PRIN Project: Advanced mechanical modeling of new materials and technologies for the solution of 2020 European challenges

Target problem: *Health care devices to treat cardiovascular pathologies* (UNIROMA2 research unit)

Towards a patient-specific constitutive modeling of soft biological tissues: the multiscale structural approach

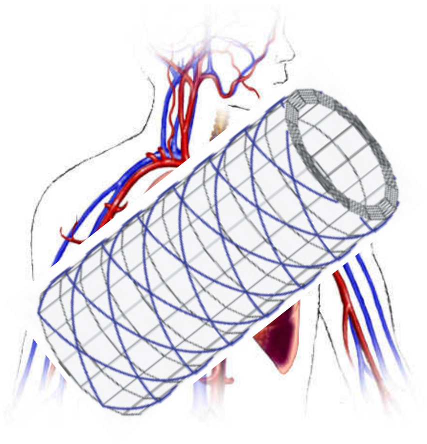
Michele Marino

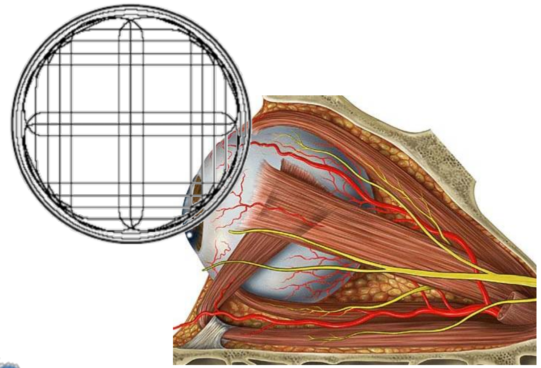
Seminar

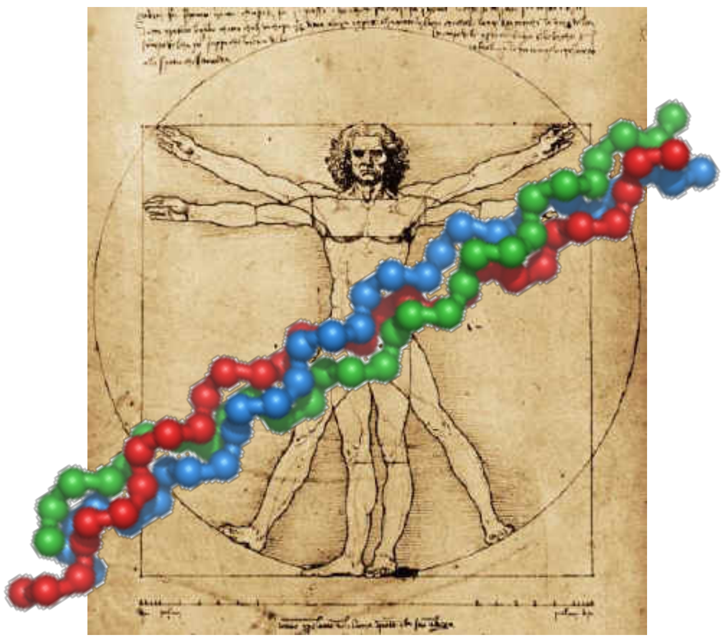
DICAr, Pavia, Italy

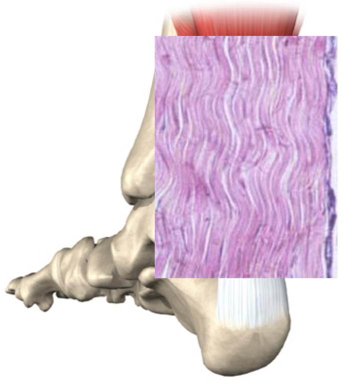
Tuesday, October 29

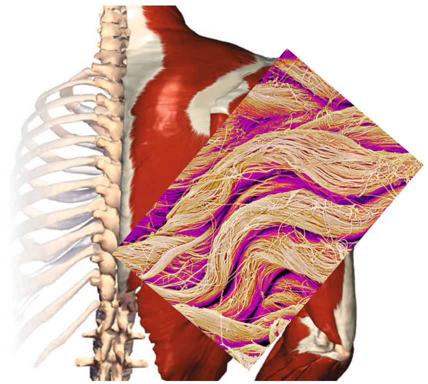
University of Rome "Tor Vergata"











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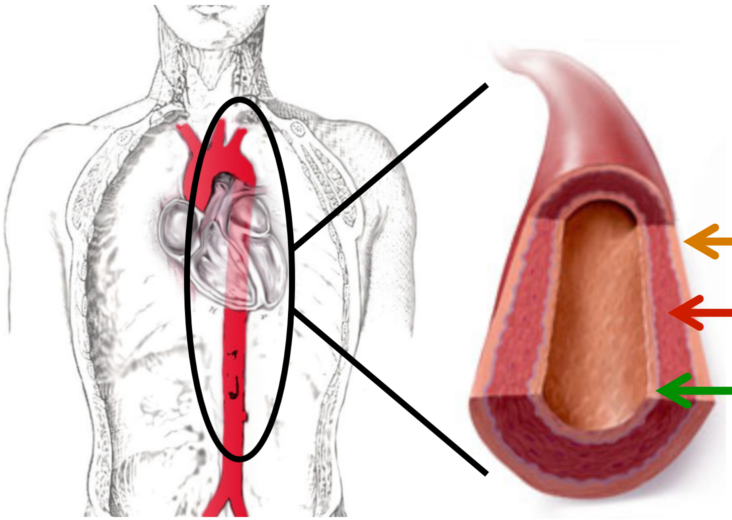


ADVENTITIA

MEDIA

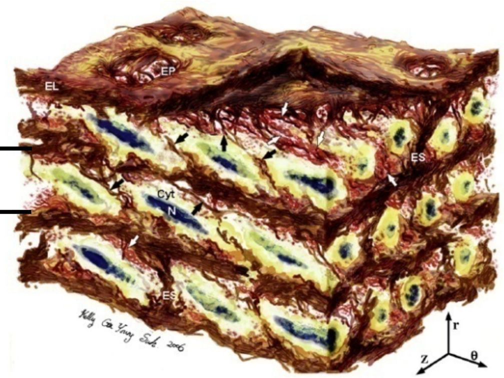
INTIMA

Medial Lamellar Unit

MLU

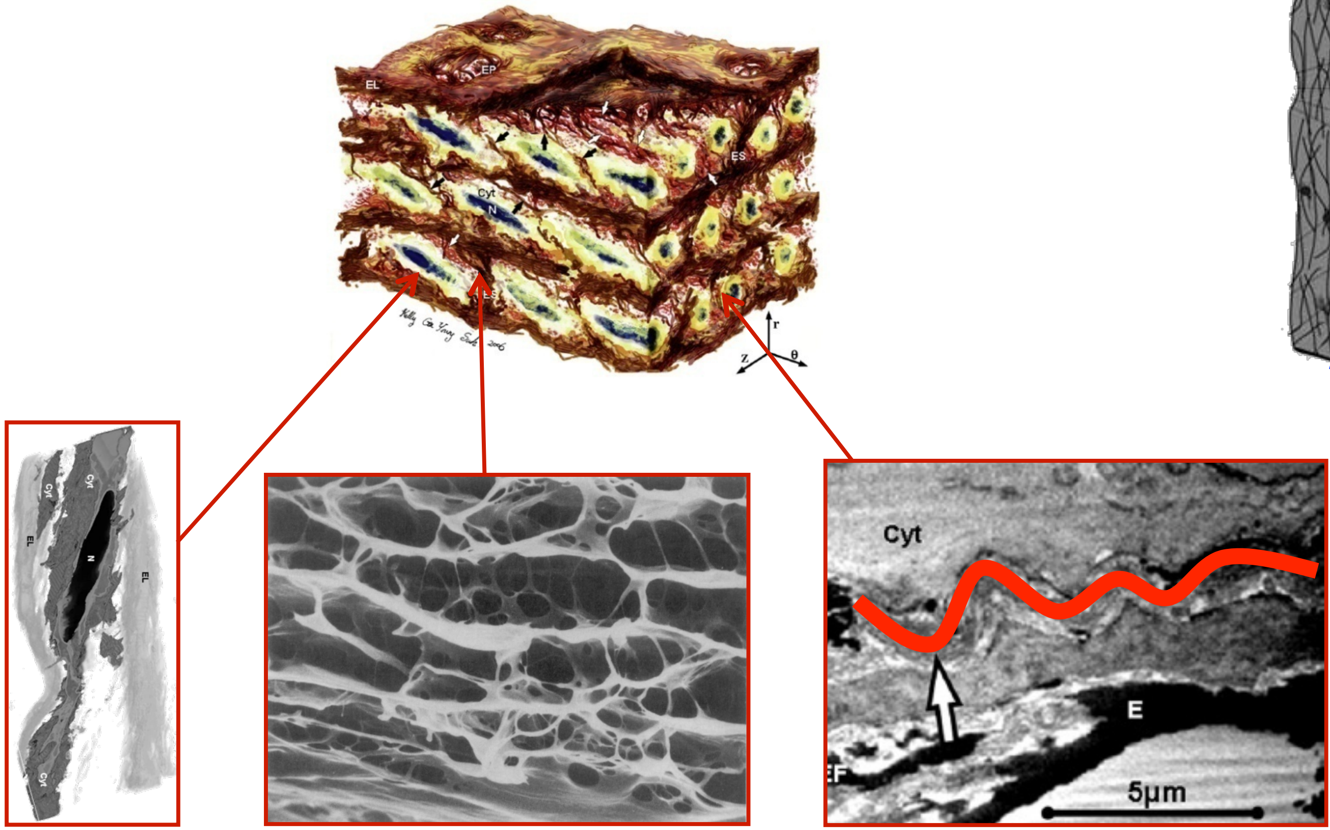
ELASTIN

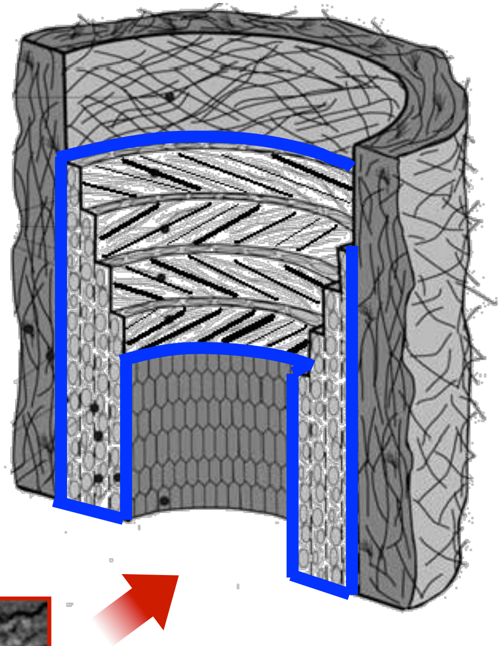
CELLS
ELASTIN
COLLAGEN



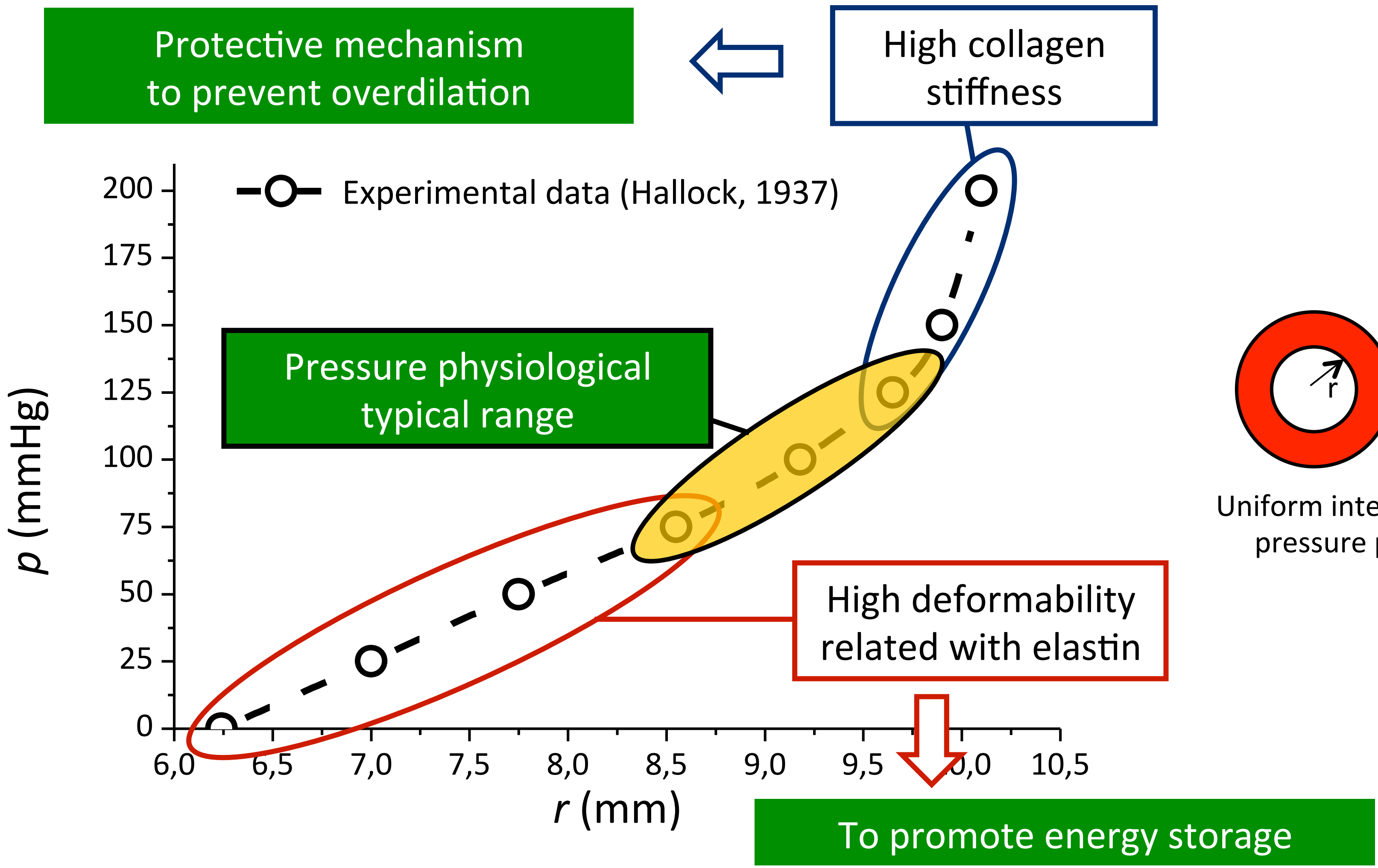
M.K. O'Connell et al., The Three-dimensional Micro- and Nanostructure of the Aortic Medial Lamellar Unit Measured Using 3D Confocal and Electron Microscopy Imaging. *Matrix Biol.* 27, 2008

AORTIC MEDIA:





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

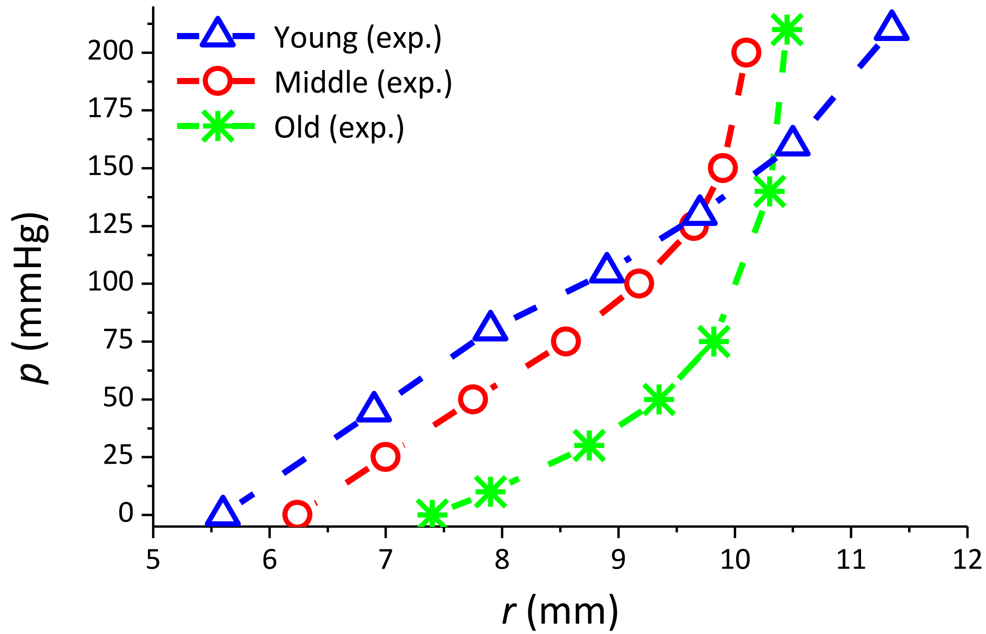

Protective mechanism
to prevent overdilation
High collagen
stiffness
Experimental data (Hallock, 1937)
Pressure physiological
typical range
High deformability
related with elastin
To promote energy storage
p (mmHg)
r (mm)
200
175
150
125
100
75
50
25
0
6,0
6,5
7,0
7,5
8,0
8,5
9,0
9,5
10,0
10,5
r
Uniform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

