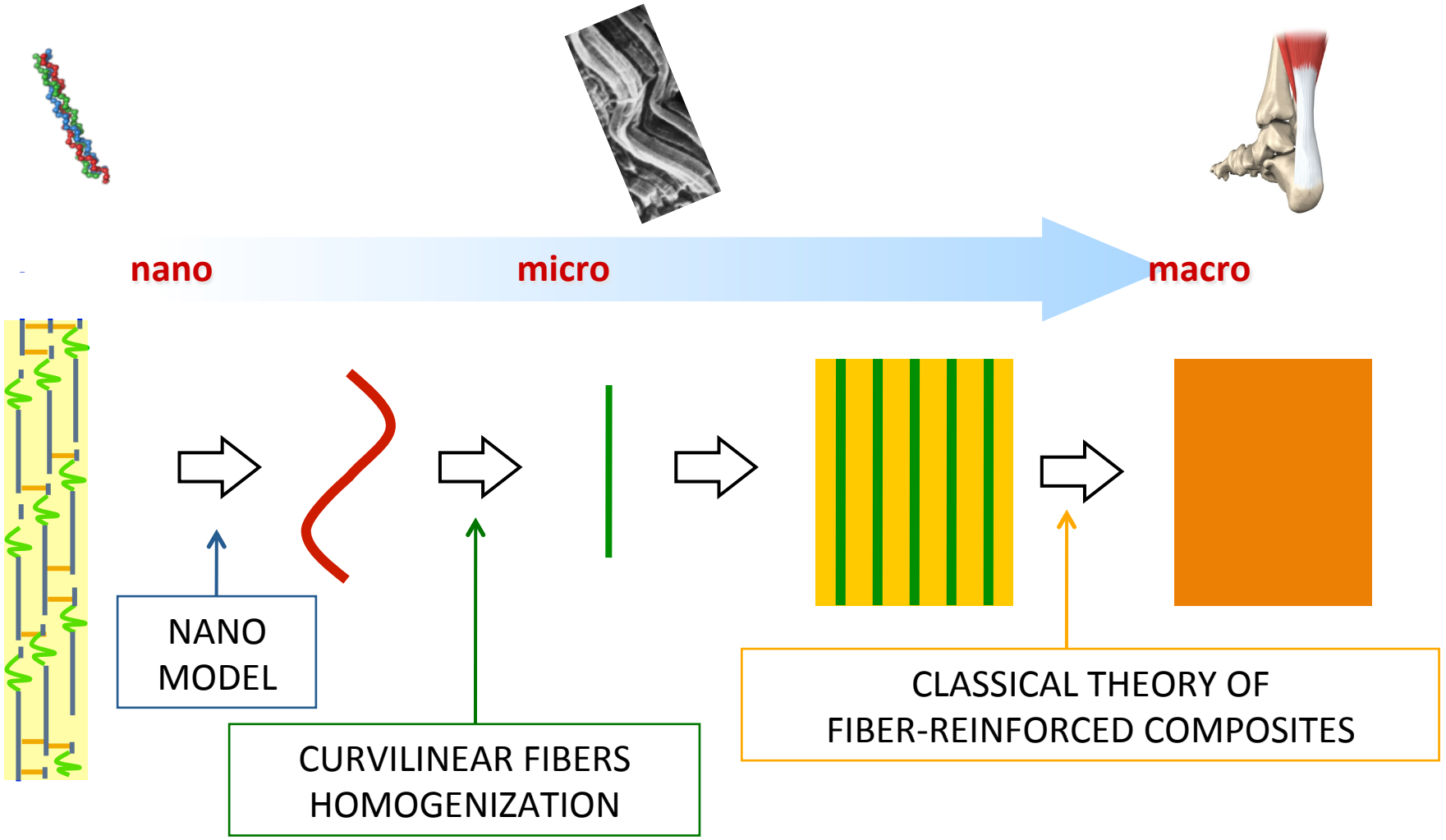
- To date, nanomechanics is predicted by molecular dynamical simulations (MDS)
(Buehler, 2008; Deriu et al., 2010)

Computational efforts of MDS make them completely useless at the **macroscale**

STATE OF THE ART



TENDON STRUCTURAL MULTISCALE MODEL

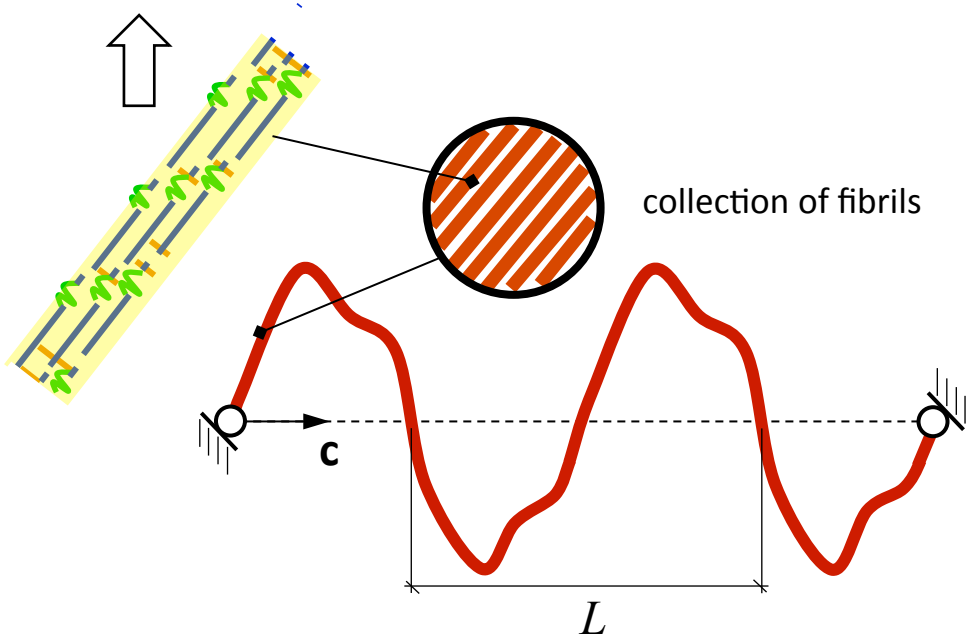


MULTISCALE APPROACH

$$E_f(\varepsilon_f) = \mu \left[\frac{1}{E_m(\varepsilon_m)} + \frac{A_m}{\lambda k_{cl} \ell_{m,o}} \right]^{-1}$$

Compatibility solved by the differential problem

$$\dot{\varepsilon}_m = \frac{E_f(\varepsilon_f)}{\mu E_m(\varepsilon_m)} \dot{\varepsilon}_f$$



MATERIAL NON-LINEARITIES

GEOMETRIC NON-LINEARITIES

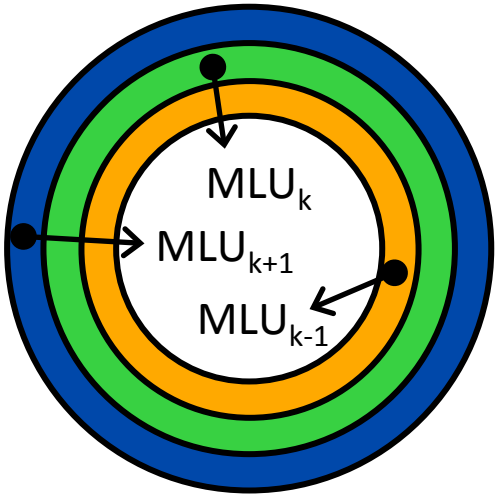
$$E_{eq}(\varepsilon_F) = E_\ell I_F \langle \cos\alpha \rangle \left[I_F \langle \cos^2\alpha \rangle + A_F \langle f(x, \varepsilon_F)^2 \rangle \right]^{-1}$$

with $E_\ell = E_f(\varepsilon_f)$

M. Marino, G. Vairo, "Multiscale Elastic Models of Collagen Bio-structures: From Cross-Linked Molecules to Soft Tissues", In: *Multiscale Computer Modeling in Biomechanics and Biomedical Engineering*, Springer 2013.

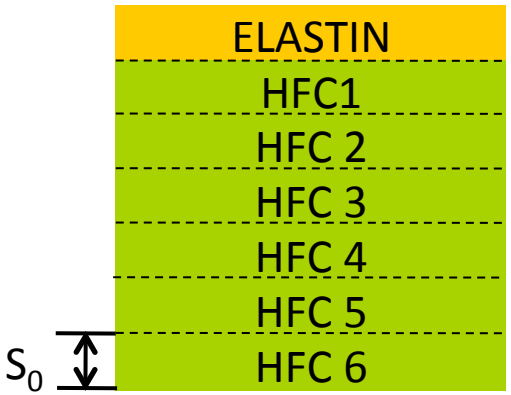
AORTIC MODEL: MULTISCALE STRUCTURAL APPROACH

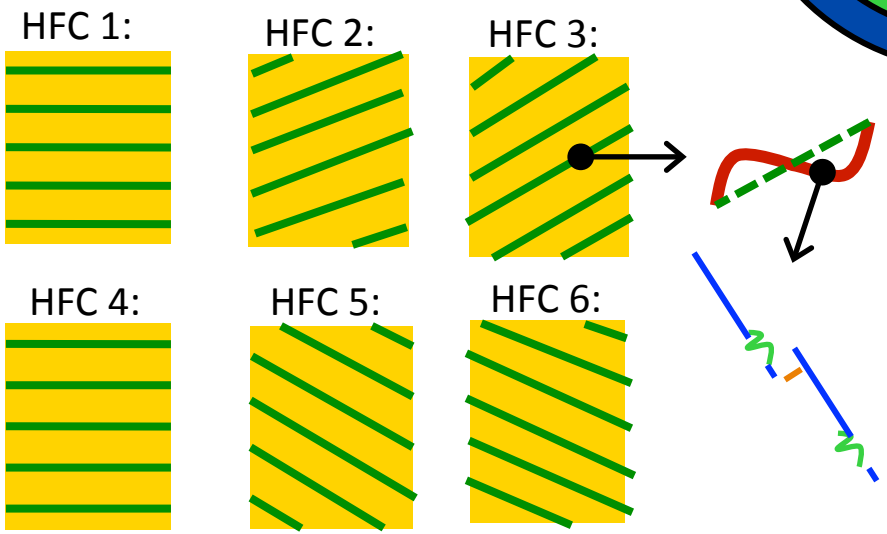
- Multi-layered thick cyinder
- Each layer is a MLU
- Each MLU is a laminate
- Nano-micro-macro homogenization



k = 1 … N

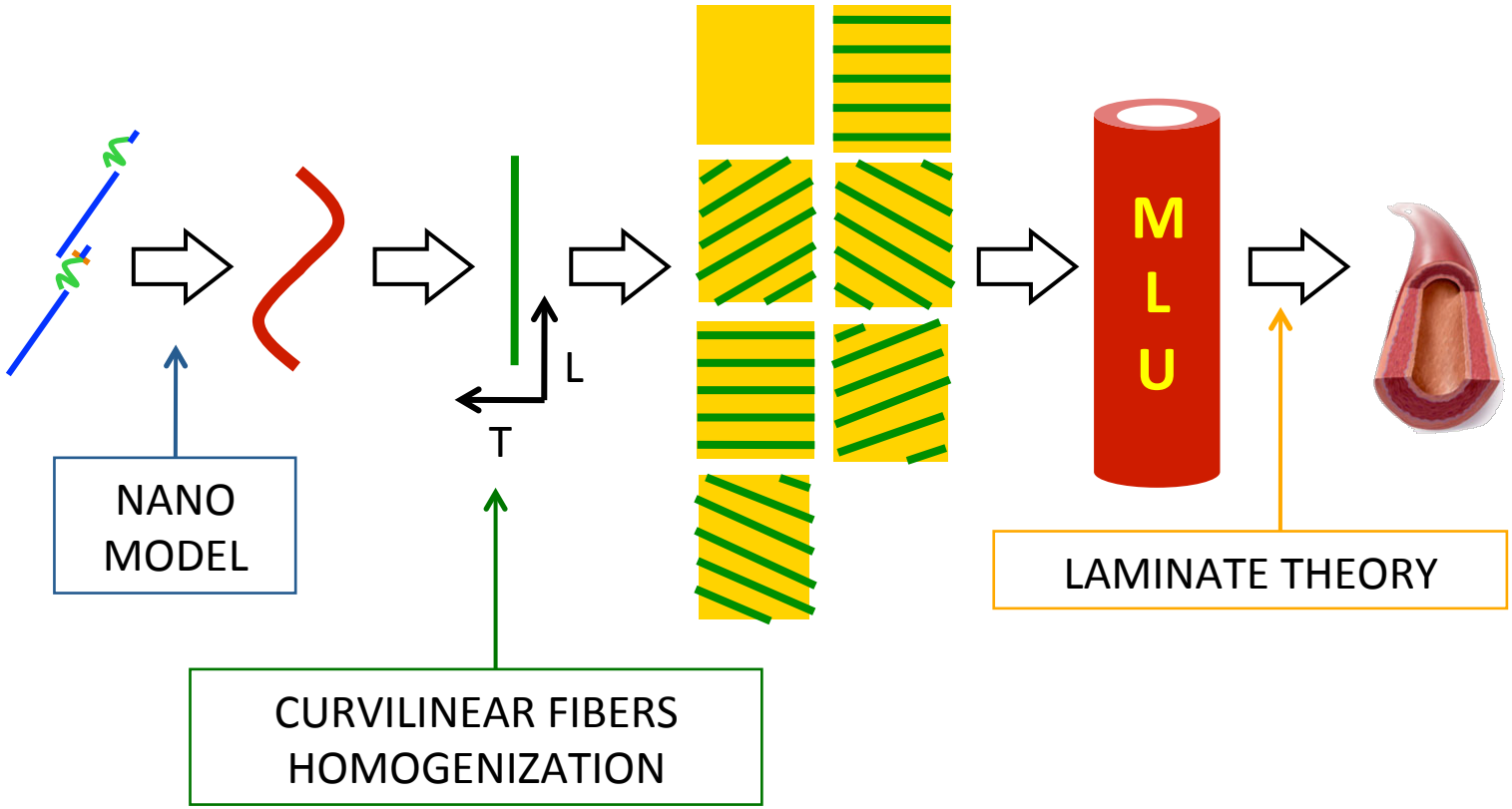
MLU_k:





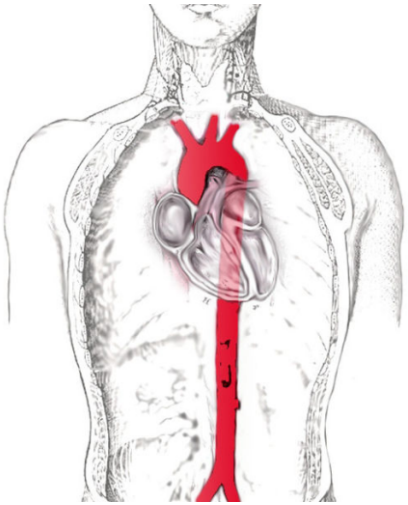
Helically-Arranged-Fiber-Reinforced-Composite-Materials: HFC

AORTIC MODEL: MULTISCALE STRUCTURAL APPROACH



AORTIC MODEL

Human aorta (media) – middle age
(Hallock, 1937)



Geometry:

	Value	Reference
S_0	1.42 µm	Ästrand, 2008
N	60	Wolinsky, 1967
$r_{p=0}$	6.2 mm	Ästrand, 2008

Boundary conditions:

Free estremities

Loading:

Uniform internal pressure

Material properties:

Multiscale model

Nanoscale parameters:

	Value	Reference
ℓ_c	285 nm	Sun, 2002
ℓ_p	14.5 nm	Sun, 2002
ℓ_{kinks}	22 nm	Graham, 2004
$\widehat{E}$	80 GPa	Buehler, 2008
λk_{cl}	10	-

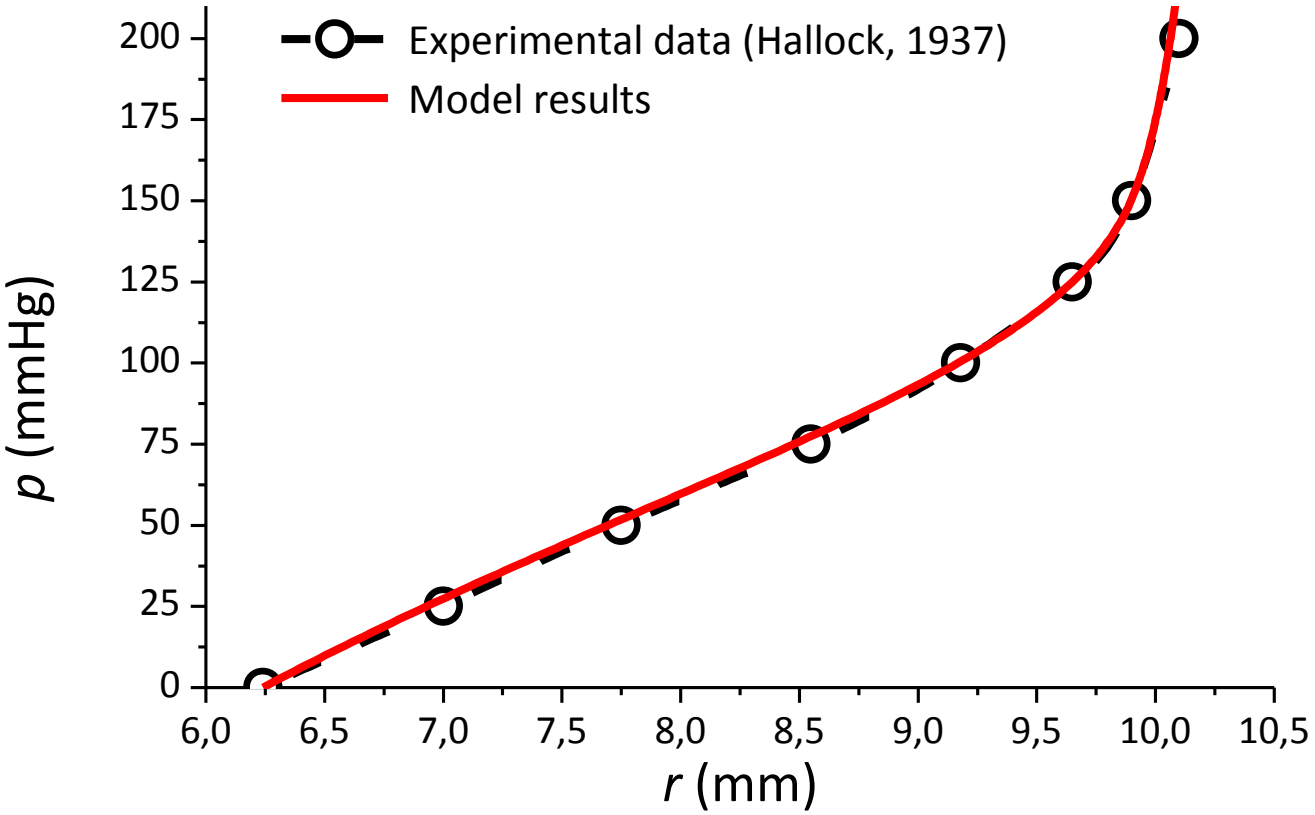
Microscale parameters:

	Value	Reference
L_0	3.4 µm	O'Connell, 2008
H_0 / L_0	0.3	O'Connell, 2008
r_F	100 nm	O'Connell, 2008

Macroscale parameters:

	Value	Reference
V_f	30%	Behmoaras, 2005
E_M	24 kPa	Ästrand, 2008
$F(\theta_f)$	-	O'Connell, 2008

AORTIC MODEL: RESULTS



F. Maceri, M. Marino, G. Vairo, "A unified multiscale mechanical model for soft collagenous tissues with regular fiber arrangement", *Journal of Biomechanics* 43, 2010.

AORTIC MODEL: APPLICATIONS

Age-related remodeling

		EVIDENCE	REFERENCE
NANO	Elastin stiffness	↗	Bruel, 1997
NANO	Cross-link density	↗	Bailey, 2001
MICRO	Elastin content	↘	Bruel, 1997
MICRO	Collagen content	↘	Bruel, 1997
MICRO	Fiber straightening	↗	Astrand, 2001
MACRO	Diameter at p=0	↗	Astrand, 2008
MACRO	Media thickness	↗	Astrand, 2008

Quantitative and qualitative indications from experimental data:

Age [yrs.]	λk_{cl} [pN/nm]	H_o/L_o [-]	L_o [µm]	V_F [%]	E_e [kPa]	Φ_e [-]	S_a [mm]	$r\|_{p=0}$ [mm]
20-23	5	0,4	2,6	40	60	0,0	0,6	5,6
36-42	10	0,3	3,4	30	80	-0,3	0,6	6,2
71-78	100	0,2	3,7	20	100	-0,6	0,7	7,4

AORTIC MODEL: APPLICATIONS

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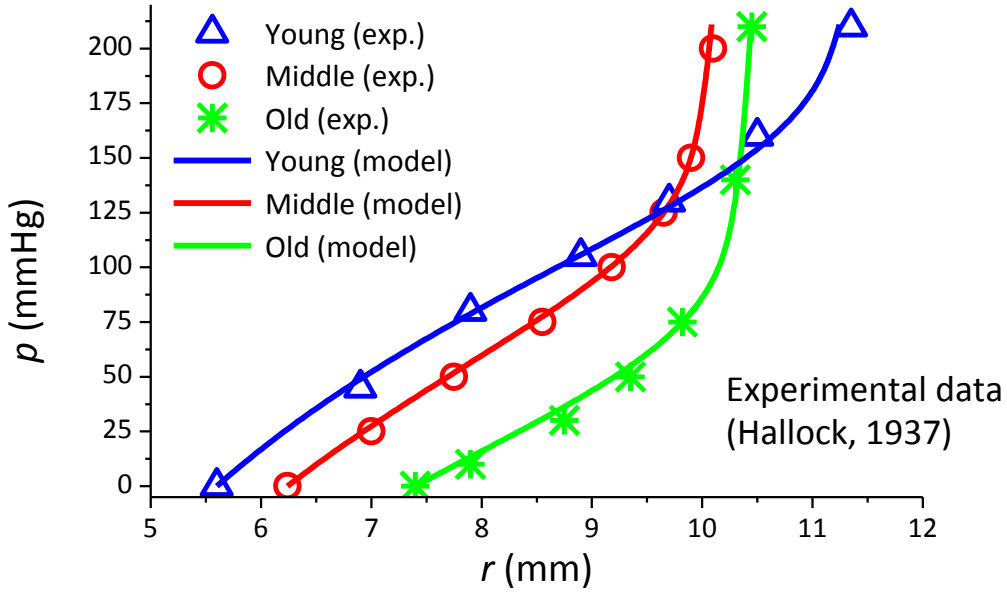
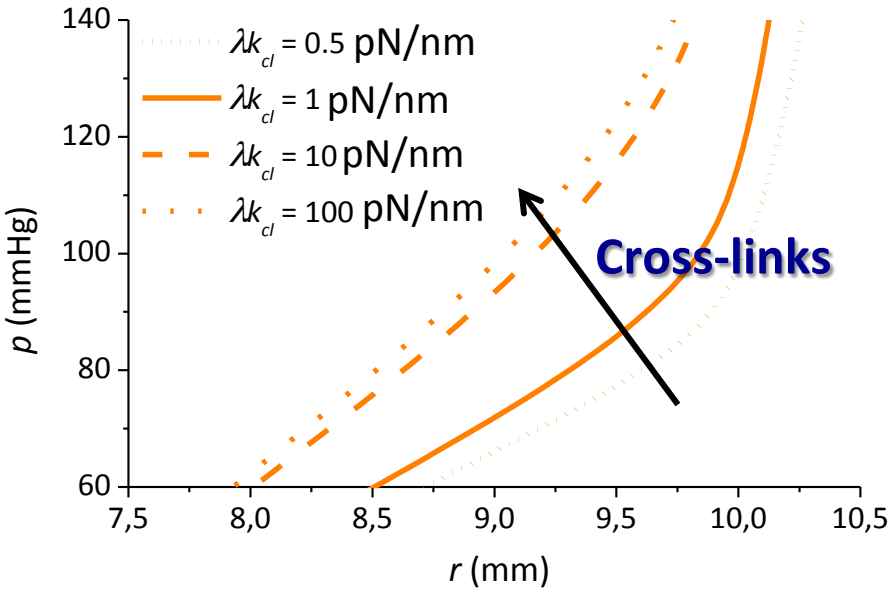