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

Age-dependent histological alterations

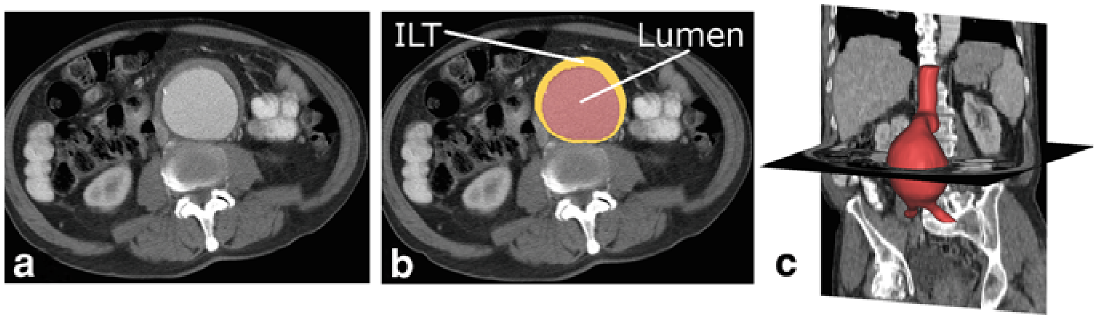
… corresponding to relevant alterations in arterial mechanics

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)



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

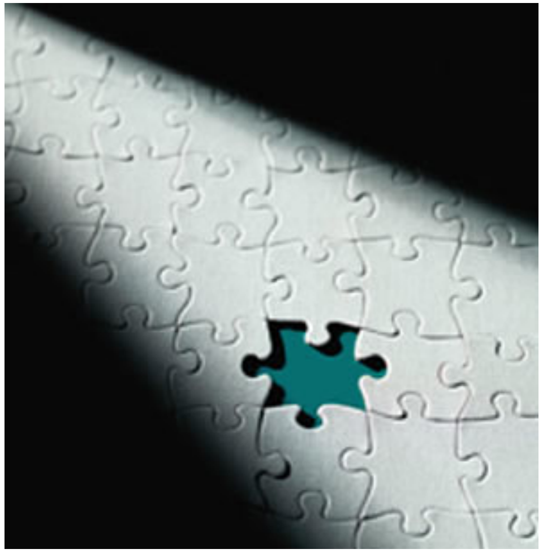
The **puzzle**:
"Our understanding of aortic diseases continues to advance as new partnerships between surgeons, biologists, engineers and mathematicians [...]."

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

STATE OF THE ART

Two main approaches:

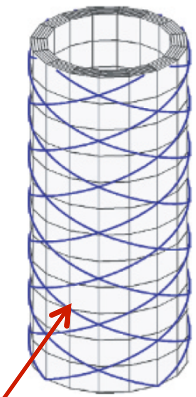
1) Phenomenological laws (Fung, 1973; Yin and Elliott, 2004)

2) Structural models: incorporate structure-based parameters

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

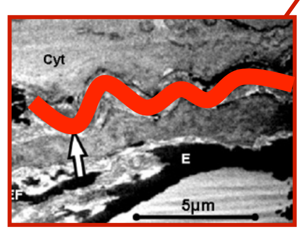
$$\overline{\Psi}(\bar{I}_1, \bar{I}_4, \bar{I}_6) = \overline{\Psi}_{\mathrm{g}}(\bar{I}_1) + \overline{\Psi}_{\mathrm{f}}(\bar{I}_4, \bar{I}_6)$$

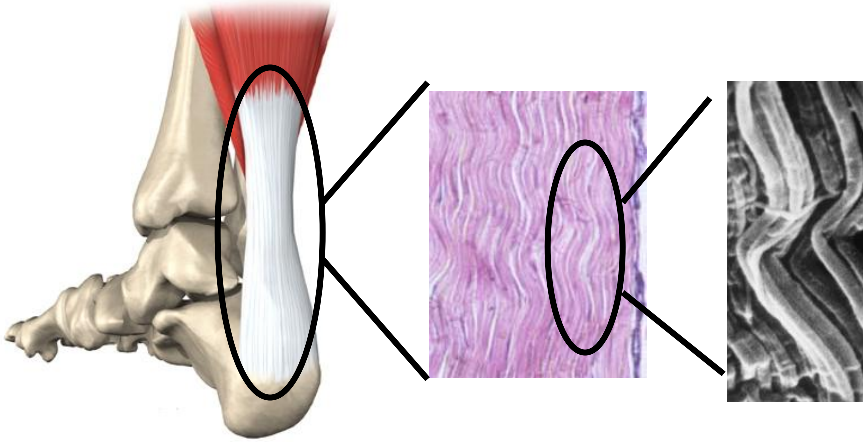
$$\Psi_{\mathrm{g}}(\bar{I}_1) = \frac{c}{2}(\bar{I}_1 - 3) \qquad \overline{\Psi}_{\mathrm{f}}(\bar{I}_4, \bar{I}_6) = \frac{k_1}{2k_2} \sum_{i=4,6} \{\exp[\boxed{k_2}(\bar{I}_i - 1)^2] - 1\}$$

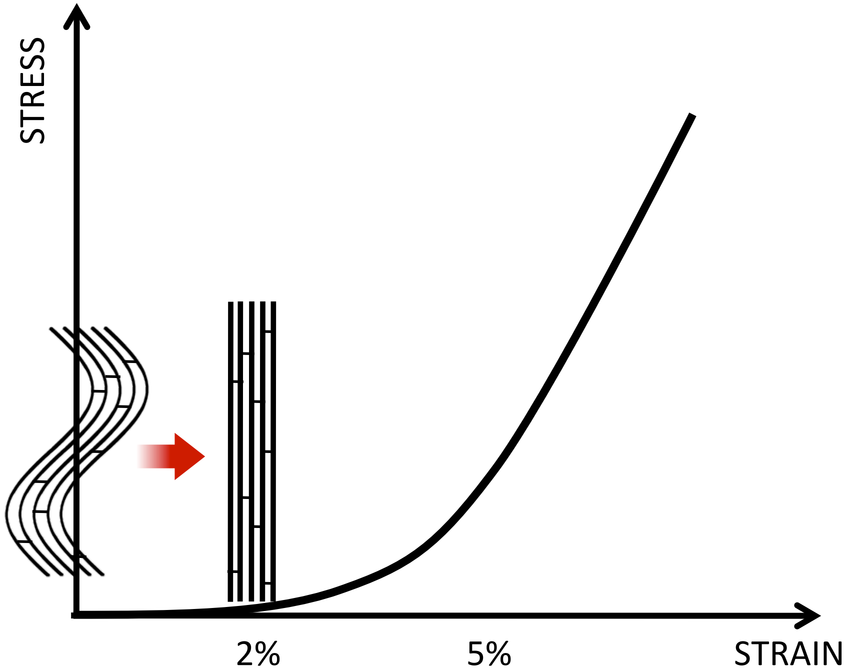


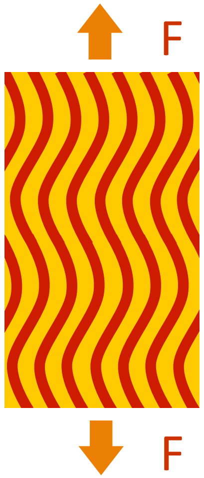
$$\bar{I}_4 = \mathbf{C} : \mathbf{A}_1 \qquad \bar{I}_6 = \mathbf{C} : \mathbf{A}_2$$

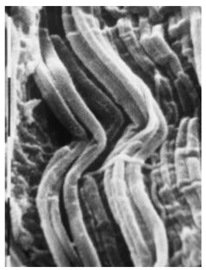
$$\mathbf{A}_1 = \mathbf{M} \otimes \mathbf{M} \qquad \mathbf{A}_2 = \mathbf{M}' \otimes \mathbf{M}'$$

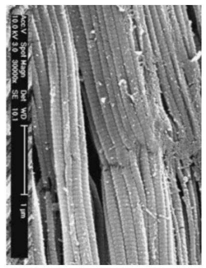


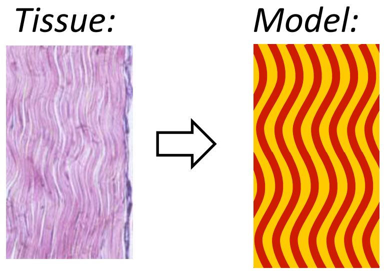



STRESS
2%
5%
STRAIN

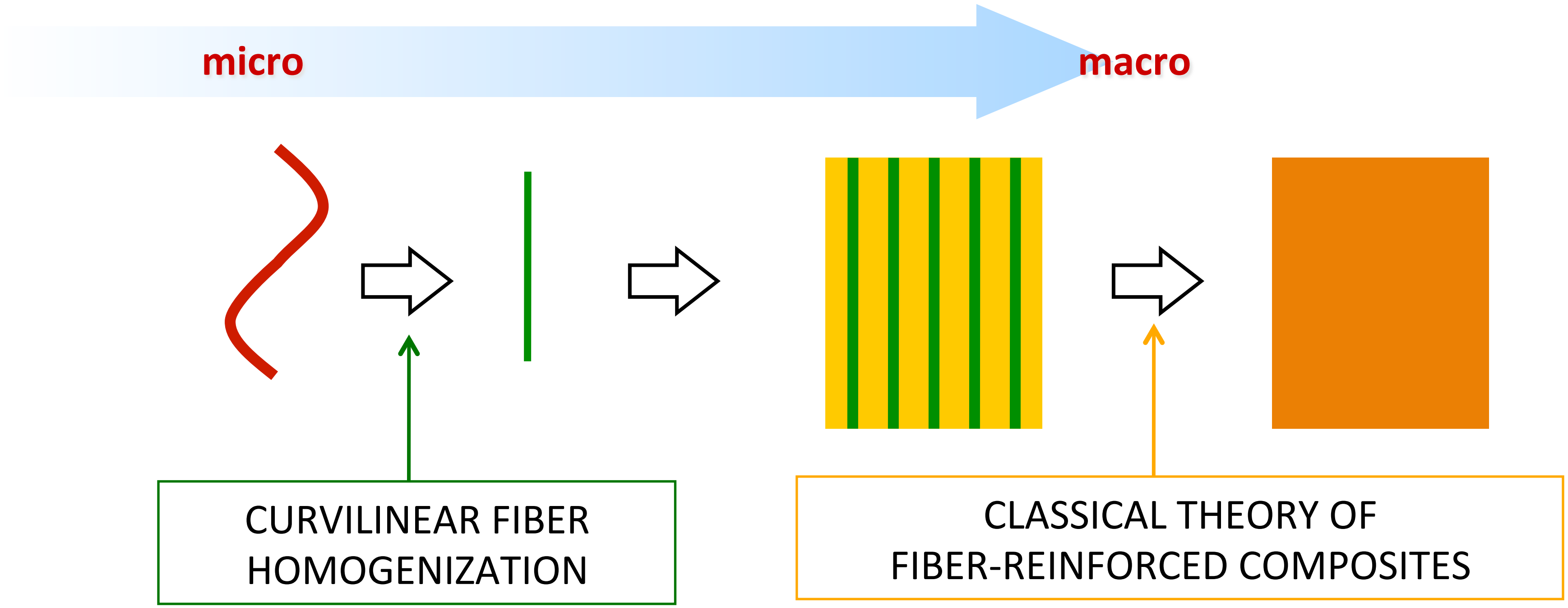

F
F



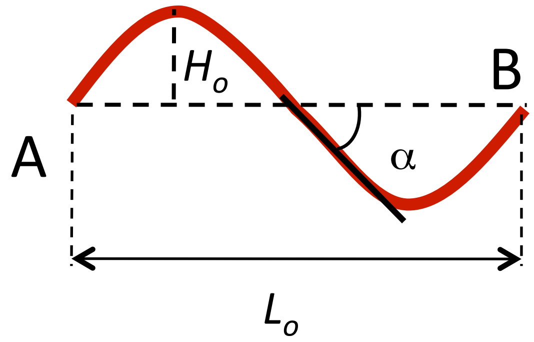




Double homogenization step



MICRO MECHANICS



- Beam theories

Frish-Fay, Flexible Bars, Butterworths1962,

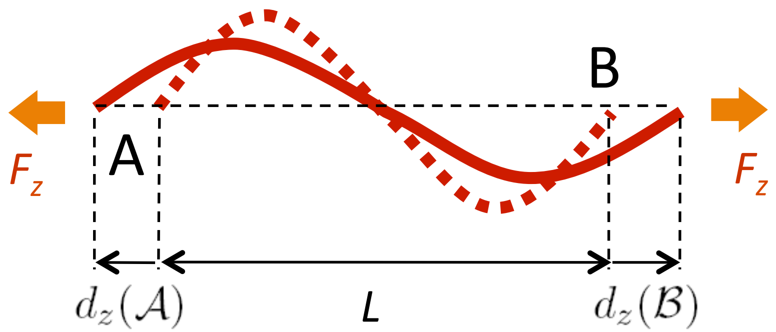
- Asymptotic expansion homogenization methods

M. Potier-Ferry, L. Said, "Geometrical homogenization of a corrugated beam", *Comptes Rendus de l'Académie des Sciences* 314, 1992.

- Energetic approach

M. Marino, G. Vairo, "Equivalent Stiffness and Compliance of Curvilinear Elastic Fibers", In: *Mechanics, Models and Methods in Civil Engineering* 61, 2012.

$f(x)=H_o\sin(2\pi x/L_o)$

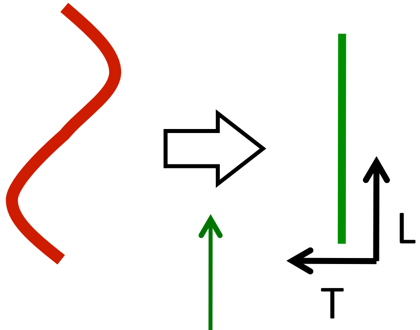


$$\varepsilon_F = \frac{d_z(\mathcal{B}) - d_z(\mathcal{A})}{L}$$

$$F_z = (EA)_{eq}\, \varepsilon_F$$

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

MICRO MECHANICS



CURVILINEAR FIBER HOMOGENIZATION

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

Transversely isotropic fiber:

$$E_{F,\,L}(\varepsilon_F) = E_{eq}(\varepsilon_F), \qquad E_{F,\,T} = E_M\,,$$
$$\nu_{F,\,LT} = \nu_{F,\,TT} = \nu_M, \qquad G_{F,\,LT} = E_M/[2(1+\nu_M)],$$

Collagen volume fraction: V_f

Mixture rule

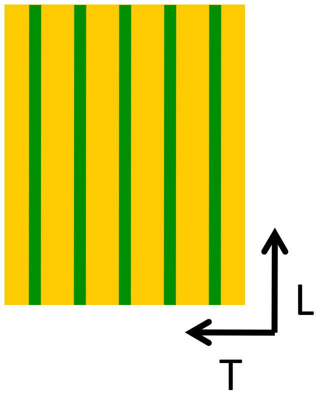
$$E_L(\varepsilon_F) = V_f E_{F,\,L}(\varepsilon_F) + (1-V_f)E_M, \qquad E_T = \frac{E_{F,\,T}E_M}{E_{F,\,T}(1-V_f)+E_M V_f},$$
$$G_{LT} = \left(\frac{V_f}{G_{F,\,LT}} + \frac{1-V_f}{G_M}\right)^{-1}, \qquad G_{TT} = \left(\frac{V_f}{G_{F,\,TT}} + \frac{1-V_f}{G_M}\right)^{-1},$$
$$\nu_{LT} = V_f \nu_{F,\,LT} + V_m \nu_M, \qquad \nu_{TT} = \frac{E_T}{2G_{TT}} - 1,$$