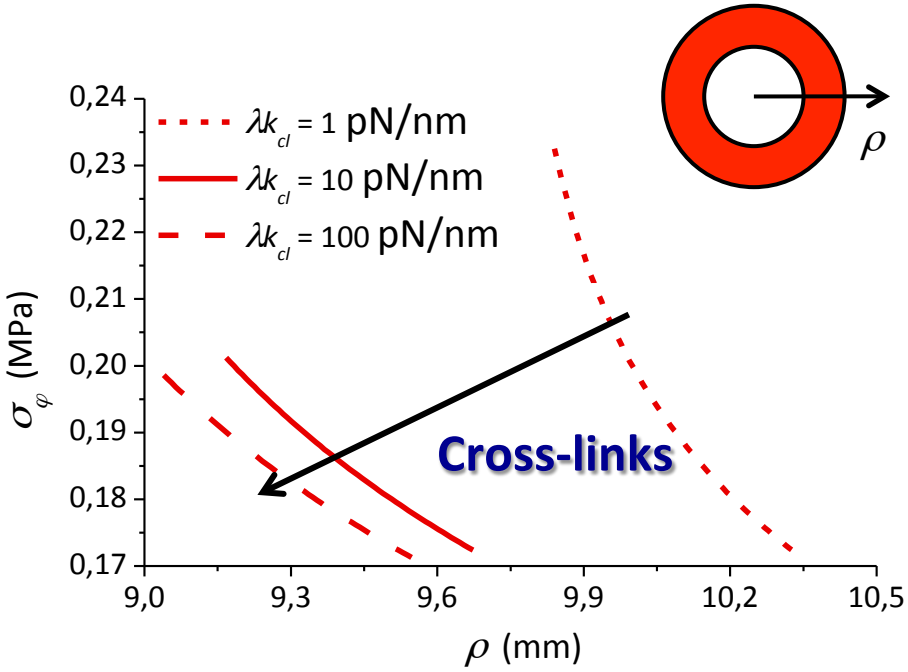
F. Maceri, M. Marino, G. Vairo, "Age-dependent arterial mechanics via a multiscale elastic approach", *International Journal for Computational Methods in Engineering Science and Mechanics* 14, 2013.

AORTIC MODEL: APPLICATIONS

Cross-links reduction

- Aortic dilation
- Rupture risk
(Bruel et al., 1998)





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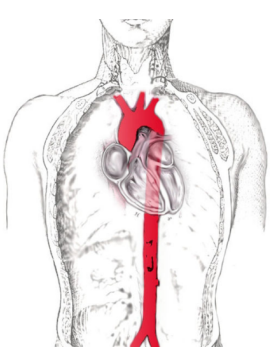
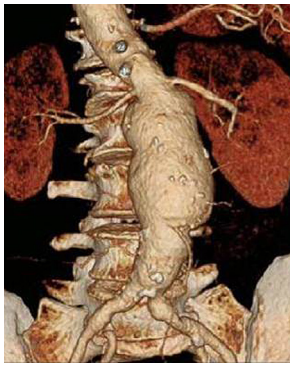
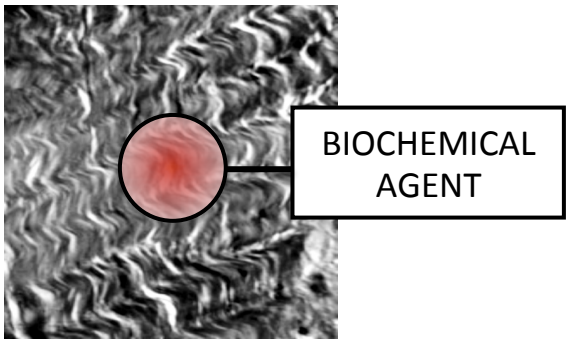
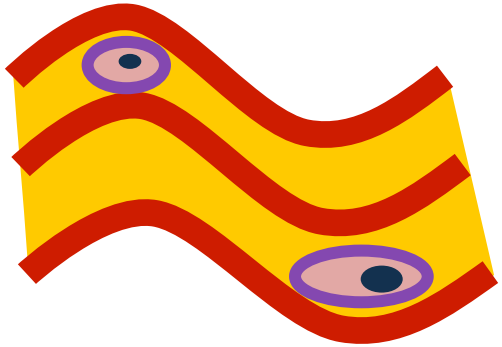


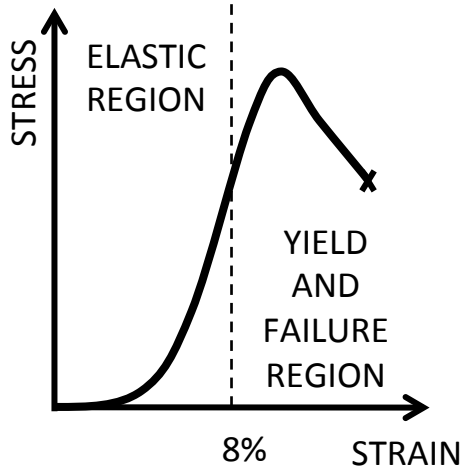
?



?

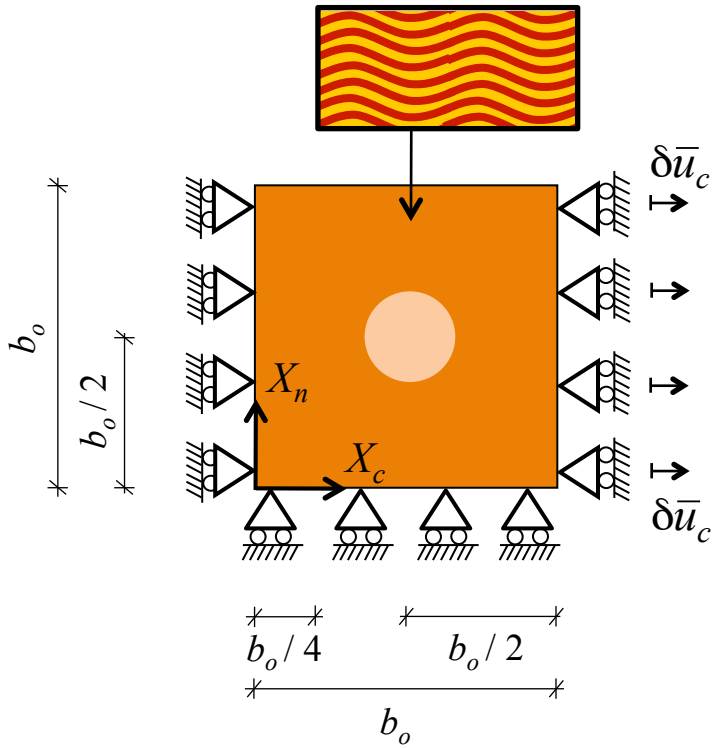

BIOCHEMICAL
AGENT



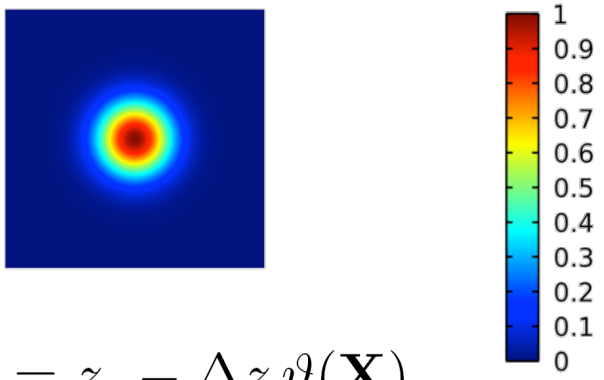

STRESS
ELASTIC
REGION
YIELD
AND
FAILURE
REGION
8%
STRAIN

TISSUE DEFECT

Cross-links density defect: $z = \lambda k_{cl}$



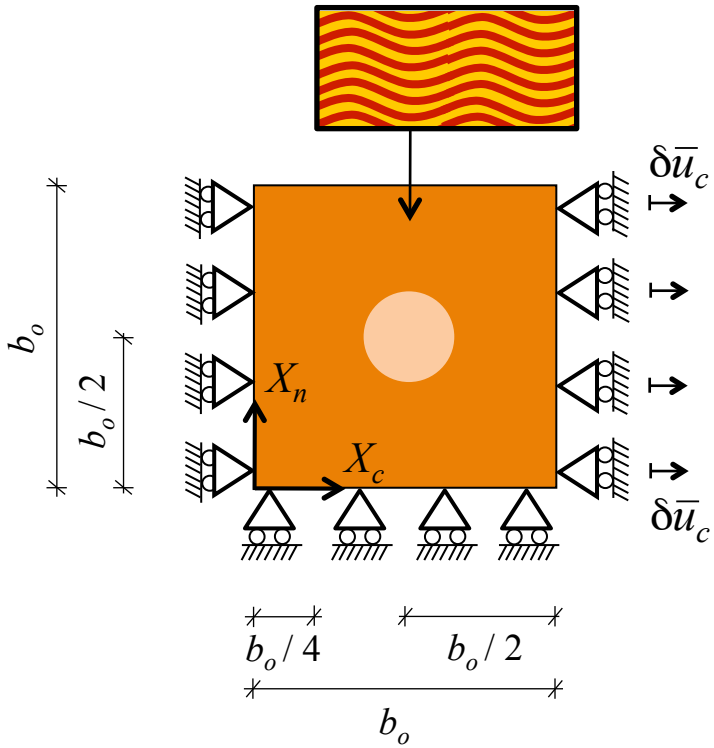
$\vartheta(\mathbf{X})$

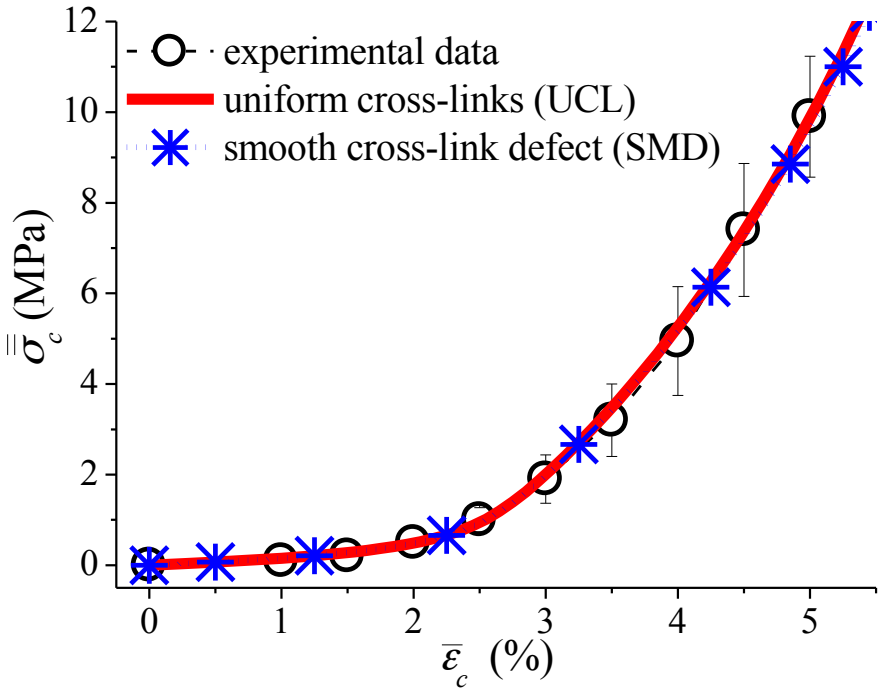


$$z(\mathbf{X}) = z_o - \Delta z\, \vartheta(\mathbf{X})$$

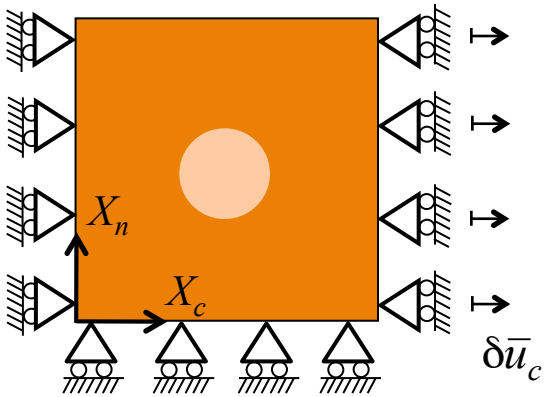
M. Marino, G. Vairo, "Stress and strain localization in stretched collagenous tissues via a multiscale modelling approach", *Computer Methods in Biomechanics and Biomedical Engineering*, published online since 2012.

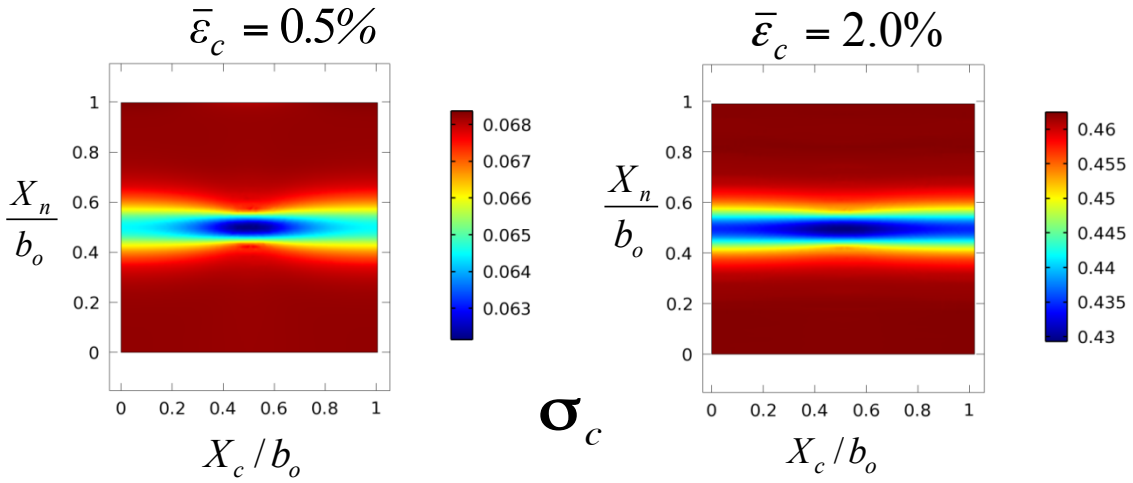
TISSUE DEFECT

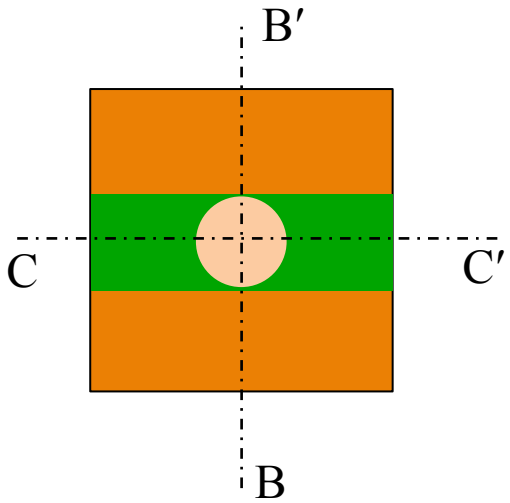


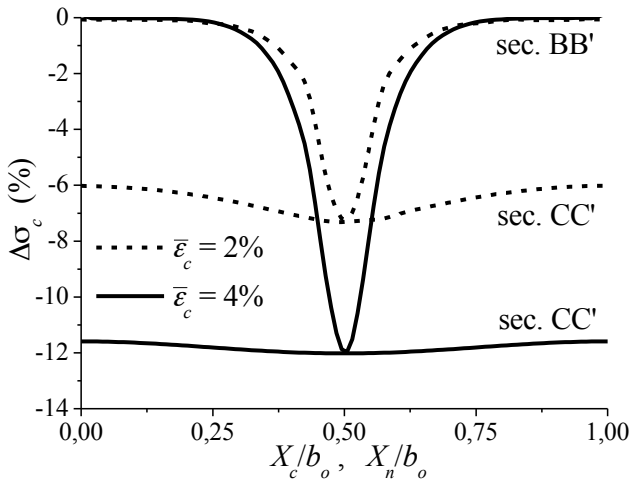


TISSUE DEFECT









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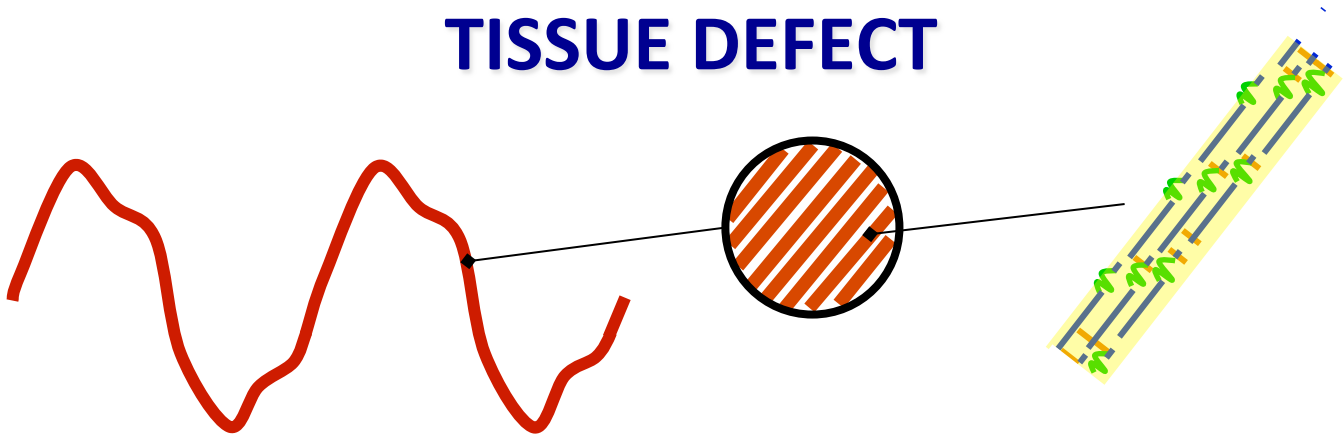
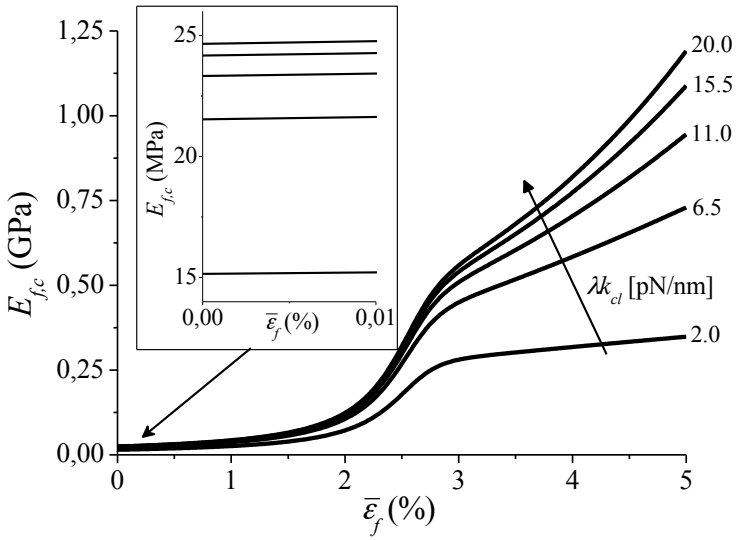
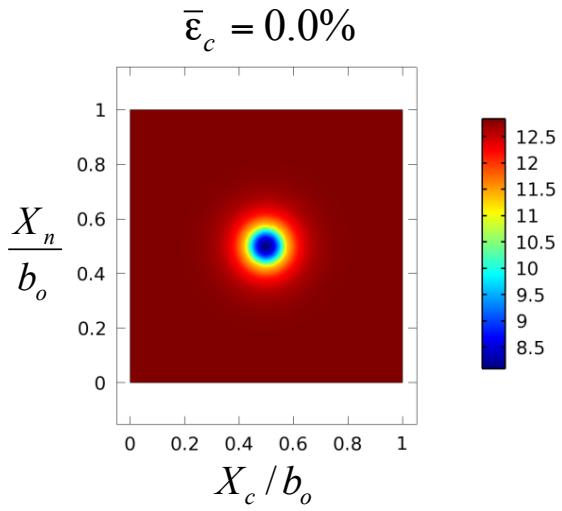


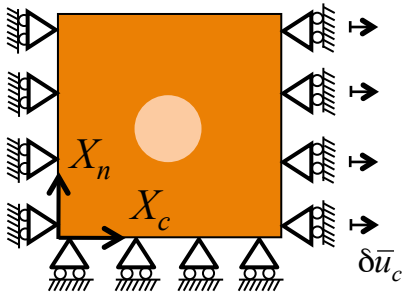


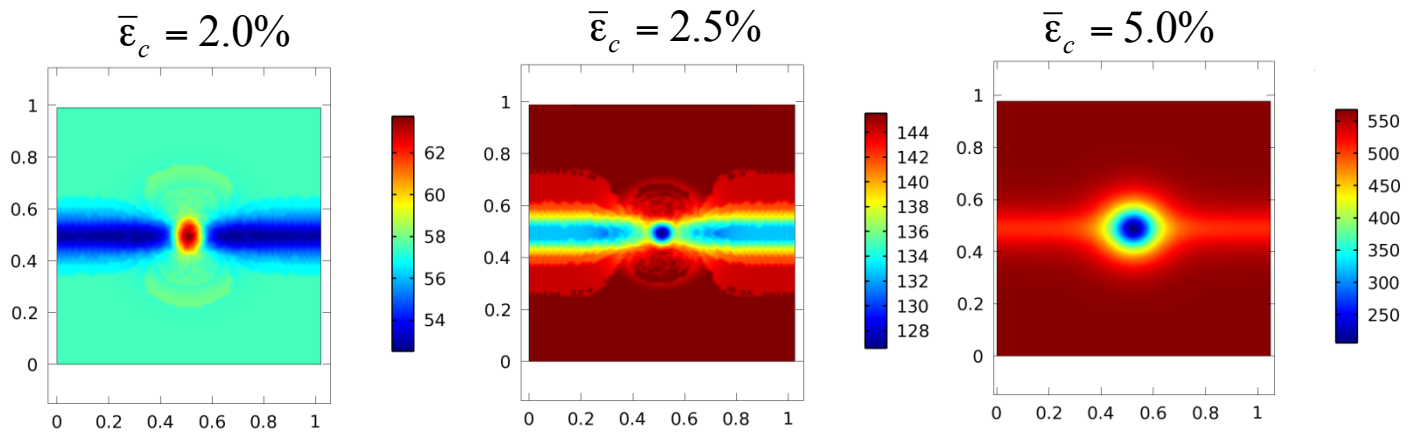
Fiber equivalent along-the-chord tangent modulus vs. the fiber along-the-chord nominal strain