Linearly elastic isotropic matrix

E_M, ν_M

MACRO MECHANICS

- TRANSVERSELY ISOTROPIC MATERIAL IN LOCAL FRAME



$$[\mathbb{L}] = \frac{1}{D}\begin{bmatrix} E_L(1-\nu_{TT}^2) & E_T\nu_{LT}(1+\nu_{TT}) & E_T\nu_{LT}(1+\nu_{TT}) \\ E_T\nu_{LT}(1+\nu_{TT}) & E_T(1-\frac{E_T}{E_L}\nu_{LT}^2) & E_T(\nu_{TT}+\frac{E_T}{E_L}\nu_{LT}^2) \\ E_T\nu_{LT}(1+\nu_{TT}) & E_T(\nu_{TT}+\frac{E_T}{E_L}\nu_{LT}^2) & E_T(1-\frac{E_T}{E_L}\nu_{LT}^2) \end{bmatrix}$$

$$[\mathbb{M}] = \begin{bmatrix} \frac{E_T}{2(1+\nu_{TT})} & 0 & 0 \\ 0 & G_{LT} & 0 \\ 0 & 0 & G_{LT} \end{bmatrix} \qquad D = 1-\nu_{TT}^2 - 2(1+\nu_{TT})\frac{E_T}{E_L}\nu_{LT}^2$$

$$[\mathbb{C}^L] = \begin{bmatrix} [\mathbb{L}] & [0] \\ [0] & [\mathbb{M}] \end{bmatrix}$$

In the global coordinate system:

$$[\mathbb{C}] = \left[\hat{\mathbb{T}}_\sigma\right]\left[\mathbb{C}^L\right]\left[\hat{\mathbb{T}}_\varepsilon\right]^{-1}$$

Stress and strain transformation matrices

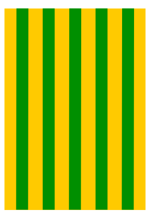
MICRO-MACRO MODEL

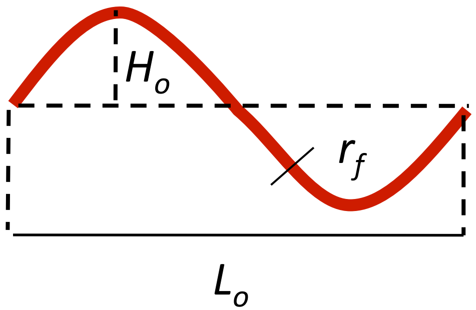
Few parameters, experimentally measurable

MECHANICAL PARAMETERS: E_M - E_ℓ

GEOMETRIC PARAMETERS:

$$\underbrace{V_f}_{\text{MACRO}} \qquad \underbrace{r_f \; L_o \; H_o}_{\text{MICRO}}$$



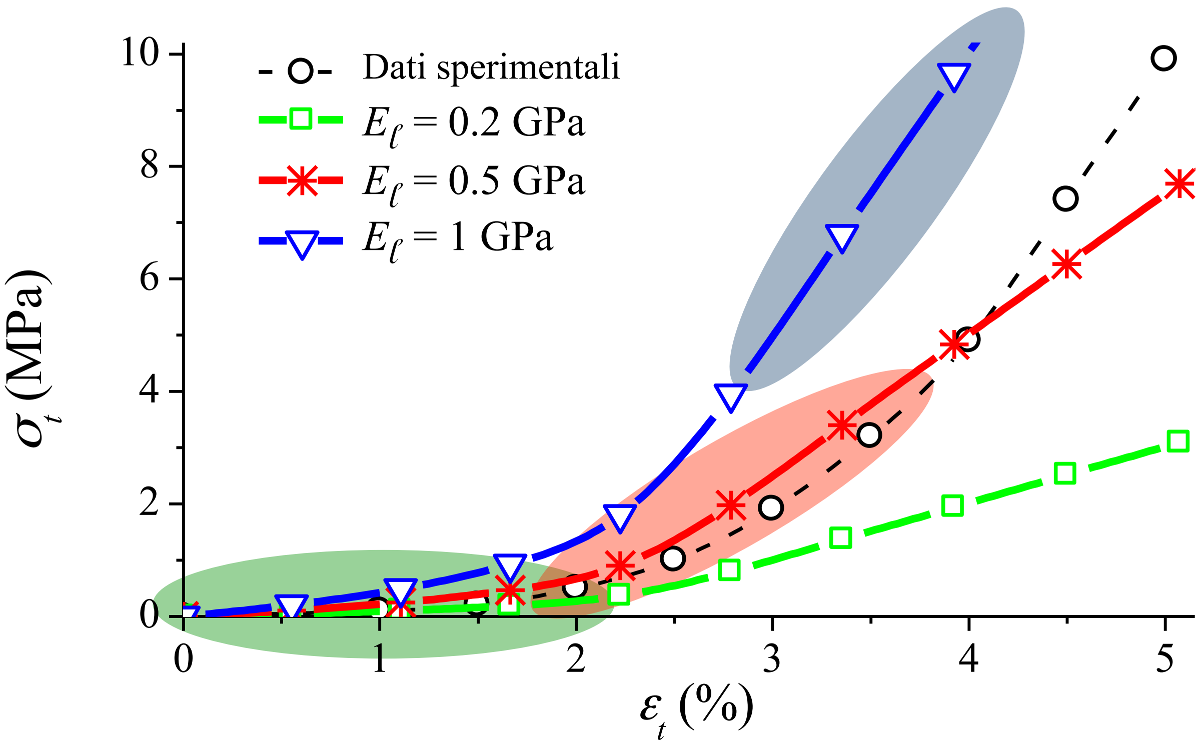


	Tendon	**Ref.**
L_o	240 µm	Hansen et al., 2002
H_o	10.8 µm	Maceri et al., 2009
r_f	4.0 µm	Kannus,2000
V_f	50%	Silver et al., 2001
ν_m	0.49	Lavagnino et al., 2008
E_M	1 MPa	Lavagnino et al., 2008

E_ℓ : 0.1-40 GPa (Fratzl, 2008)

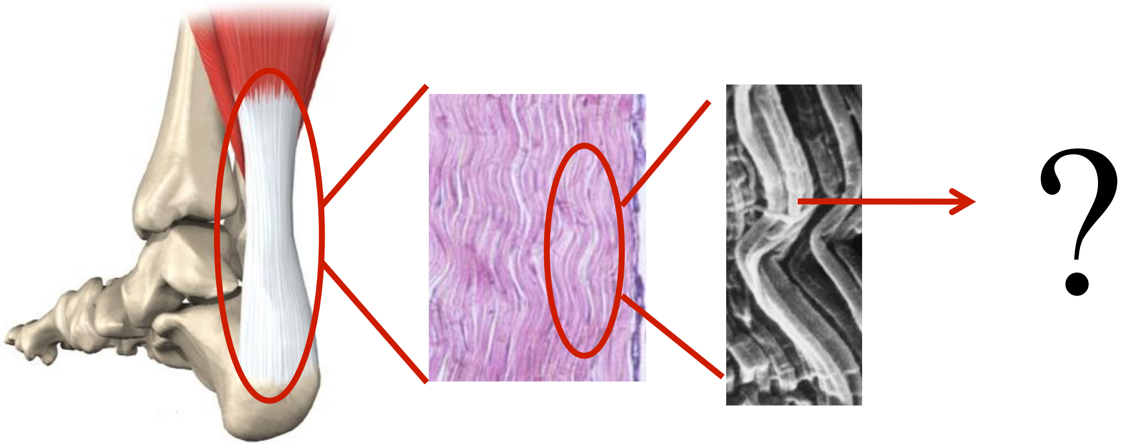
MICRO-MACRO MODEL: RESULTS

Non-constant collagen elastic modulus?

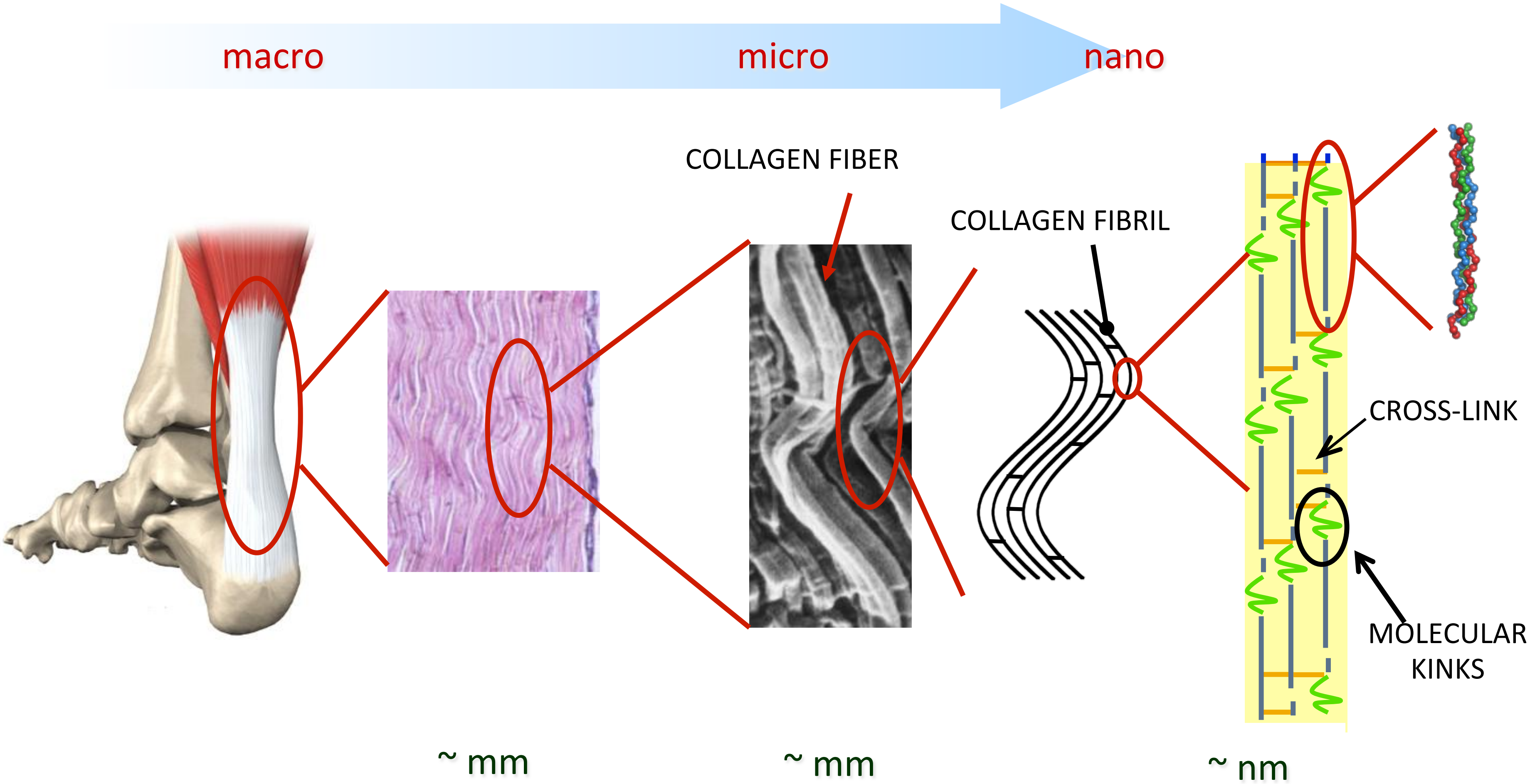



CHANCE

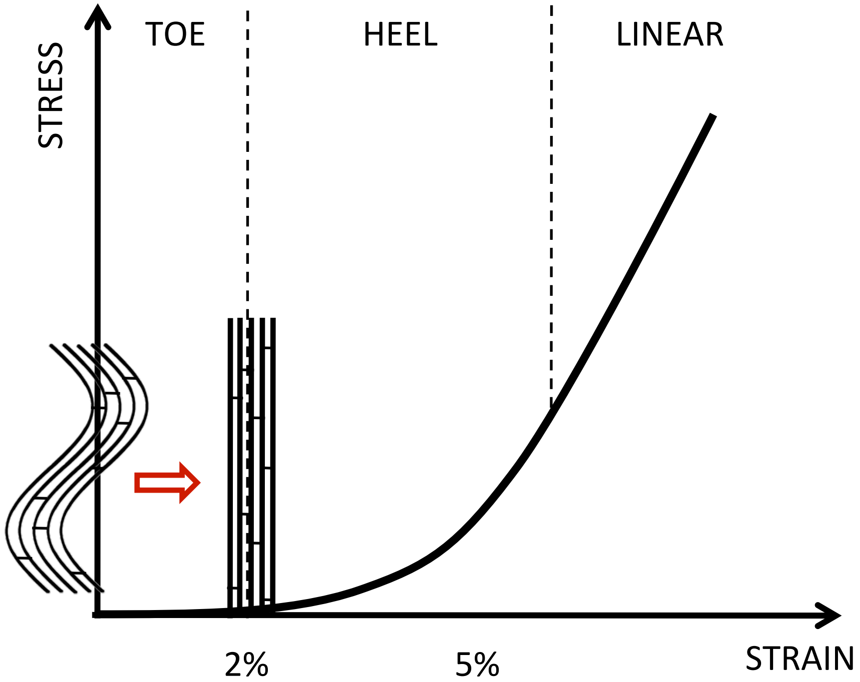

GO


?

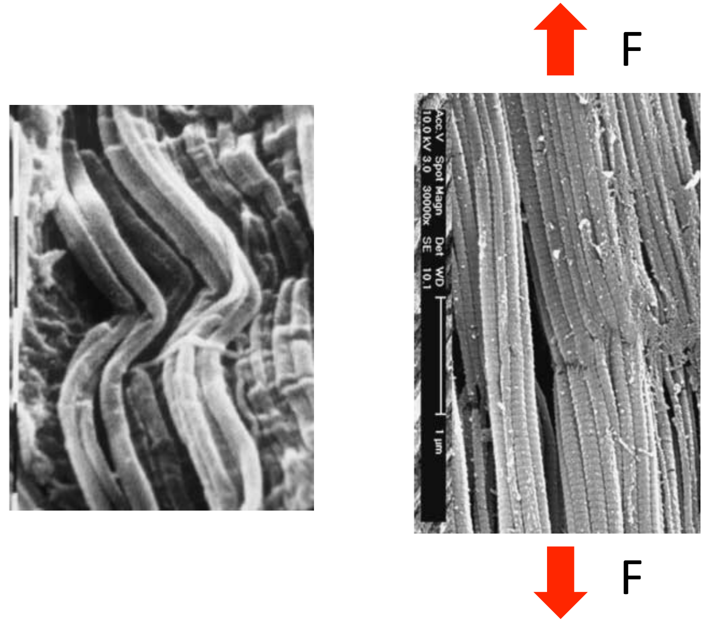
FROM MACRO TO NANO STRUCTURE



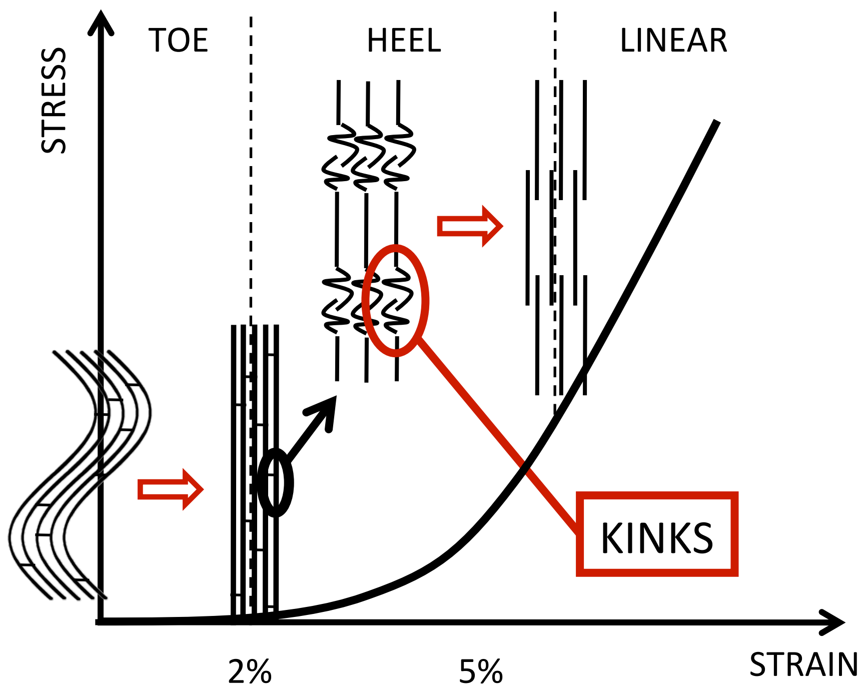
FROM MACRO TO NANO MECHANICS



"TOE REGION": microscopic crimp removal



FROM MACRO TO NANO MECHANICS

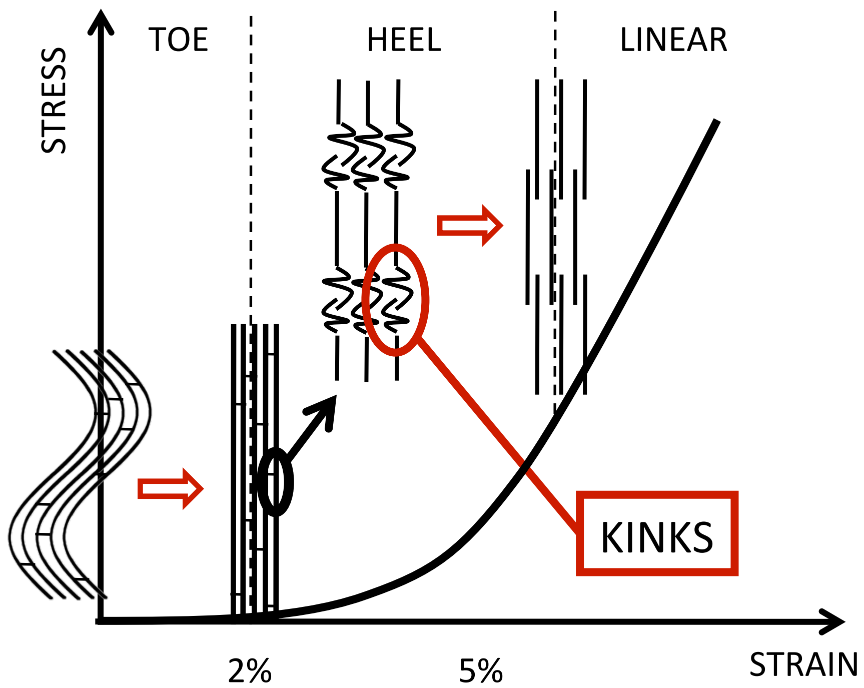


"TOE REGION": microscopic crimp removal

↓

"HEEL REGION": molecular kinks straightening (entropic mechanisms)