Distribution of the macroscale tissue tangent stiffness C_{cccc} (MPa)

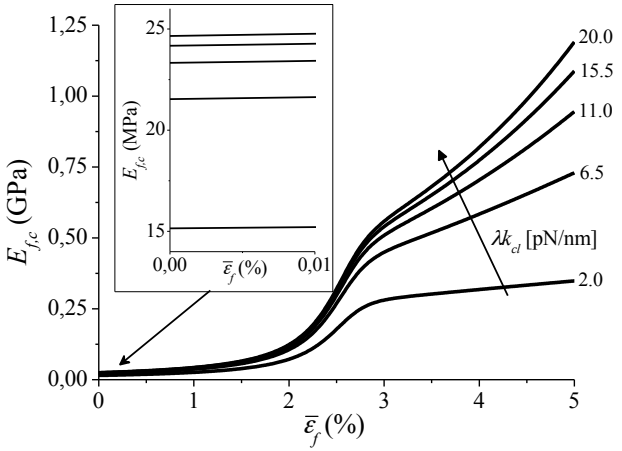
TISSUE DEFECT



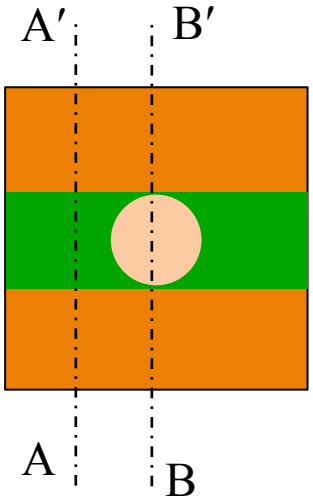


Distribution of the macroscale tissue tangent stiffness C_{cccc} (MPa)

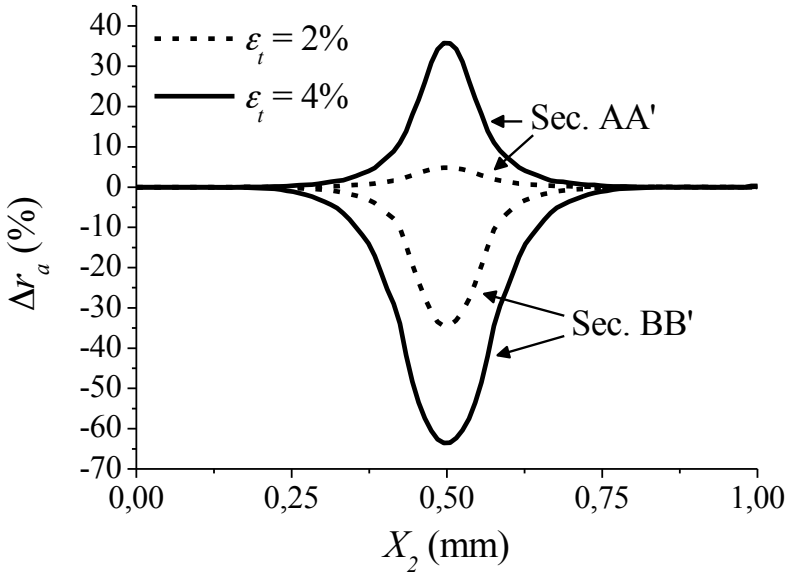
A nanoscale alteration (reduction in cross-links) seems to couple with some other mechanism

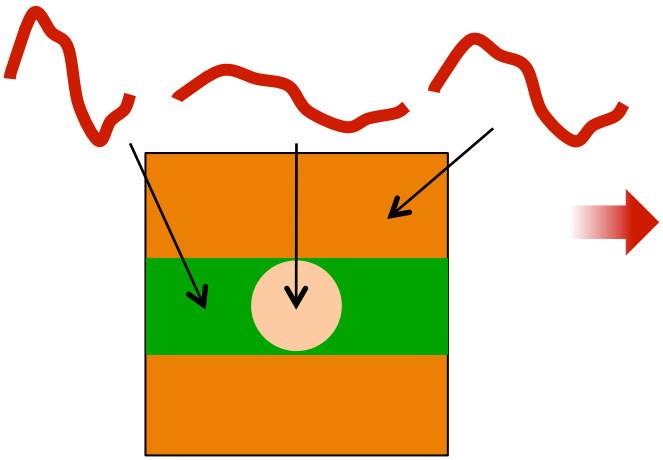


TISSUE DEFECT



$$\Delta r_a(\mathbf{x}) = (r_{a,\vartheta}/r_a - 1)$$



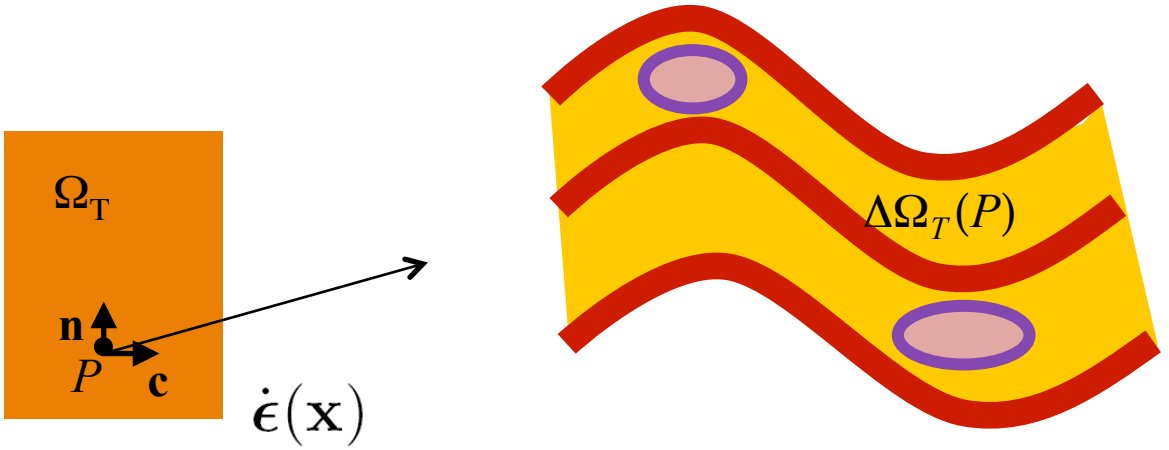


Fibers straightening try to compensates reduction in cross-links

Multiscale modeling allows the understanding of **coupling effects** between different biological structures

REMODELING

SUBMODELING TECHNIQUE



$$d\varepsilon_f = [\dot{\boldsymbol{\epsilon}}(\mathbf{x})\mathbf{c}(\mathbf{x})] \cdot \mathbf{c}(\mathbf{x})\, d\tau$$

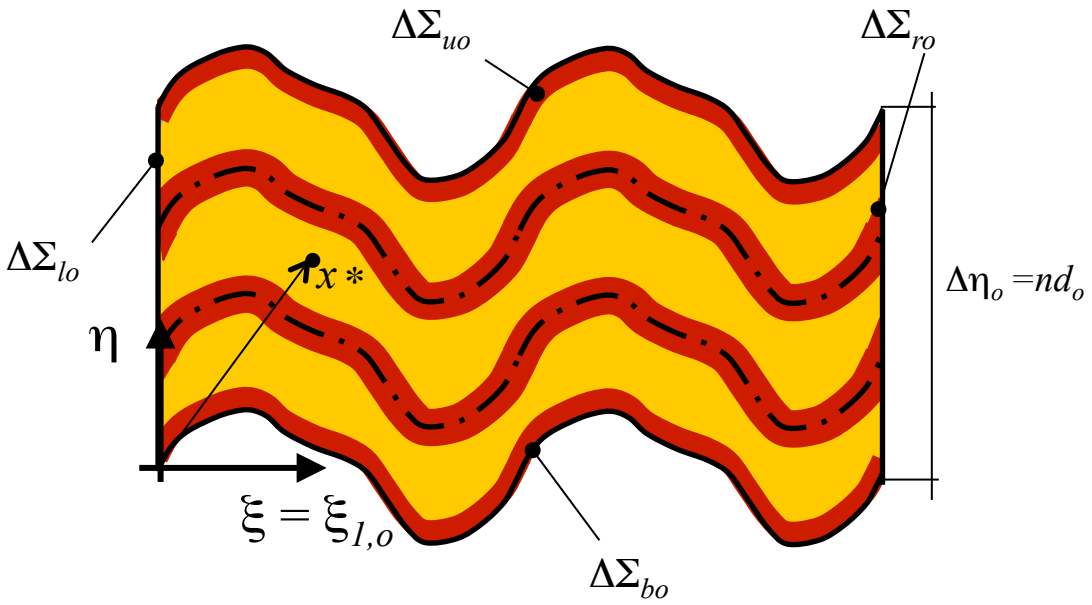
$$d\varepsilon_n = [\dot{\boldsymbol{\epsilon}}(\mathbf{x})\mathbf{n}(\mathbf{x})] \cdot \mathbf{n}(\mathbf{x})\, d\tau$$

$$d\gamma_f = 2\,[\dot{\boldsymbol{\epsilon}}(\mathbf{x})\mathbf{c}(\mathbf{x})] \cdot \mathbf{n}(\mathbf{x})\, d\tau$$

The submodeling procedure consists in finding the local displacement field associated with $d\varepsilon_f$, $d\gamma_f$ and $d\varepsilon_n$

REMODELING

SUBMODELING TECHNIQUE

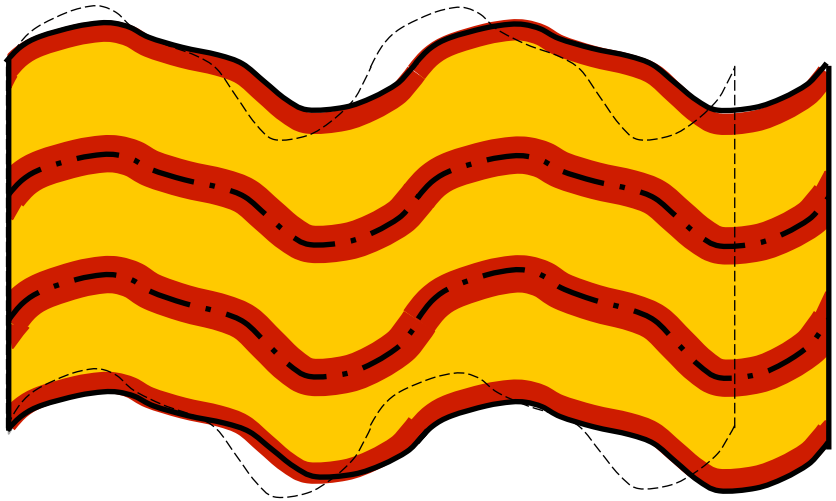


A series of linearly elastic equilibrium problems at the microscale:

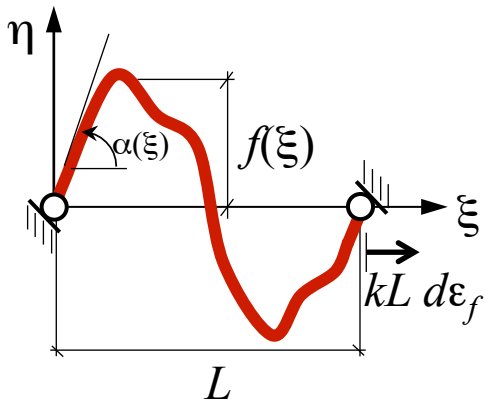
$$\begin{cases} \nabla^* \cdot \dot{\boldsymbol{\sigma}}^* = \mathbf{0} \\ \dot{\boldsymbol{\epsilon}}^* = \hat{\nabla}^* \dot{\mathbf{u}}^* \\ \dot{\boldsymbol{\sigma}}^* = \mathcal{C}^* \dot{\boldsymbol{\epsilon}}^* \end{cases} \quad \text{in } \Delta\Omega_T$$

B.C. $$\dot{\mathbf{u}}^*(\mathbf{x}^*) = \dot{\mathbf{u}}^{*(d\varepsilon_f)} + \dot{\mathbf{u}}^{*(d\gamma_f)} + \dot{\mathbf{u}}^{*(d\varepsilon_n)} \quad \text{on } \Delta\Sigma_T$$

REMODELING
SUBMODELING TECHNIQUE



$$\dot{\mathbf{u}}^*(\mathbf{x}^*) = \dot{\mathbf{u}}^{*(d\varepsilon_f)} + \dot{\mathbf{u}}^{*(d\gamma_f)} + \dot{\mathbf{u}}^{*(d\varepsilon_n)} \quad \text{on } \Delta\Sigma_T$$



By the Principle of Virtual Works: $d\mathbf{s}^{(d\varepsilon_f)}(\xi) = \dfrac{E_{f,c}}{E_{F,1}}\left[a_1(\xi)\,\mathbf{c} + a_2(\xi)\,\mathbf{n}\right] d\varepsilon_f$

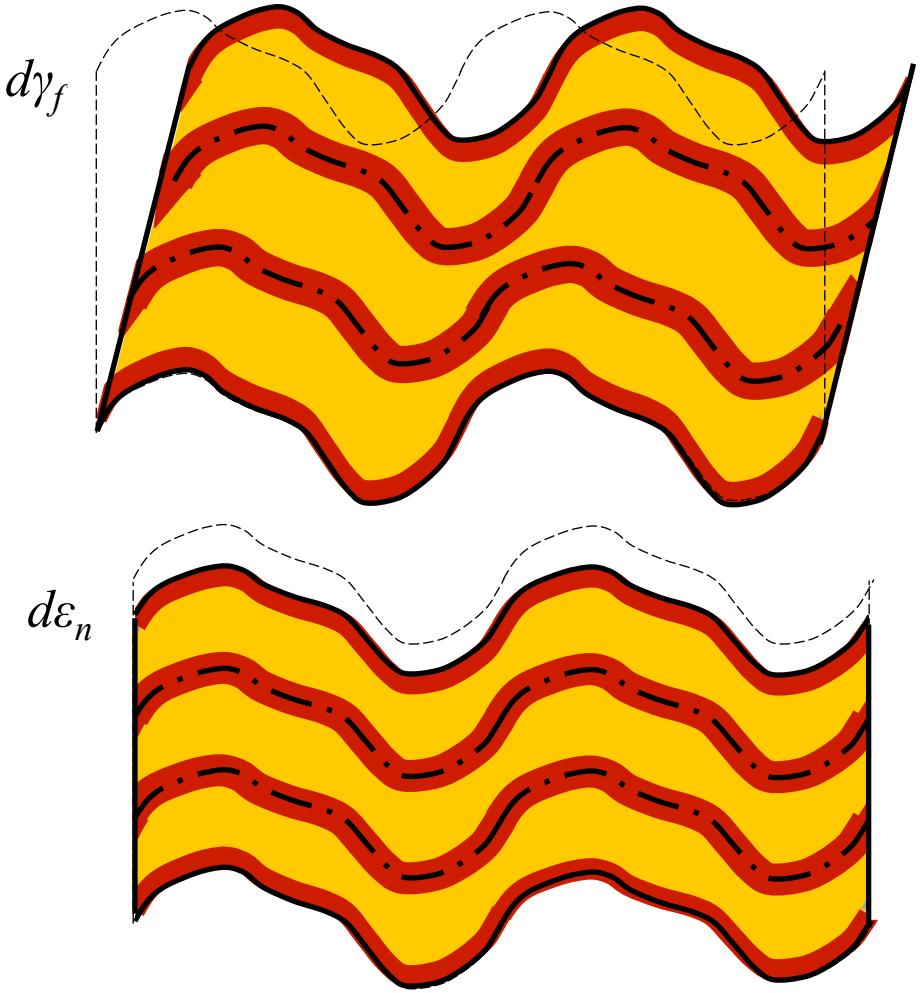
$$a_1(\xi) = \bar{a} f(\xi) + \int_0^{\xi}\left[c_\alpha(\zeta) + \frac{A}{I}\frac{f^2(\zeta)}{c_\alpha(\zeta)}\right] d\zeta + f(\xi)\frac{A}{I}\int_{\xi}^{kL}\frac{f(\zeta)}{c_\alpha(\zeta)}\,d\zeta$$

$$a_2(\xi) = -\bar{a}\xi + \int_0^{\xi}\left[s_\alpha(\zeta) - \frac{A}{I}\frac{\zeta\, f(\zeta)}{c_\alpha(\zeta)}\right] d\zeta - \xi\frac{A}{I}\int_{\xi}^{kL}\frac{f(\zeta)}{c_\alpha(\zeta)}\,d\zeta$$

$$\bar{a} = \underbrace{\langle s_{\alpha(\xi)}\rangle}_{\sin\alpha(\xi)} - \frac{A}{I}\left\langle \frac{\xi\, f(\xi)}{\underbrace{c_{\alpha(\xi)}}_{\cos\alpha(\xi)}}\right\rangle$$

REMODELING

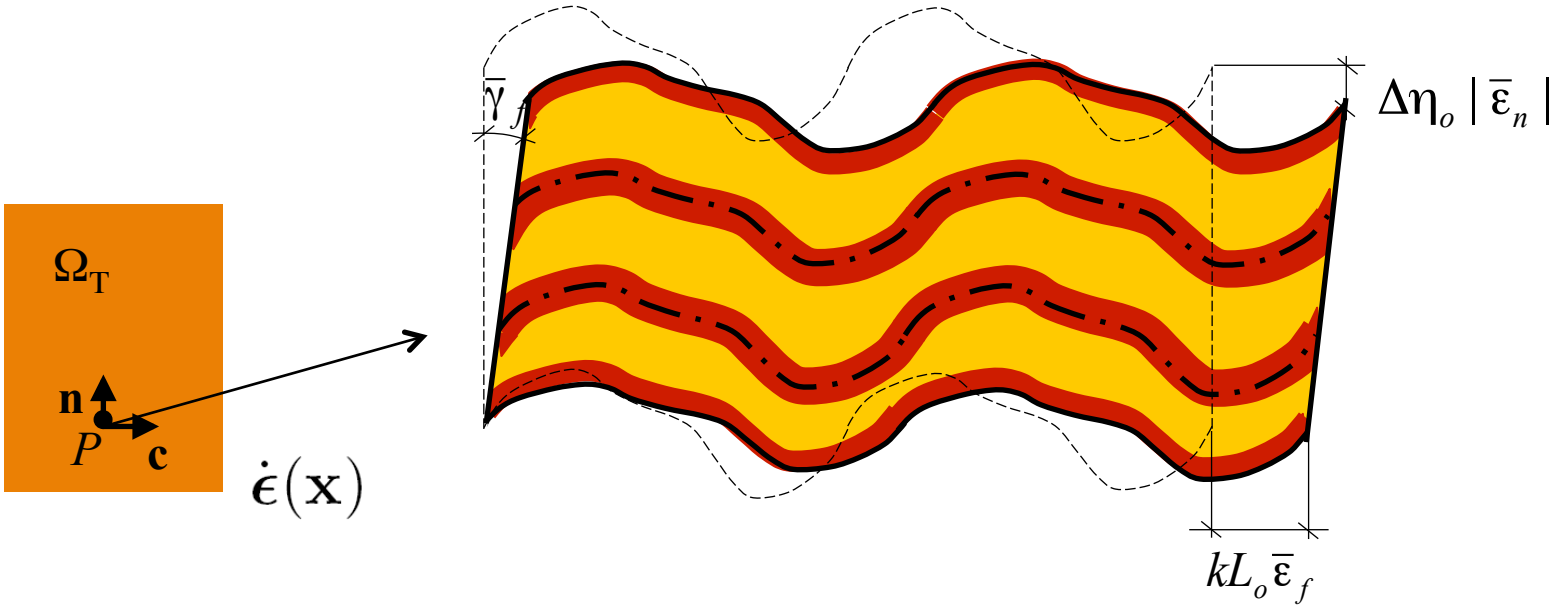
SUBMODELING TECHNIQUE



$$\dot{\mathbf{u}}^*(\mathbf{x}^*) = \dot{\mathbf{u}}^{*(d\varepsilon_f)} + \dot{\mathbf{u}}^{*(d\gamma_f)} + \dot{\mathbf{u}}^{*(d\varepsilon_n)} \quad \text{on } \Delta\Sigma_T$$

REMODELING

SUBMODELING TECHNIQUE

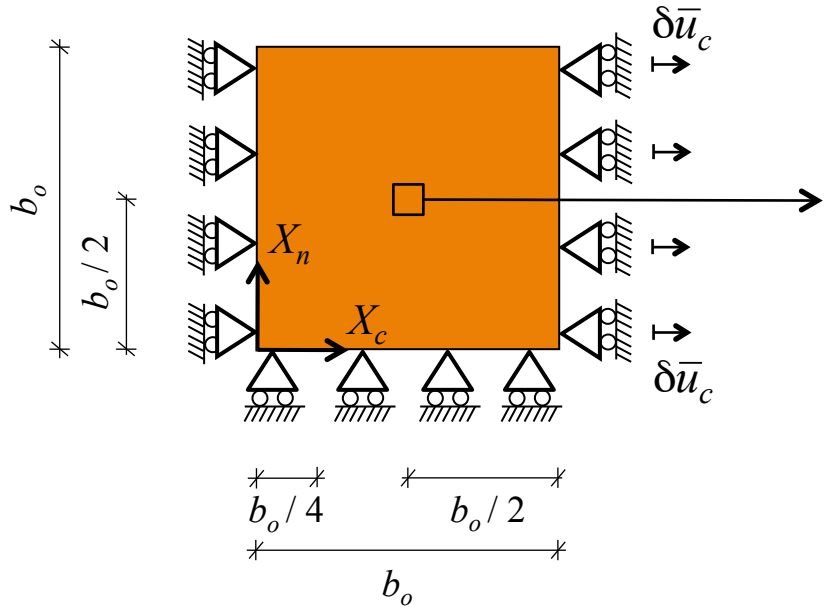


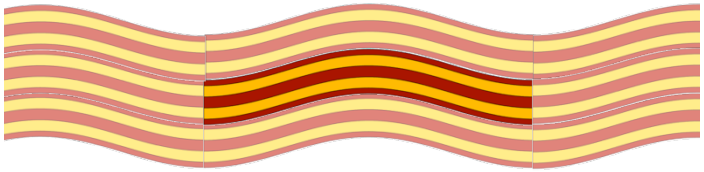
$$\dot{\mathbf{u}}^*(\mathbf{x}^*) = \dot{\mathbf{u}}^{*(d\varepsilon_f)} + \dot{\mathbf{u}}^{*(d\gamma_f)} + \dot{\mathbf{u}}^{*(d\varepsilon_n)} \quad \text{on } \Delta\Sigma_T$$

$$\dot{\mathbf{u}}^*(\mathbf{x}^*) = \frac{1}{d\tau}\begin{cases} d\mathbf{s}^{(d\varepsilon_f)}(\xi_{n+1}) + \Delta\eta[d\varepsilon_n\mathbf{n}^* + d\gamma_f\mathbf{c}^*] & \text{on } \Delta\Sigma_u \\ \eta[d\varepsilon_n\mathbf{n}^* + d\gamma_f\mathbf{c}^*] & \text{on } \Delta\Sigma_l \\ d\mathbf{s}^{(d\varepsilon_f)}(\xi_1) & \text{on } \Delta\Sigma_b \\ \eta[d\varepsilon_n\mathbf{n}^* + d\gamma_f\mathbf{c}^*] + kL\,d\varepsilon_f\mathbf{c}^* & \text{on } \Delta\Sigma_r \end{cases}$$