FROM MACRO TO NANO MECHANICS



"TOE REGION": microscopic crimp removal

↓

"HEEL REGION": molecular kinks straightening (entropic mechanisms)

↓

"LINEAR REGION": molecular and cross-links straightening

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)

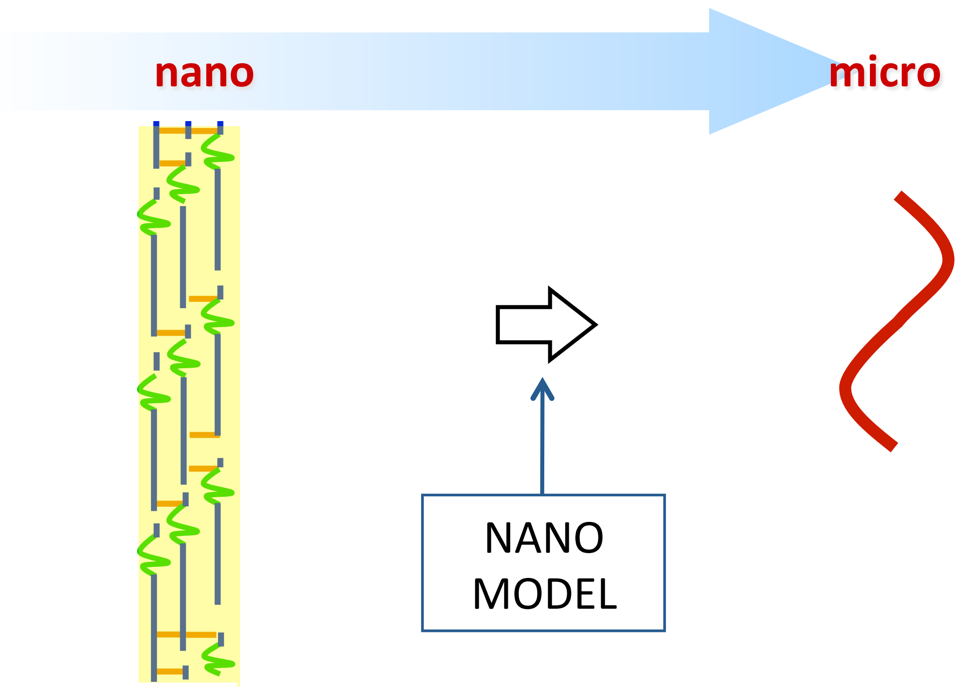
The **microscale** is the lowest scale explicitly modeled only in terms of collagen orientation

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

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

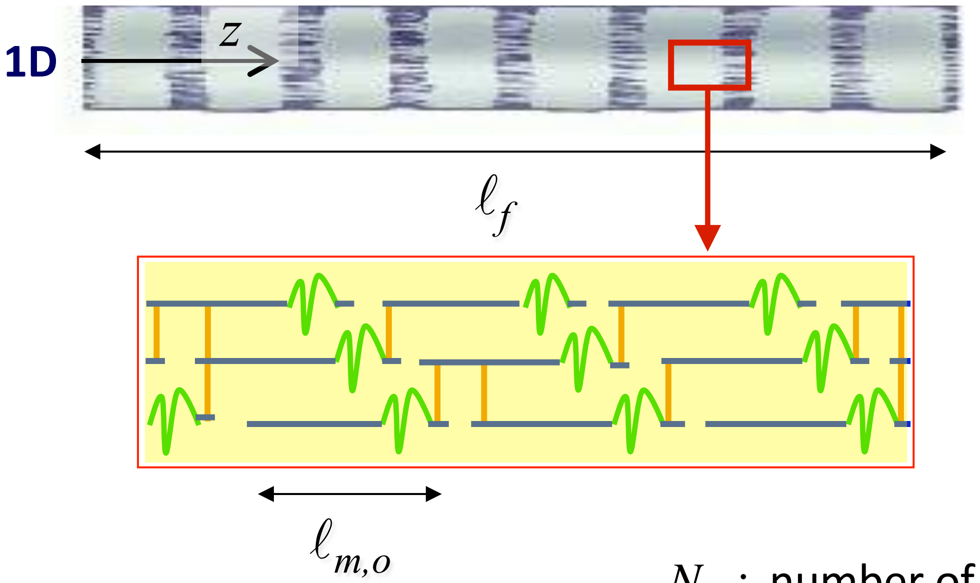
Computational efforts of MDS make them completely useless at the **macroscale**

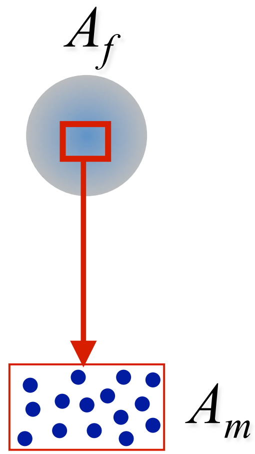
NANO-MICRO HOMOGENIZATION



NANO STRUCTURE

FIBRIL





$$N_a = A_c \,/\, A_m$$
$$A_c \approx 0.7\, A_f$$

z : material symmetry axis for fibril

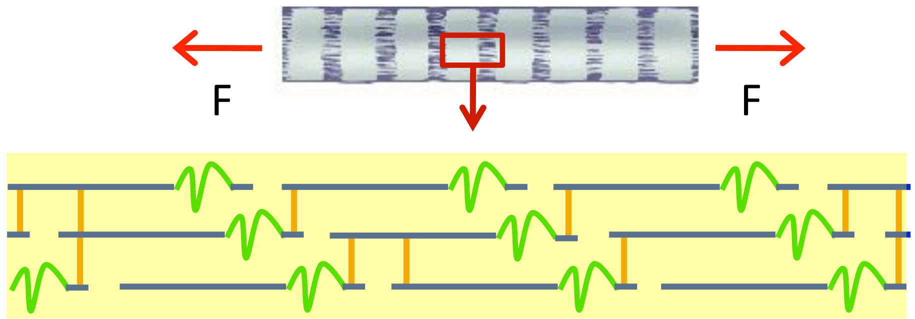
N_m : number of molecules

n_i^c : number of cross-links acting upon the ith molecule

$\lambda = \sum_{i=1}^{N_m} n_i^c / (2N_m)$: average covalent-bonds occurrence

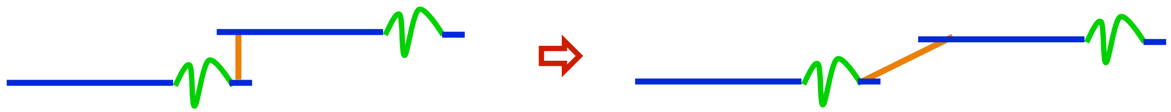
$N_c = \lambda N_m$: total number of covalent bonds

NANO MECHANICS



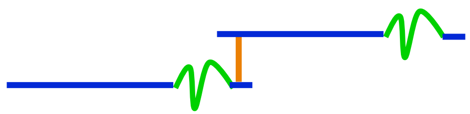
KINEMATICS: Two deformation mechanisms

- Molecular straightening: 

- Cross-links straightening: 

CONSTITUTIVE RESPONSE

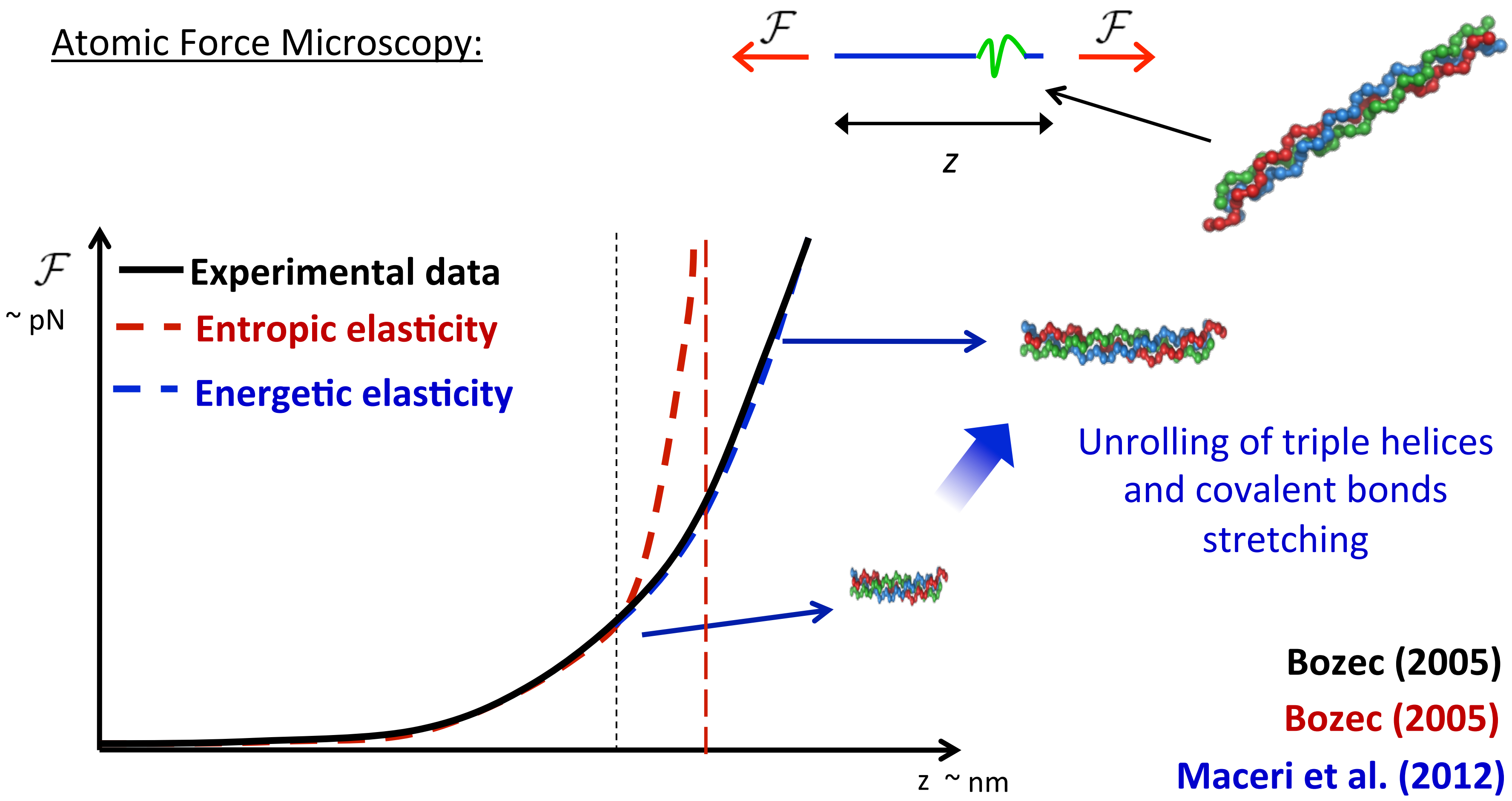
Non-linearly elastic (E_m)



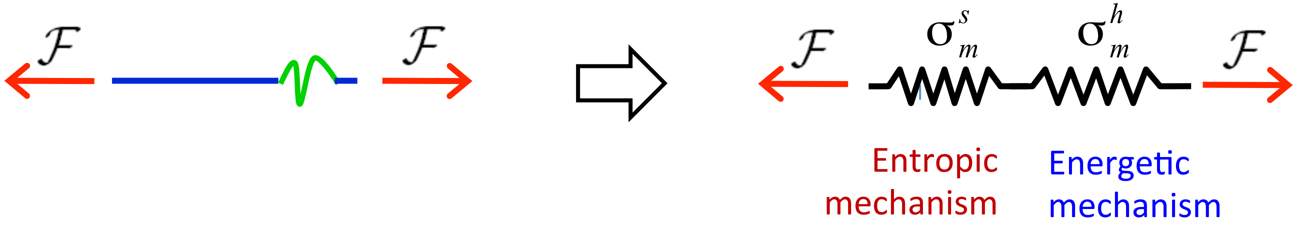
Linearly elastic (k_{cl})

NANO MECHANICS: COLLAGEN

Atomic Force Microscopy:

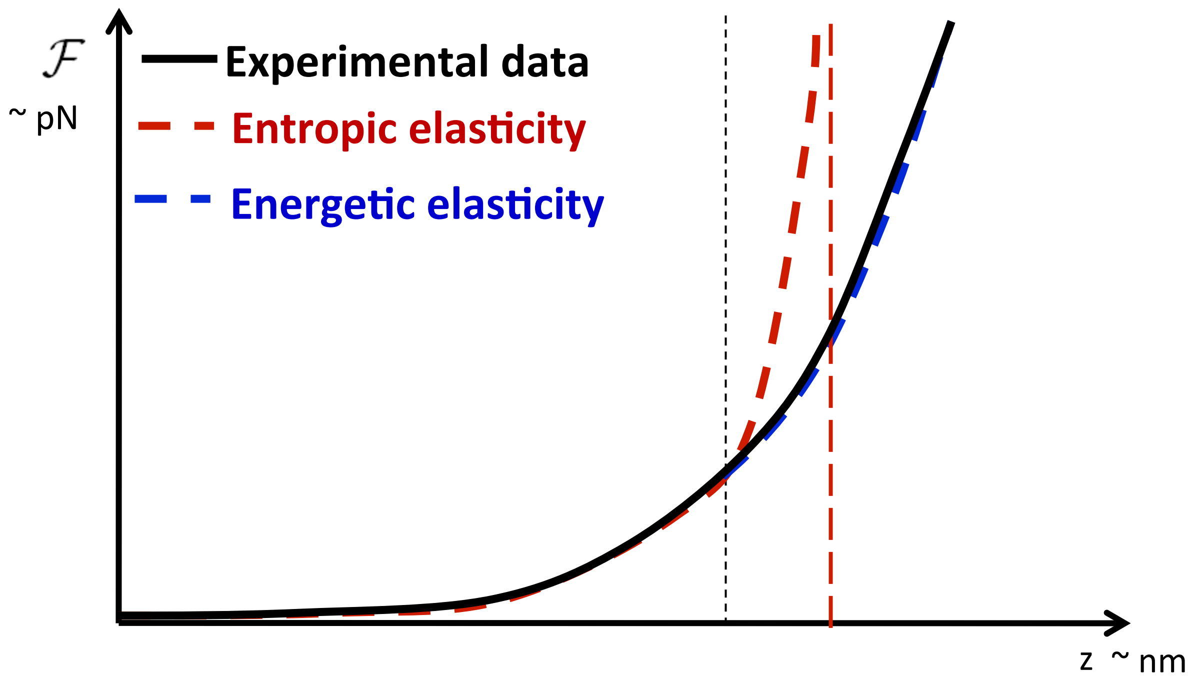


NANO MECHANICS: COLLAGEN

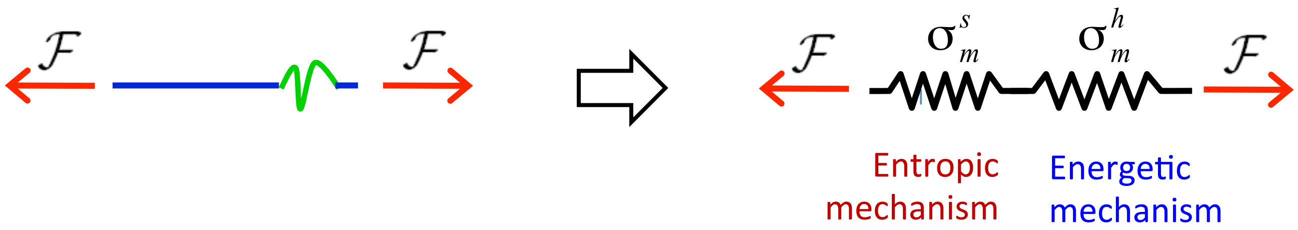


$$\sigma_m(\varepsilon_m) = \frac{\mathcal{F}}{A_m}$$

$$\varepsilon_m = \varepsilon^s_m + \varepsilon^h_m$$



NANO MECHANICS: COLLAGEN



$$\sigma_m(\varepsilon_m) = \frac{\mathcal{F}}{A_m}$$

$$\varepsilon_m = \varepsilon_m^s + \varepsilon_m^h$$

Tangent elastic modulus in entropic elasticty:

$$E_m^s = \frac{\varrho}{A_m}\left\{\frac{r_\ell}{2[1 - r_\ell(1+\varepsilon_m^s)]^3} + r_\ell\right\}$$