REMODELING

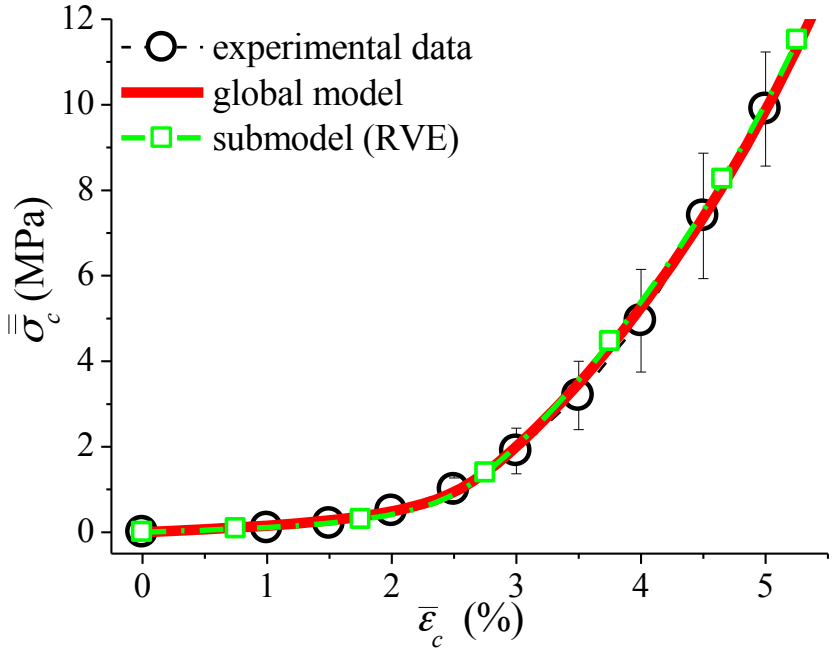
SUBMODELING TECHNIQUE





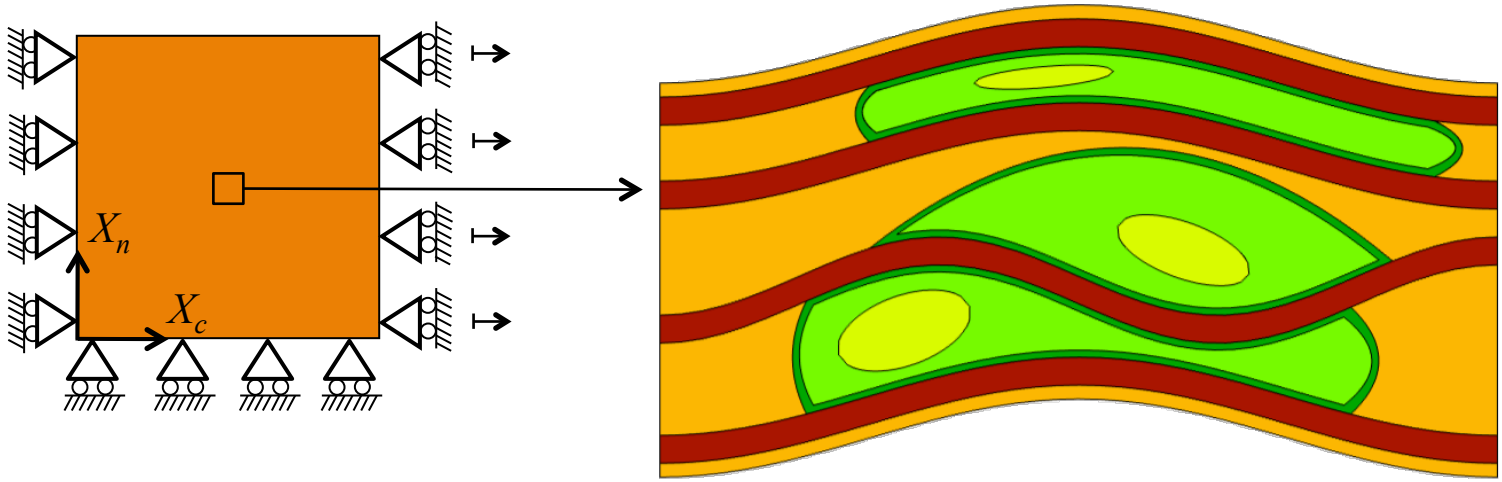
Matrix: Linearly elastic

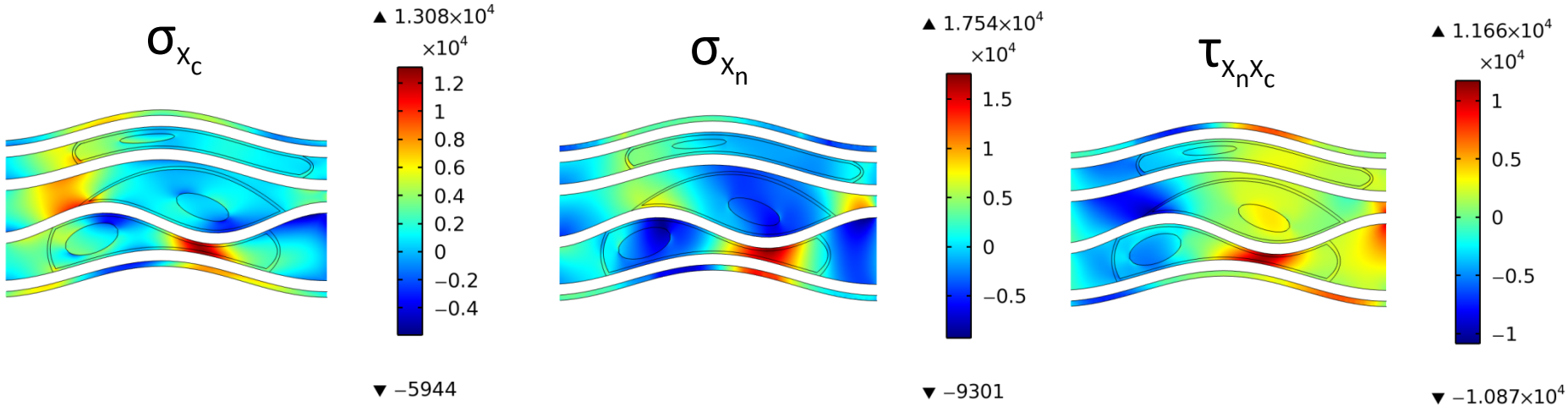
Fibers: Non-linearly elastic
(homogeneization at the nanoscale)