Recovery of the classical Worm-like chain formulation (Marko and Siggia, 1995)

$$r_\ell = \frac{\ell_m}{\ell_c}$$

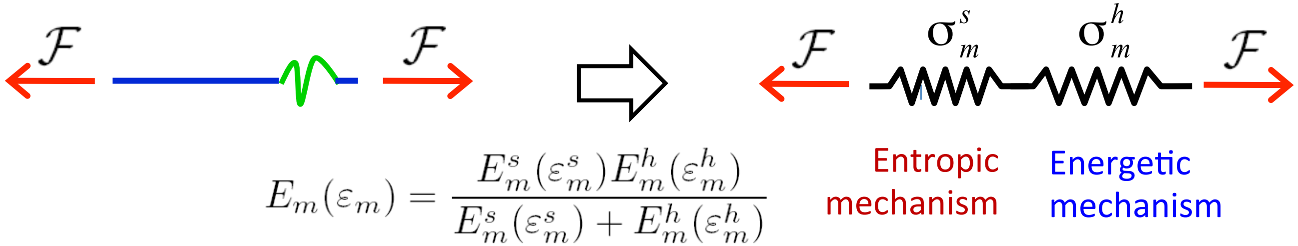
Tangent elastic modulus in energetic elasticity

$$E_m^h(\varepsilon_m^h) = \frac{\hat{E} r_\ell}{1 + e^{-k(r_\ell \varepsilon_m^h - \varepsilon_o^h)}} + \hat{E}_o r_\ell$$

Non-linearity related to unrolling of triple helices (Buehler and Wong, 2009 - Maceri et al., 2012)

$$\boxed{E_m(\varepsilon_m) = \frac{E_m^s(\varepsilon_m^s) E_m^h(\varepsilon_m^h)}{E_m^s(\varepsilon_m^s) + E_m^h(\varepsilon_m^h)}}$$

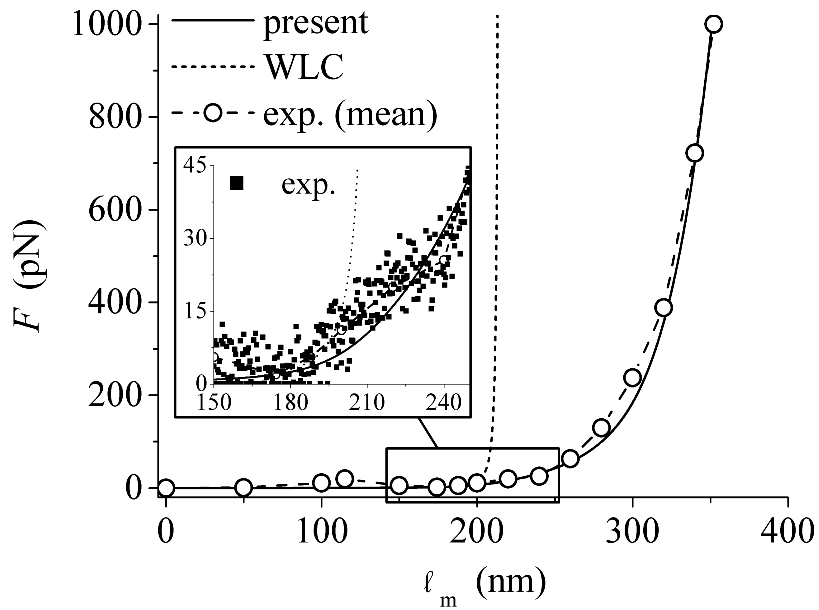
NANO MECHANICS: COLLAGEN

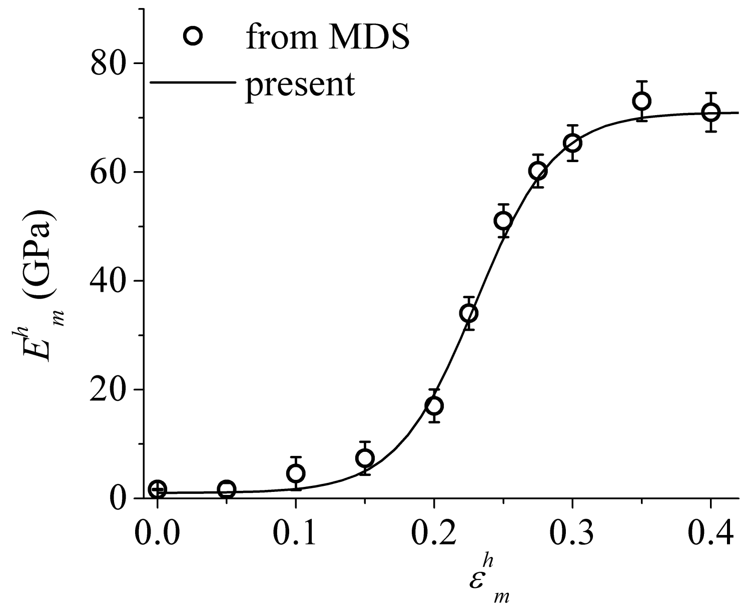


$$\sigma_m(\varepsilon_m) = \frac{\mathcal{F}}{A_m}$$

$$\varepsilon_m = \varepsilon_m^s + \varepsilon_m^h$$

$$E_m(\varepsilon_m) = \frac{E_m^s(\varepsilon_m^s)E_m^h(\varepsilon_m^h)}{E_m^s(\varepsilon_m^s) + E_m^h(\varepsilon_m^h)}$$

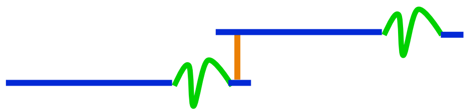




F. Maceri, M. Marino, G. Vairo "Elasto-damage modeling of biopolymer molecules response", *Computer Modeling in Engineering and Sciences* 87, 2012

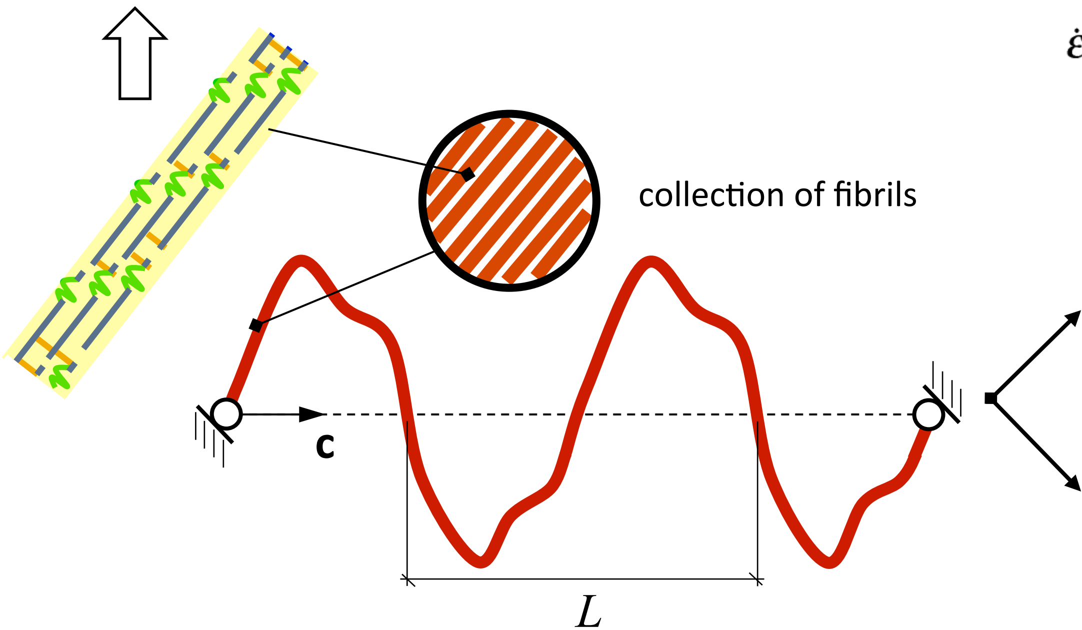
NANO-MICRO-MACRO MODEL

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



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

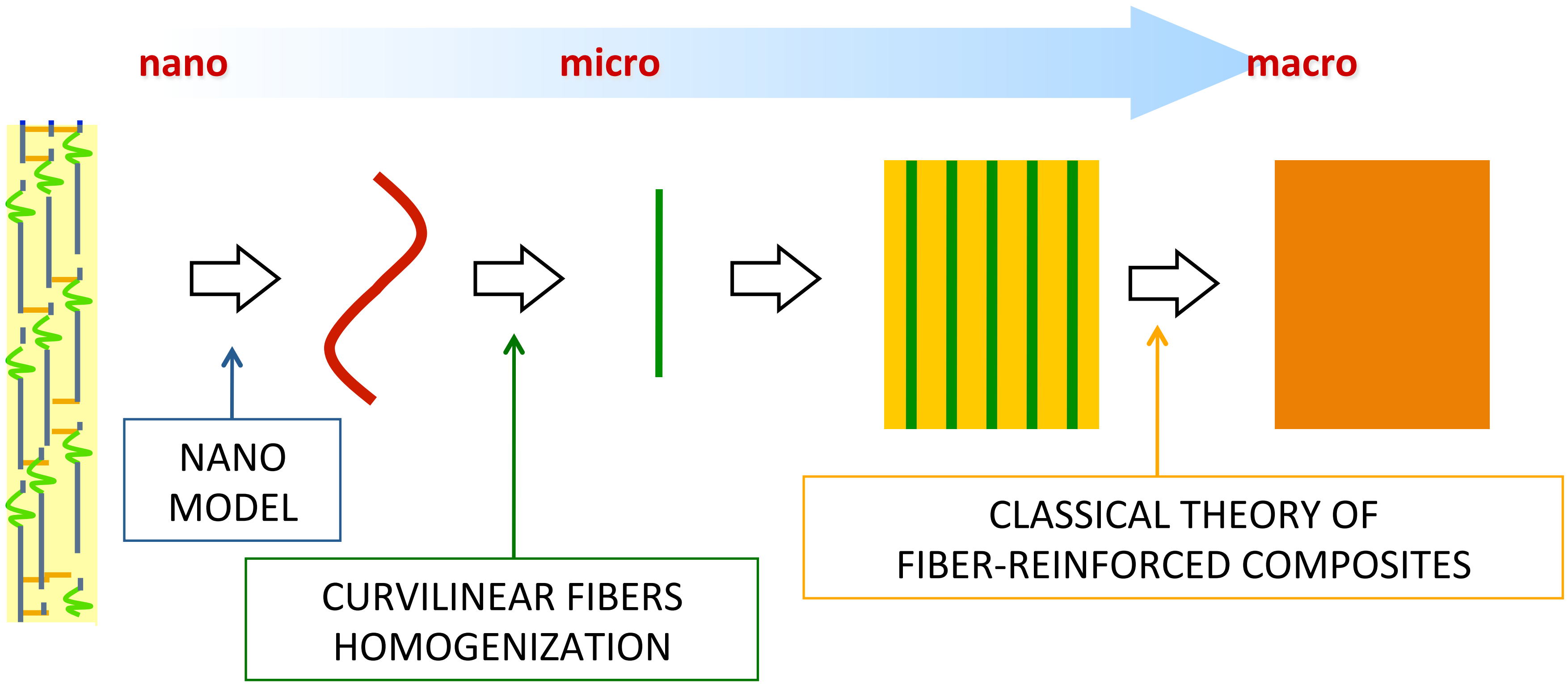
GEOMETRIC NON-LINEARITIES

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

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.

NANO-MICRO-MACRO MODEL



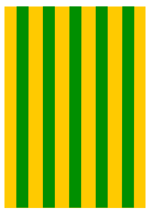
NANO-MICRO-MACRO MODEL

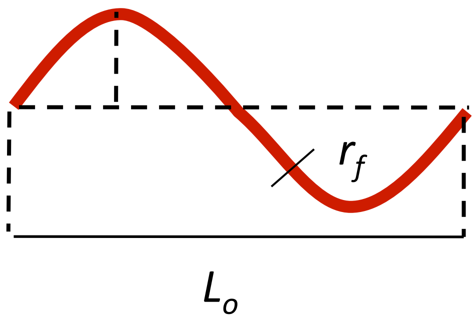
Few parameters, experimentally measurable

$$\underbrace{V_f \quad E_M}_{\text{MACRO}}$$

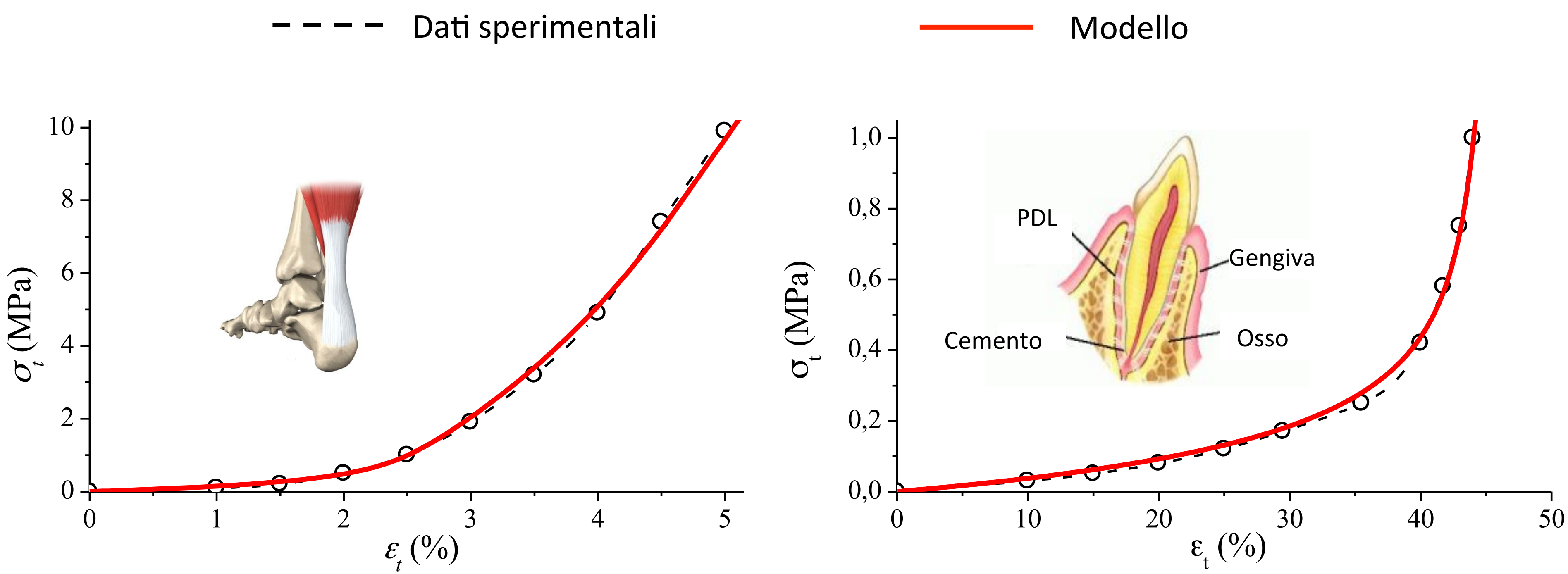
$$\underbrace{r_f \quad L_o \quad H_o}_{\text{MICRO}}$$

$$\underbrace{\lambda k_{cl} \ \text{Molecular parameters}}_{\text{NANO}}$$





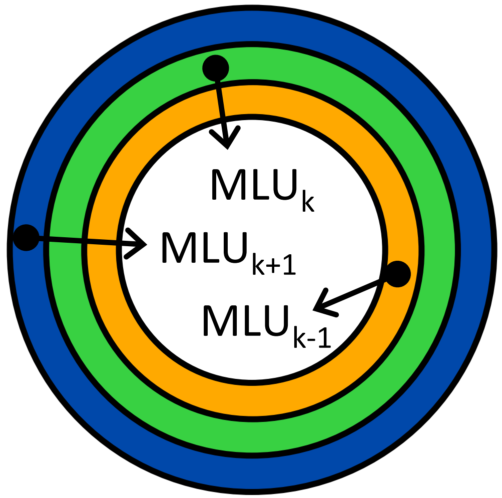
NANO-MICRO-MACRO MODEL: RESULTS



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

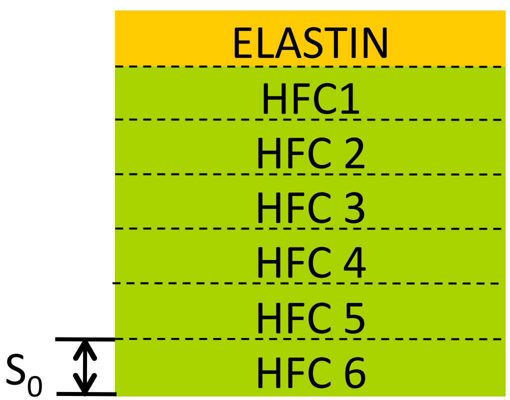
AORTIC MODEL: MULTISCALE STRUCTURAL APPROACH

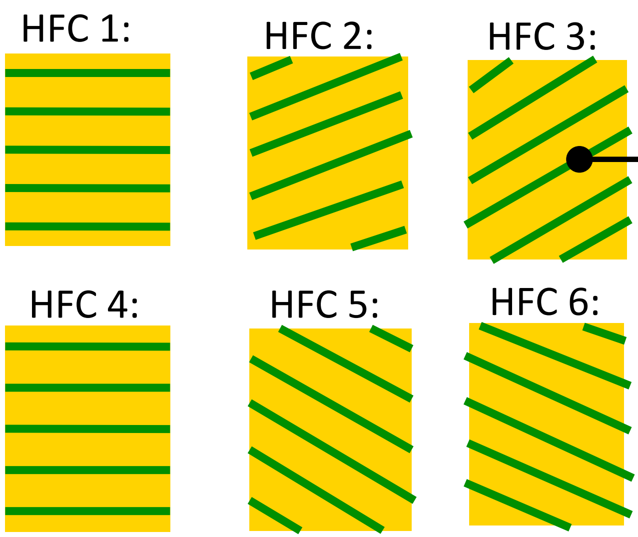
- Multi-layered thick cyinder
- Each layer is a MLU
- Each MLU is a laminate
- Nano-micro-macro homogenization

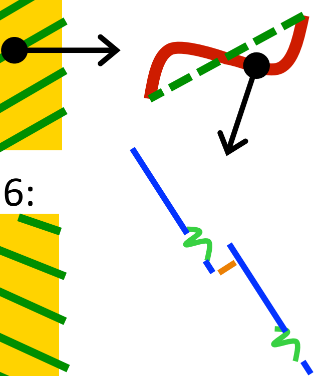


k = 1 ... N

MLU$_k$:

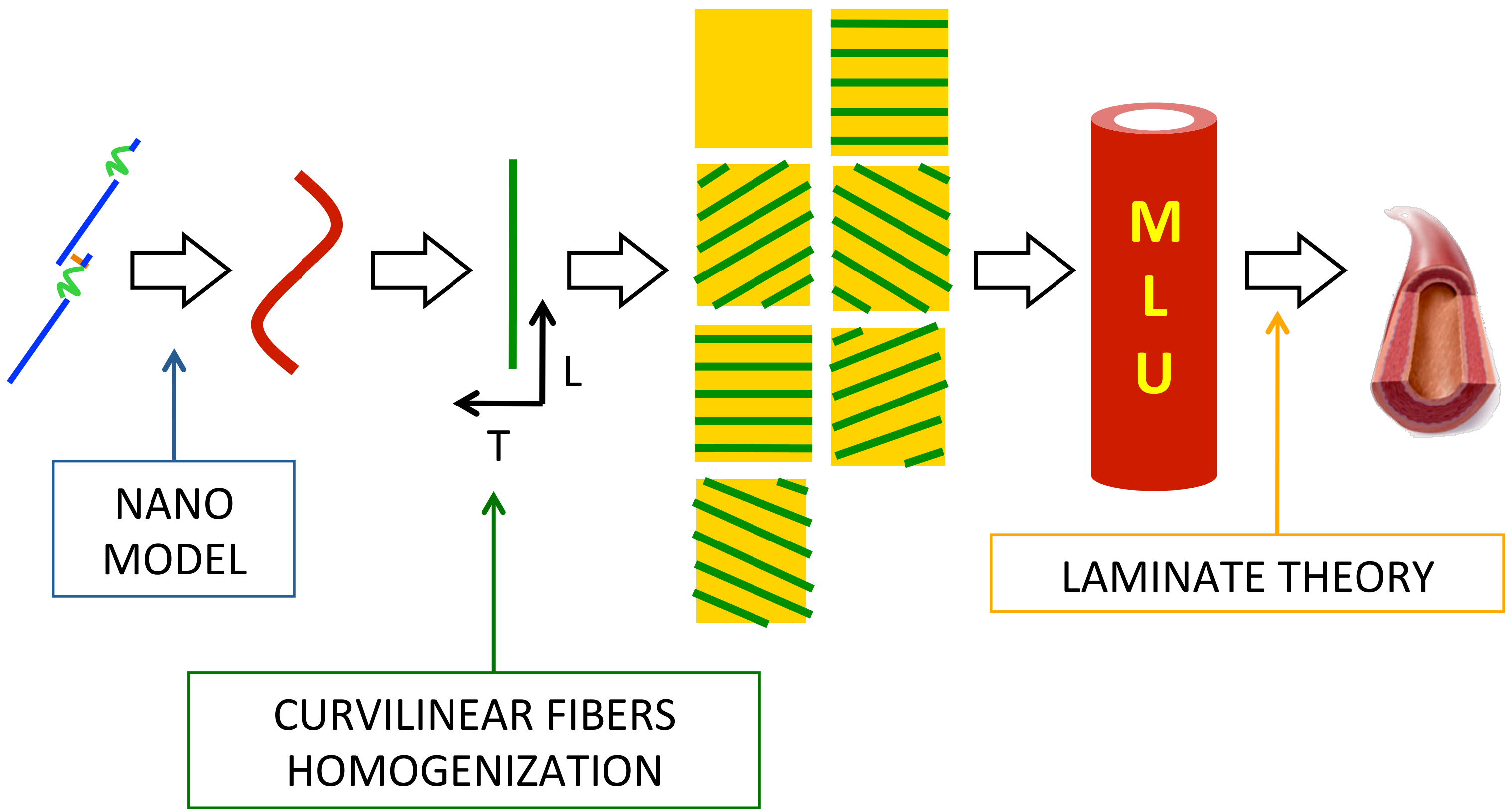






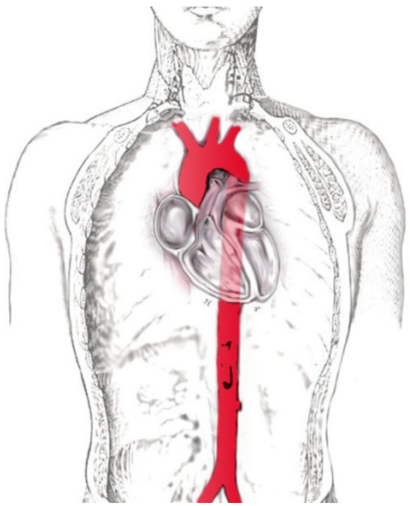
Helically-Arranged-Fiber-Reinforced-Composite-Materials: HFC

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	-

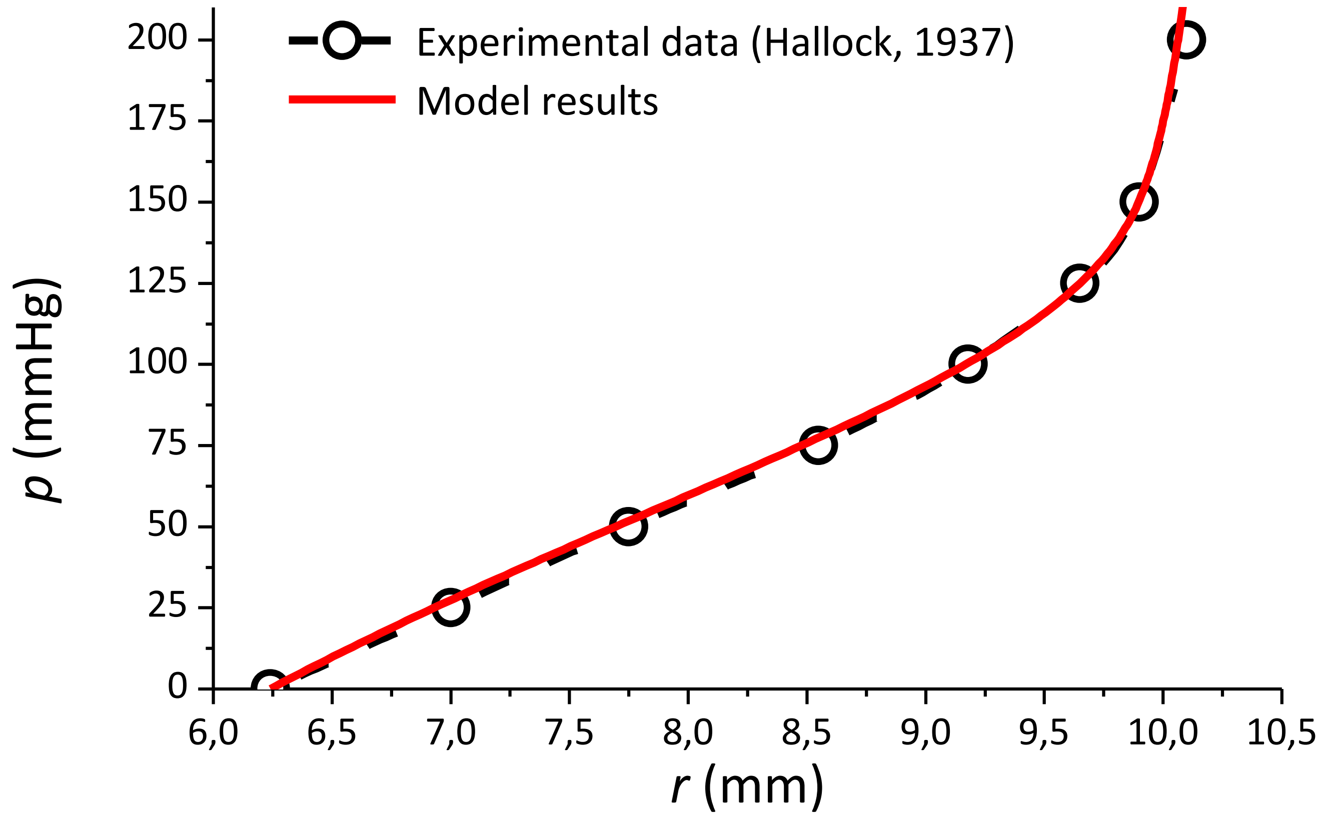
Microscale parameters:

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

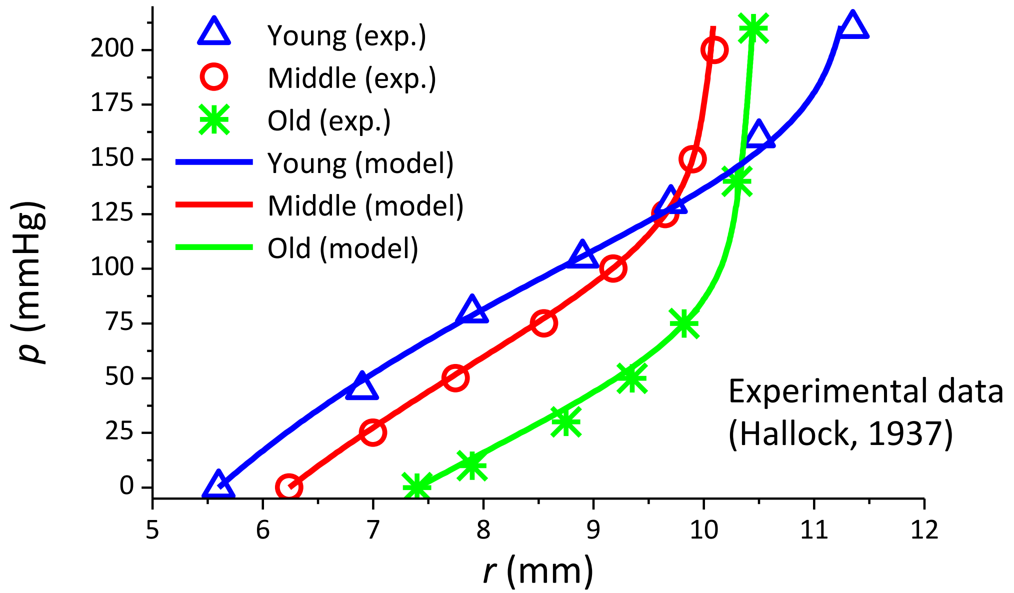
Quantitative and qualitative indications from experimental data:

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

Age-related remodeling

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



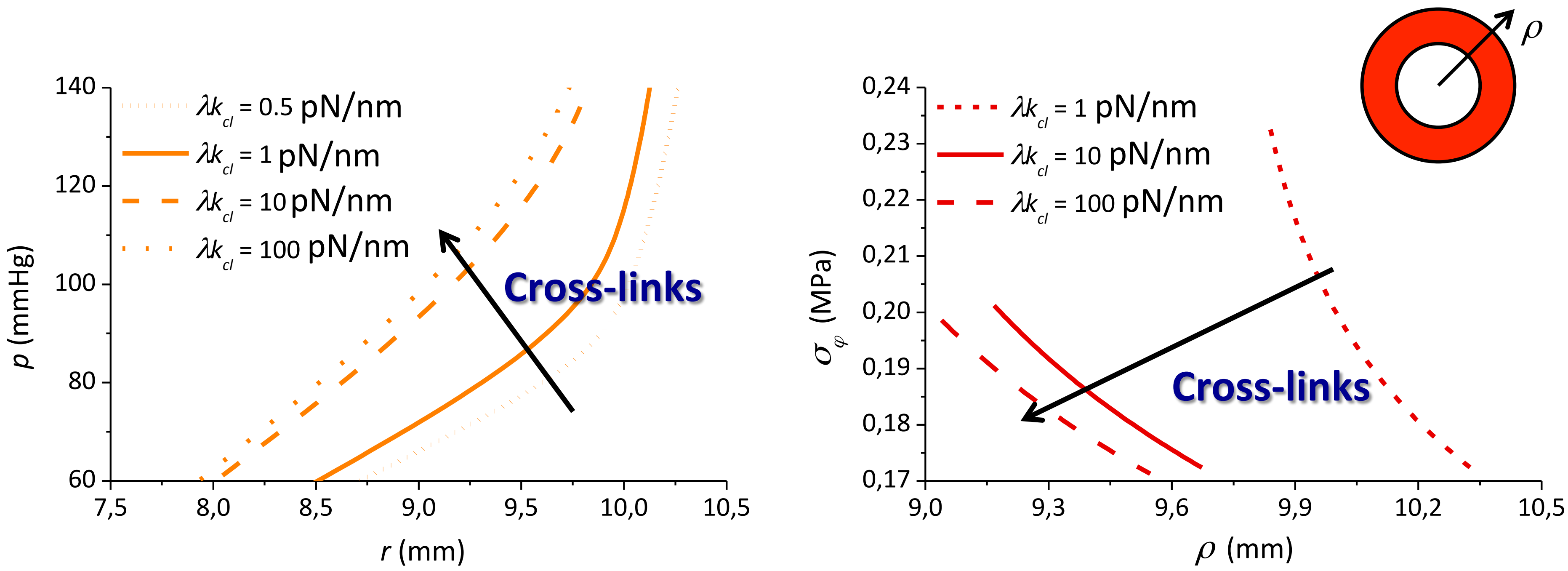
F. Maceri, M. Marino, G. Vairo, "Age-dependent arterial mechanics via a multiscale elastic approach", *International Journal for Computational Methods in Engineering Science and Mechanics* 14, 2013.