REMODELING

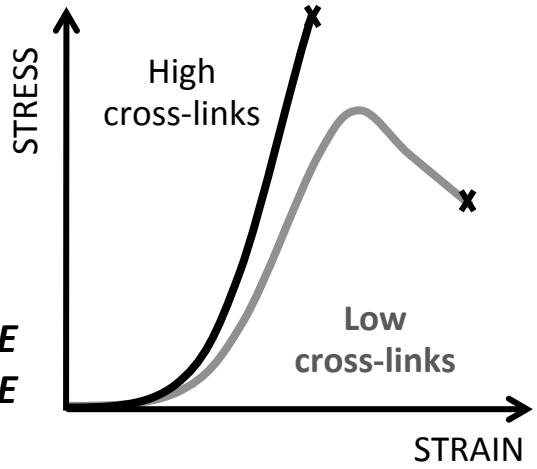
SUBMODELING TECHNIQUE



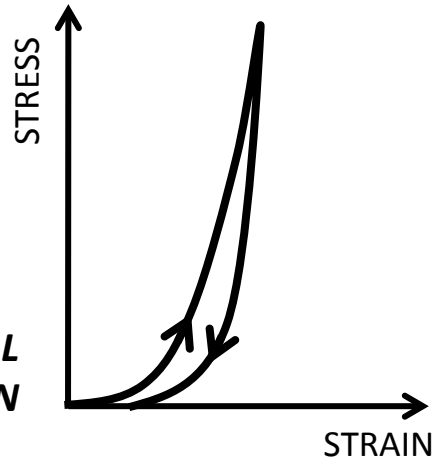


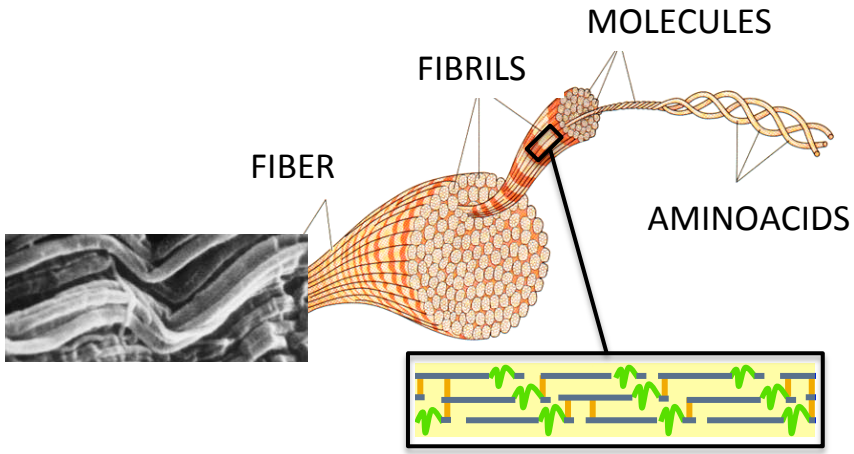
INELASTIC MECHANISMS

MULTISCALE DEPENDENCE

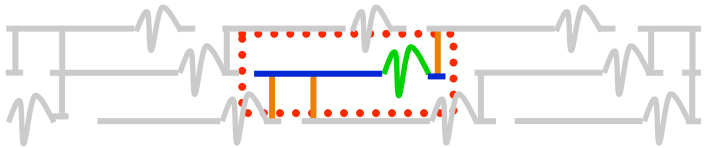


RESIDUAL STRAIN

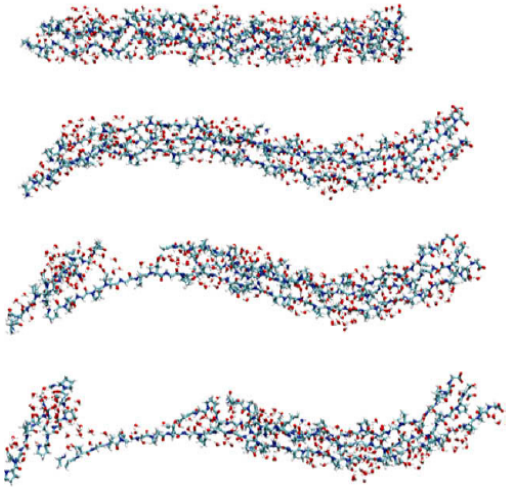




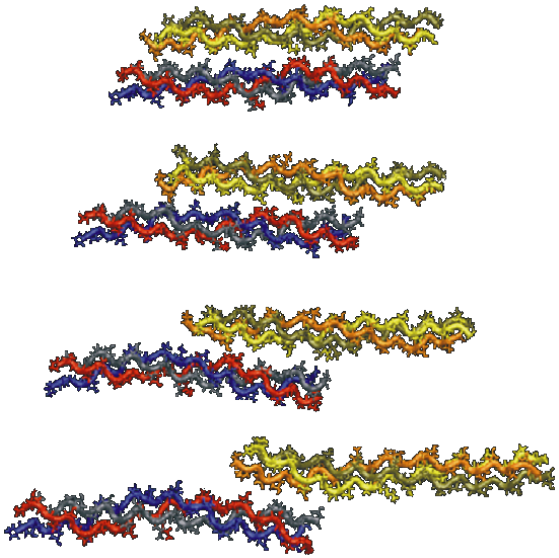
INELASTIC MECHANISMS



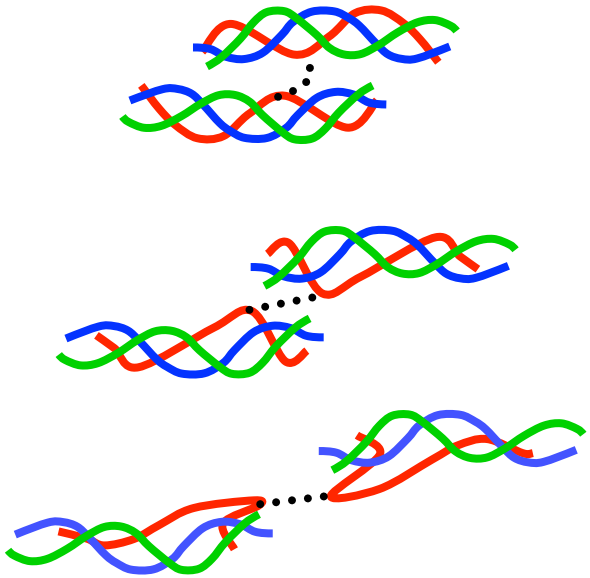
Molecular crack



Inelastic molecular sliding



weak-bonds induced



covalent-bonds induced
interstrand delamination

From: Buehler, *Theoretical and computational hierarchical nanomechanics of protein materials,* Progress in Materials Science 53, 2008

INELASTIC MECHANISMS

Equilibrium equations

$$N_k' = -q_f$$
$$h_j' - b_j = a_f$$

$(k = 1, 2)$
$(j = 1, 2, 3)$

GOVERNING EQUATIONS

Constitutive laws

$$N_k := \frac{\partial \Psi_f}{\partial w_k'} + \frac{\partial \Phi_f}{\partial \dot{w}_k'}$$
$$b_j := \frac{\partial \Psi_f}{\partial \beta_j} + \frac{\partial \Phi_f}{\partial \dot{\beta}_j}$$
$$h_j := \frac{\partial \Psi_f}{\partial \beta_j'} + \frac{\partial \Phi_f}{\partial \dot{\beta}_j'}$$

$q_f = a_f = 0$
$N_k = F_f \text{ at } z = 0, \ell_f$
$h_j = 0 \text{ at } z = 0, \ell_f$

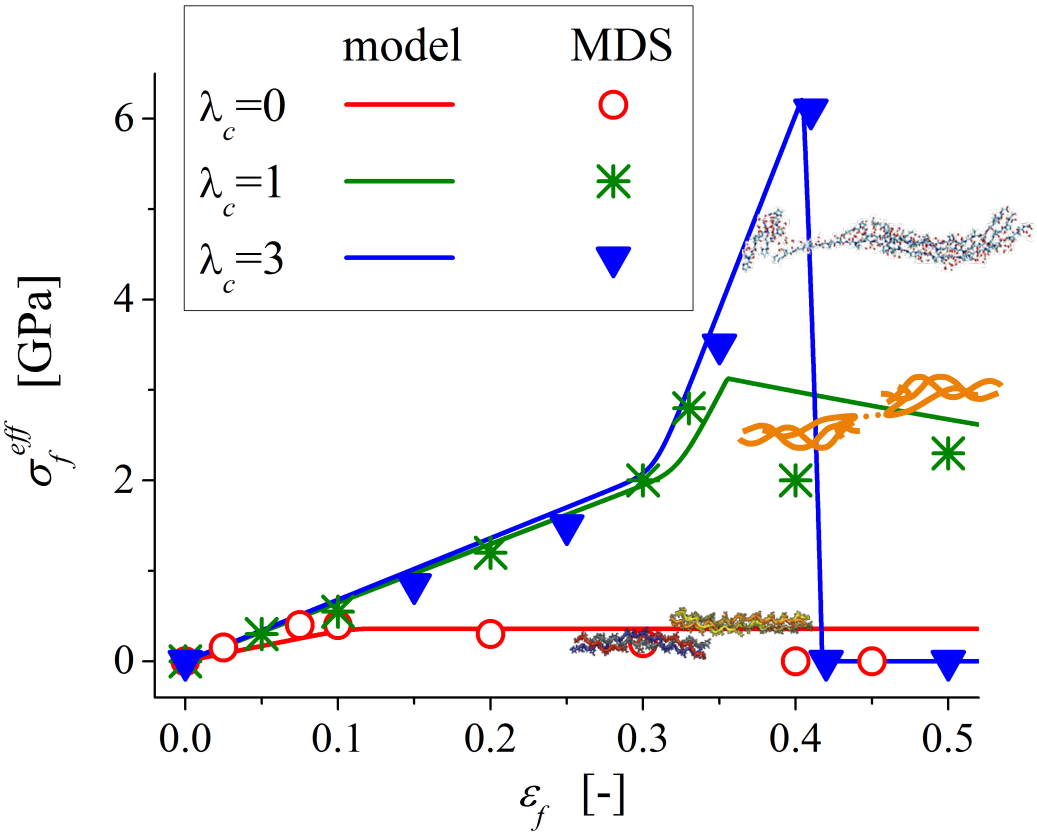
$$F_f = \bar{\beta}_m \mathcal{A}_c \{\sigma_m(\bar{\varepsilon}_m^e) + E_m(\bar{\varepsilon}_m^e)[(1-\alpha_1)\ell^{(n)} dw_1'/\ell_{m,o} - \alpha_1 \kappa_m \bar{\varepsilon}_m^e]\}$$
$$F_f = N_a \{\lambda_c(k_c \bar{\delta}_c + k_c \ell^{(n)} f_c(\bar{w}_2) dw_2') + k_w^e \bar{\delta}_w^e + k_w \ell^{(n)}(1-\alpha_2) dw_2'\}$$
$$0 \in c_m \dot{\beta}_m + \Psi_m^{el}(\bar{\varepsilon}_m^e) - w_m + a_f + \partial \mathrm{I}_{[0,1]}(\beta_m) + \partial \mathrm{I}^-(\dot{\beta}_m)$$
$$0 \in c_c \dot{\beta}_c + \mathcal{E}_c^{el} - w_c + a_f + \partial \mathrm{I}_{[0,1]}(\beta_c) + \partial \mathrm{I}^-(\dot{\beta}_c)$$
$$0 \in c_w \dot{\beta}_w + \frac{k_w(\bar{\delta}_w^e)^2}{2} - w_w + a_f + \partial \mathrm{I}_{[0,1]}(\beta_w)$$

INELASTIC MECHANISMS

COUPLED MULTISCALE MECHANISMS

Softening/brittle failure

Dependence on nanoscale quantities

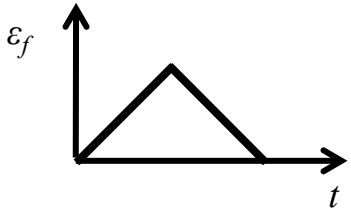


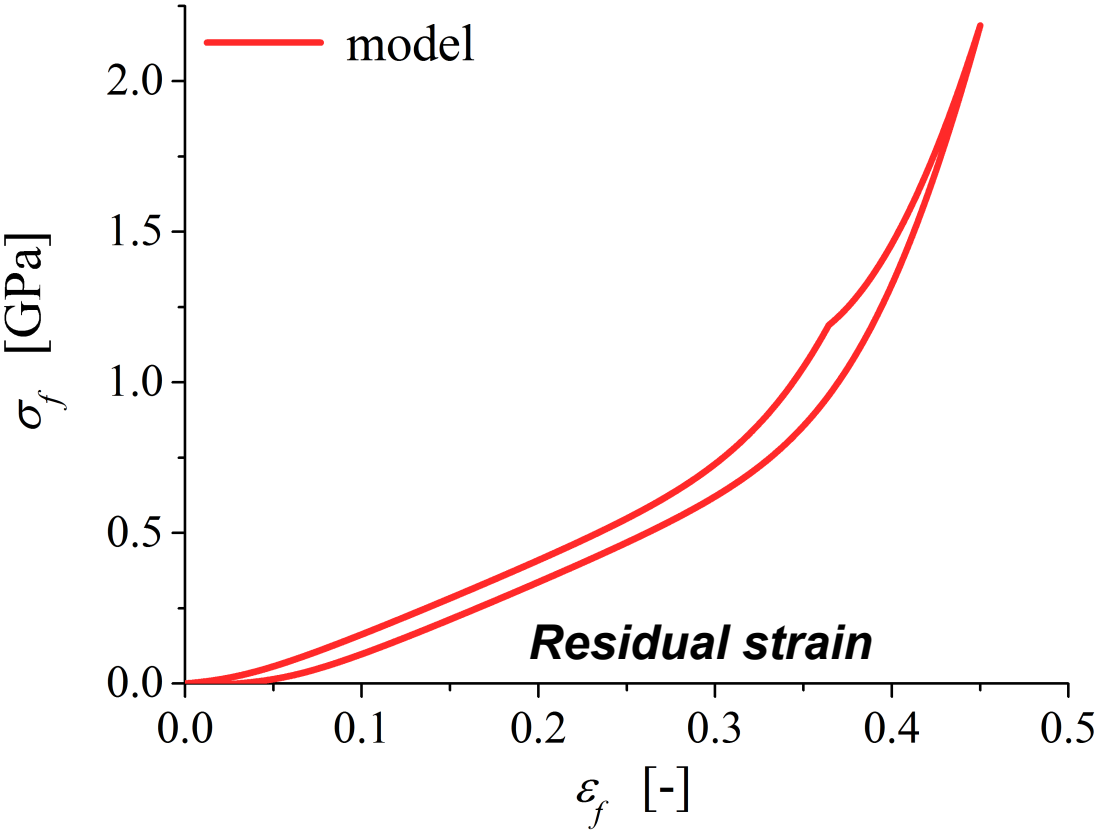
Svensson RB, Mulder H, Magnusson SP (2013) Fracture mechanics of collagen fibrils: influence of natural cross-links. *Biophysical Journal* 104:2476-2484

○ ▼ ✱ **Uzel S, Buehler MJ (2011)** Molecular structure, mechanical behavior and failure mechanism of the C-terminal cross-link domain in type I collagen. *Journal of the Mechanical Behavior of Biomedical Materials* 4:153-161

INELASTIC MECHANISMS

Loading-unloading test





MINI-COURSE

Mechanical modeling of soft biological tissues

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