AORTIC MODEL: APPLICATIONS

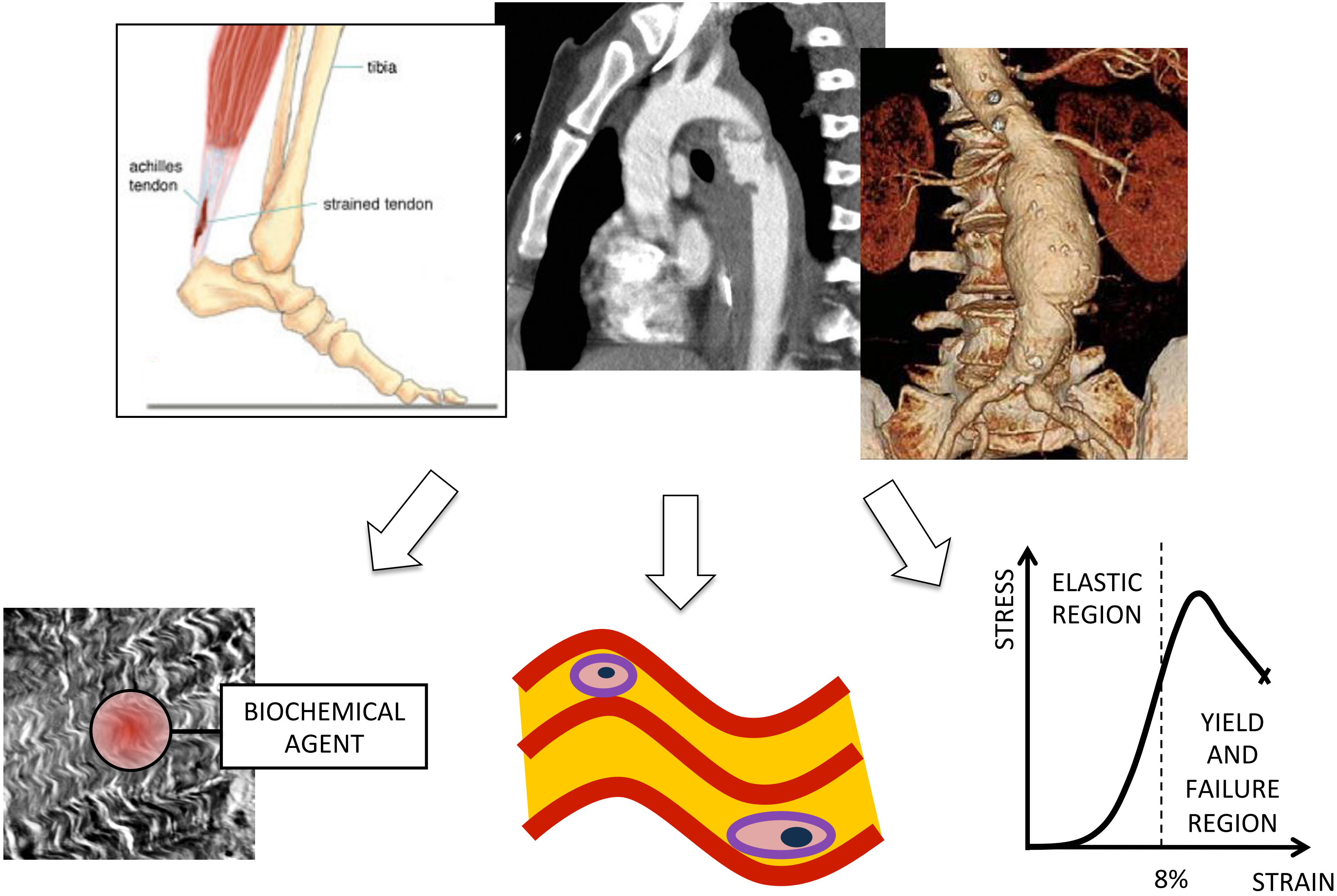
Cross-links reduction →

- Aortic dilation
- Rupture risk

(Bruel et al., 1998)

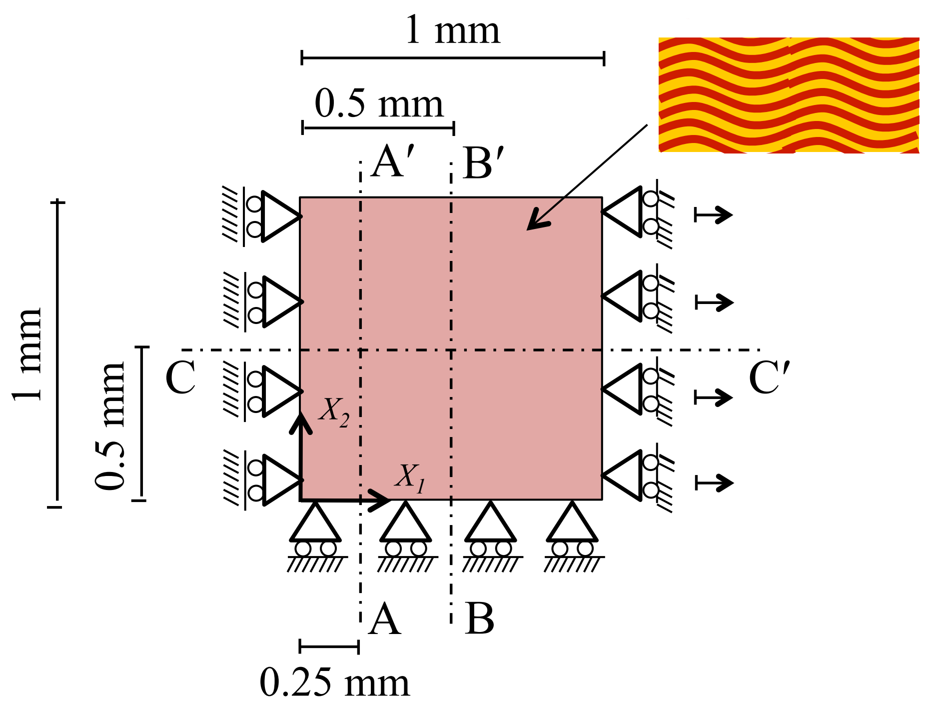


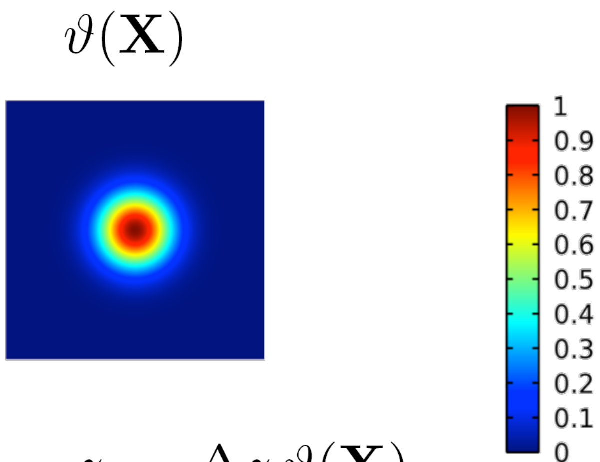
F. Maceri, M. Marino, G. Vairo, "Age-dependent arterial mechanics via a multiscale elastic approach", *International Journal for Computational Methods in Engineering Science and Mechanics* 14, 2013.


tibia
achilles tendon
strained tendon
BIOCHEMICAL AGENT
STRESS
ELASTIC REGION
YIELD AND FAILURE REGION
8%
STRAIN

TISSUE DEFECT

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





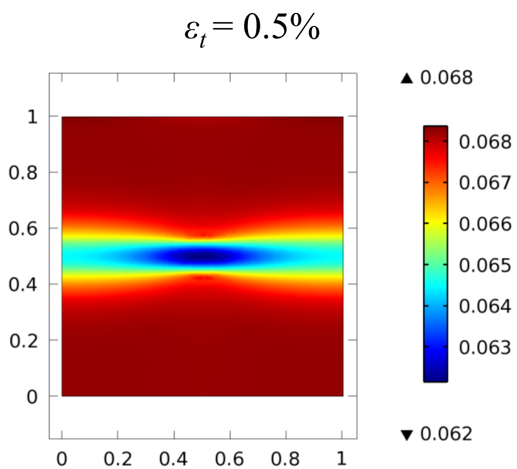
$$z(\mathbf{X}) = z_o - \Delta z\, \vartheta(\mathbf{X})$$

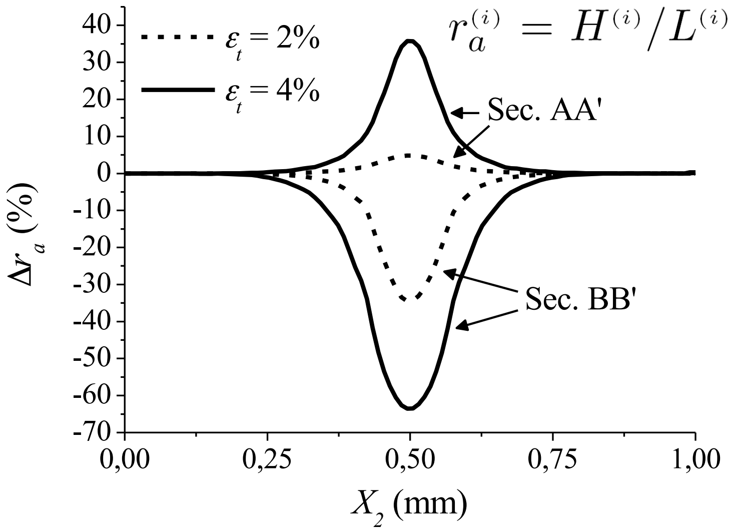
M. Marino, G. Vairo, "Stress and strain localization in stretched collagenous tissues via a multiscale modelling approach", *Computer Methods in Biomechanics and Biomedical Engineering*, published online since 2012.

TISSUE DEFECT

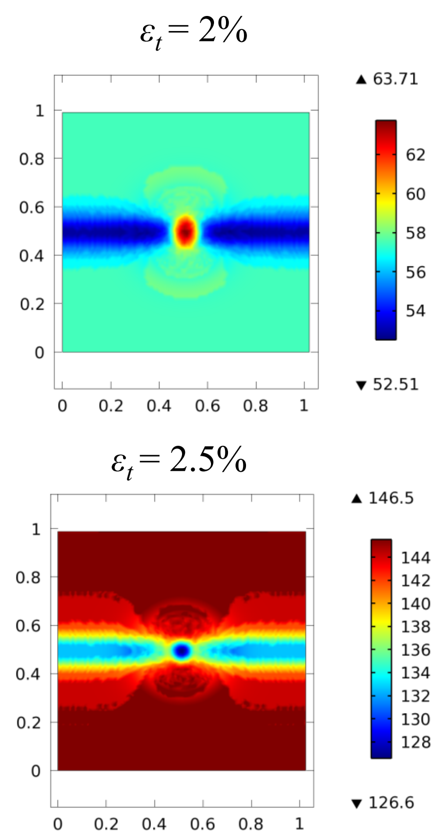
Cross-links density defect: $z = \lambda k_{cl}$

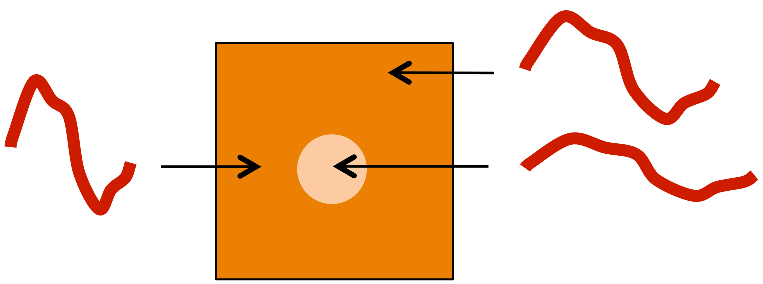
σ_{X_1} (MPa)

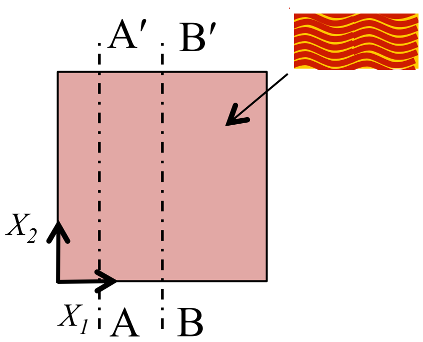




C_{1111} (MPa)

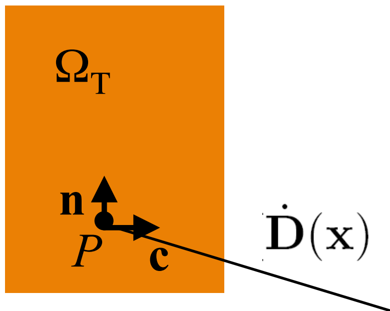






REMODELING

SUBMODELING TECHNIQUE

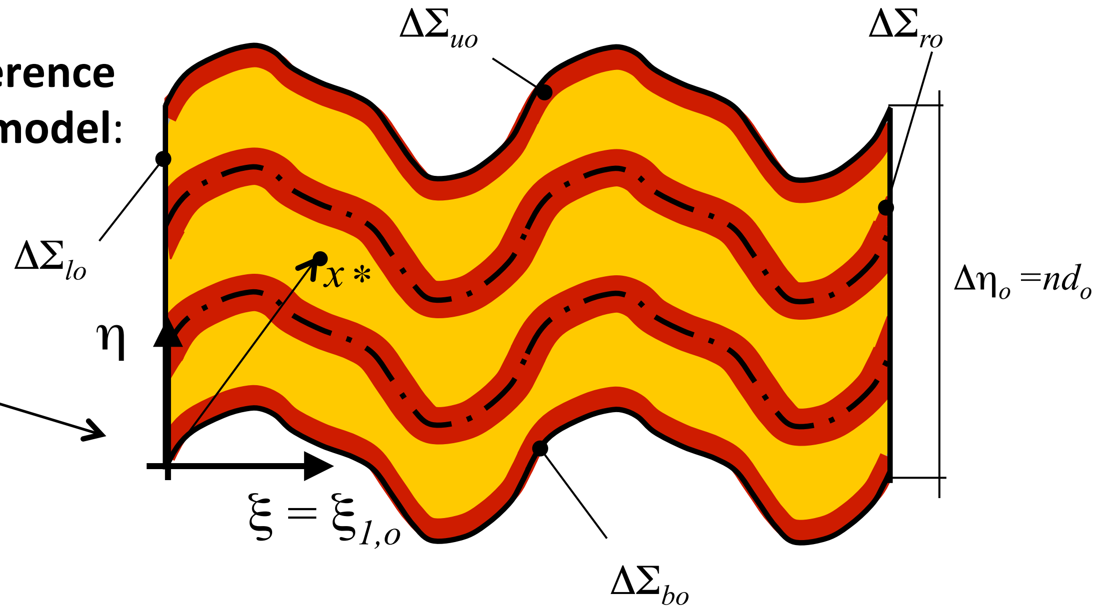


$$d\varepsilon_F = [\dot{\boldsymbol{D}}(\boldsymbol{x})\boldsymbol{c}(\boldsymbol{x})]\cdot \boldsymbol{c}(\boldsymbol{x})\ d\tau$$

$$d\gamma_F = 2[\dot{\boldsymbol{D}}(\boldsymbol{x})\boldsymbol{c}(\boldsymbol{x})]\cdot \boldsymbol{n}(\boldsymbol{x})\ d\tau$$

$$d\varepsilon_N = [\dot{\boldsymbol{D}}(\boldsymbol{x})\boldsymbol{n}(\boldsymbol{x})]\cdot \boldsymbol{n}(\boldsymbol{x})\ d\tau$$

Reference submodel:



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

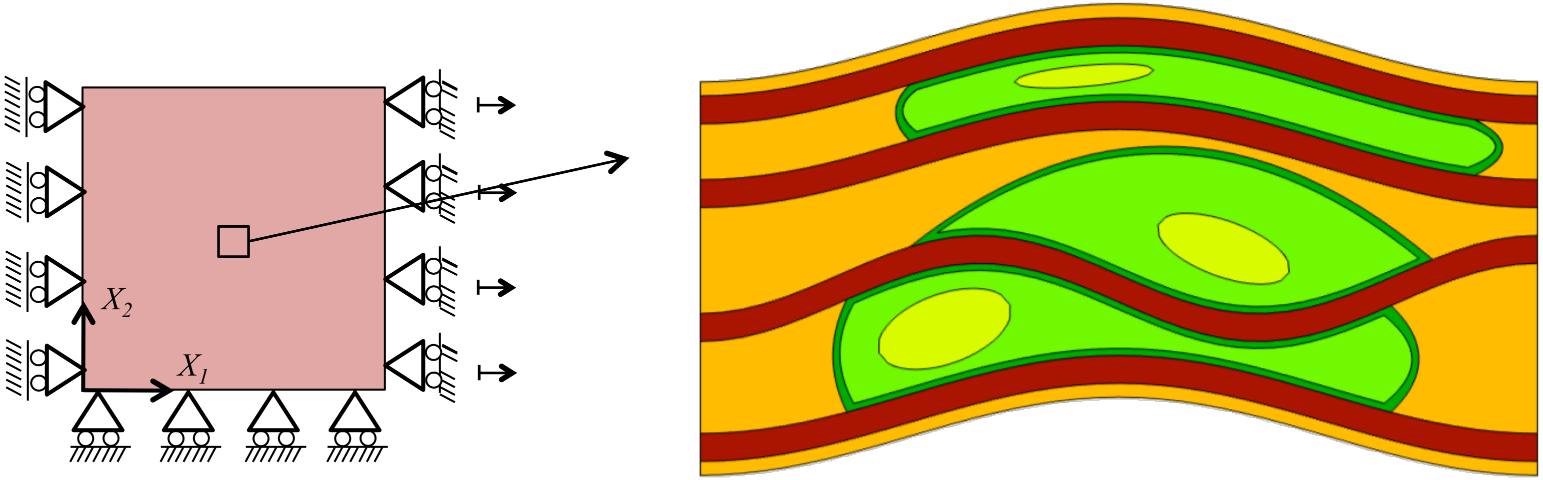
B.C.

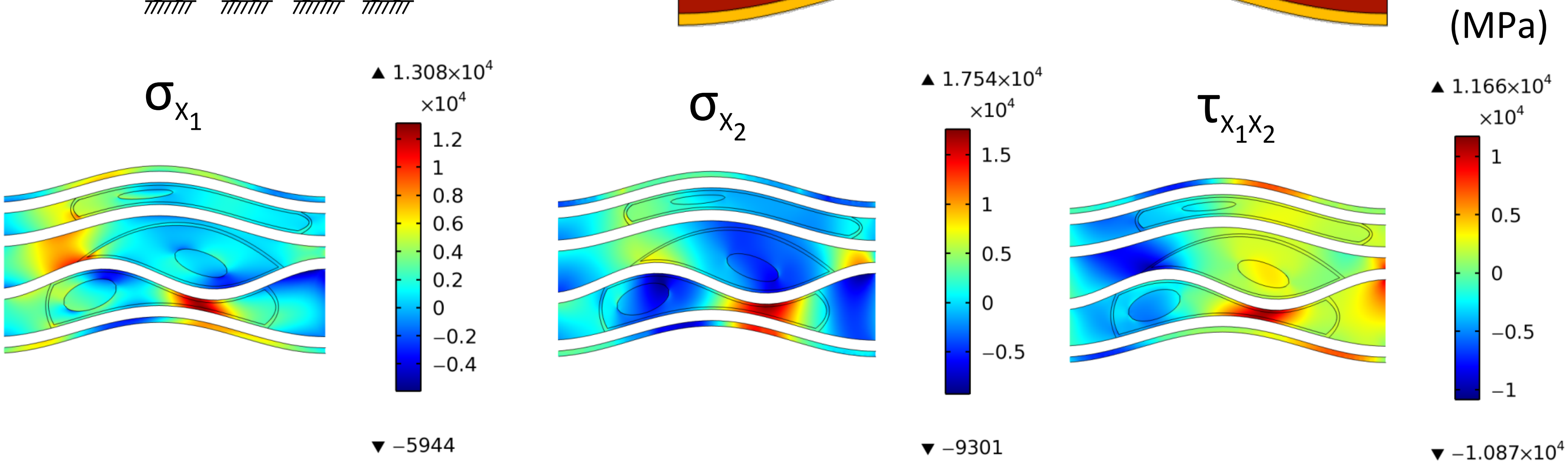
$$\dot{\mathbf{u}}^*(\mathbf{x}^*) = \dot{\mathbf{u}}^{*(d\varepsilon_F)} + \dot{\mathbf{u}}^{*(d\gamma_F)} + \dot{\mathbf{u}}^{*(d\varepsilon_N)} \quad \text{on } \Delta\Sigma_T$$

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.

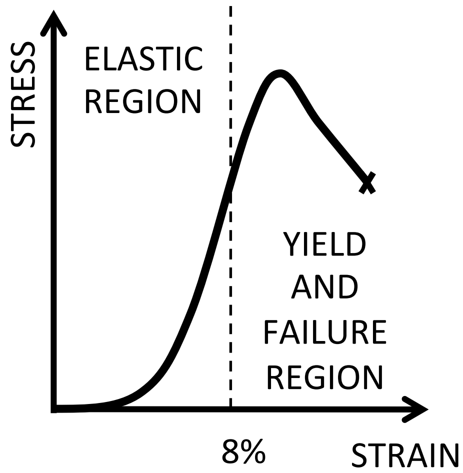
REMODELING

SUBMODELING TECHNIQUE



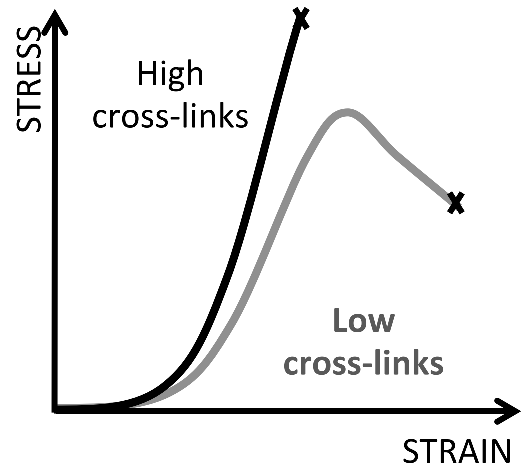


INELASTIC MECHANISMS

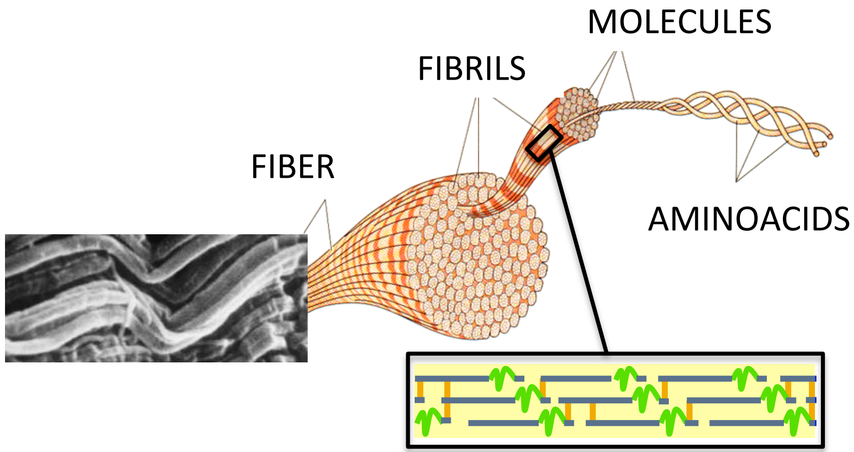


SOFTENING

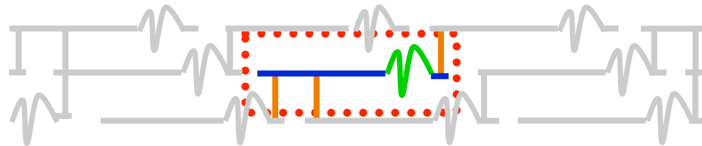
RESIDUAL STRAIN



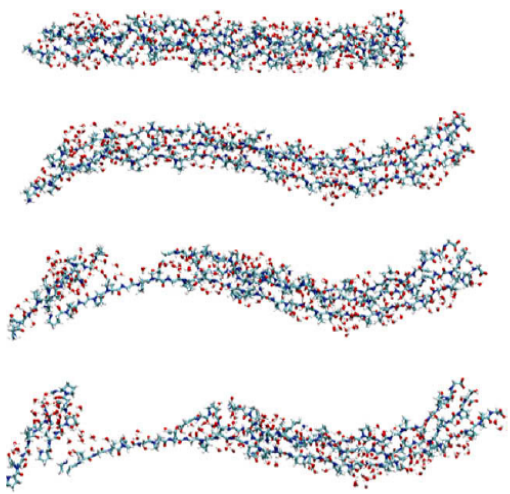
MULTISCALE DEPENDENCE



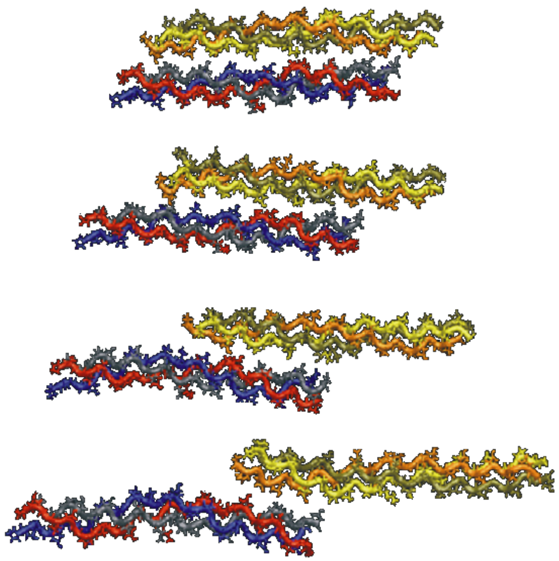
INELASTIC MECHANISMS



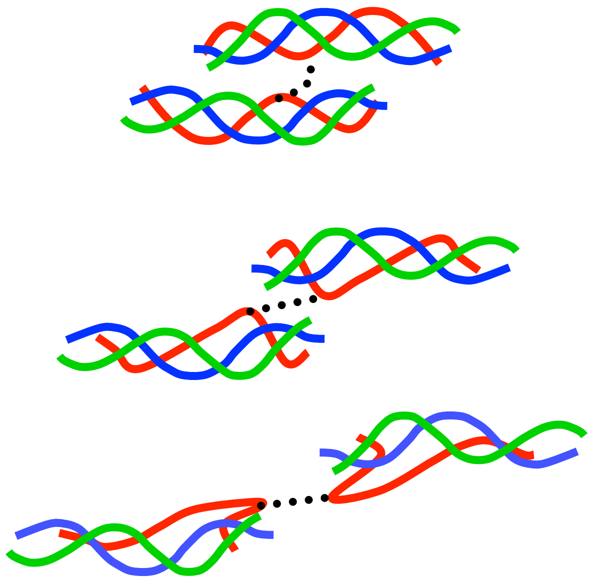
Molecular crack



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

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

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

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

Constitutive laws

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

GOVERNING EQUATIONS

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

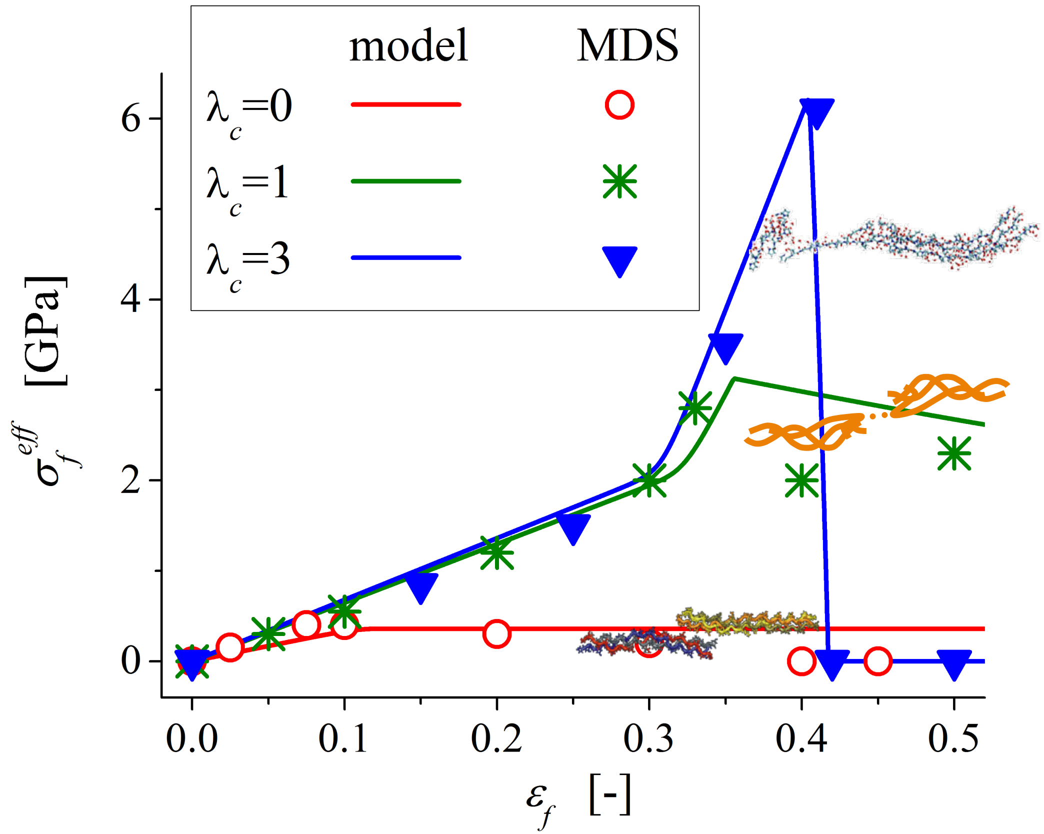
INELASTIC MECHANISMS

COUPLED MULTISCALE MECHANISMS

Softening/brittle failure

Dependence on nanoscale quantities

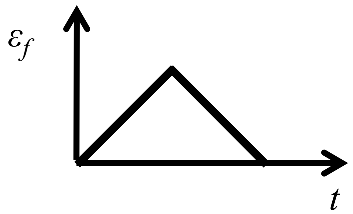
Svensson RB, Mulder H, Magnusson SP (2013) Fracture mechanics of collagen fibrils: influence of natural cross-links. *Biophysical Journal* 104:2476-2484



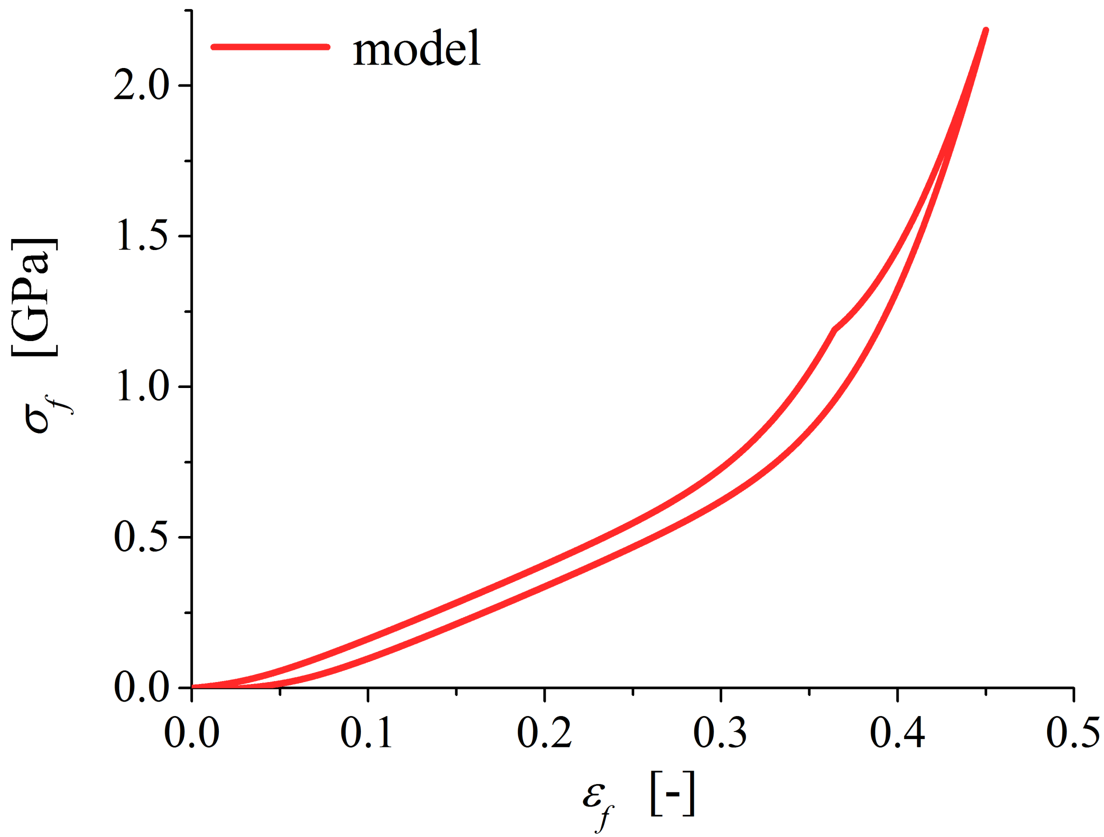
Uzel S, Buehler MJ (2011) Molecular structure, mechanical behavior and failure mechanism of the C-terminal cross-link domain in type I collagen. *Journal of the Mechanical Behavior of Biomedical Materials* 4:153-161

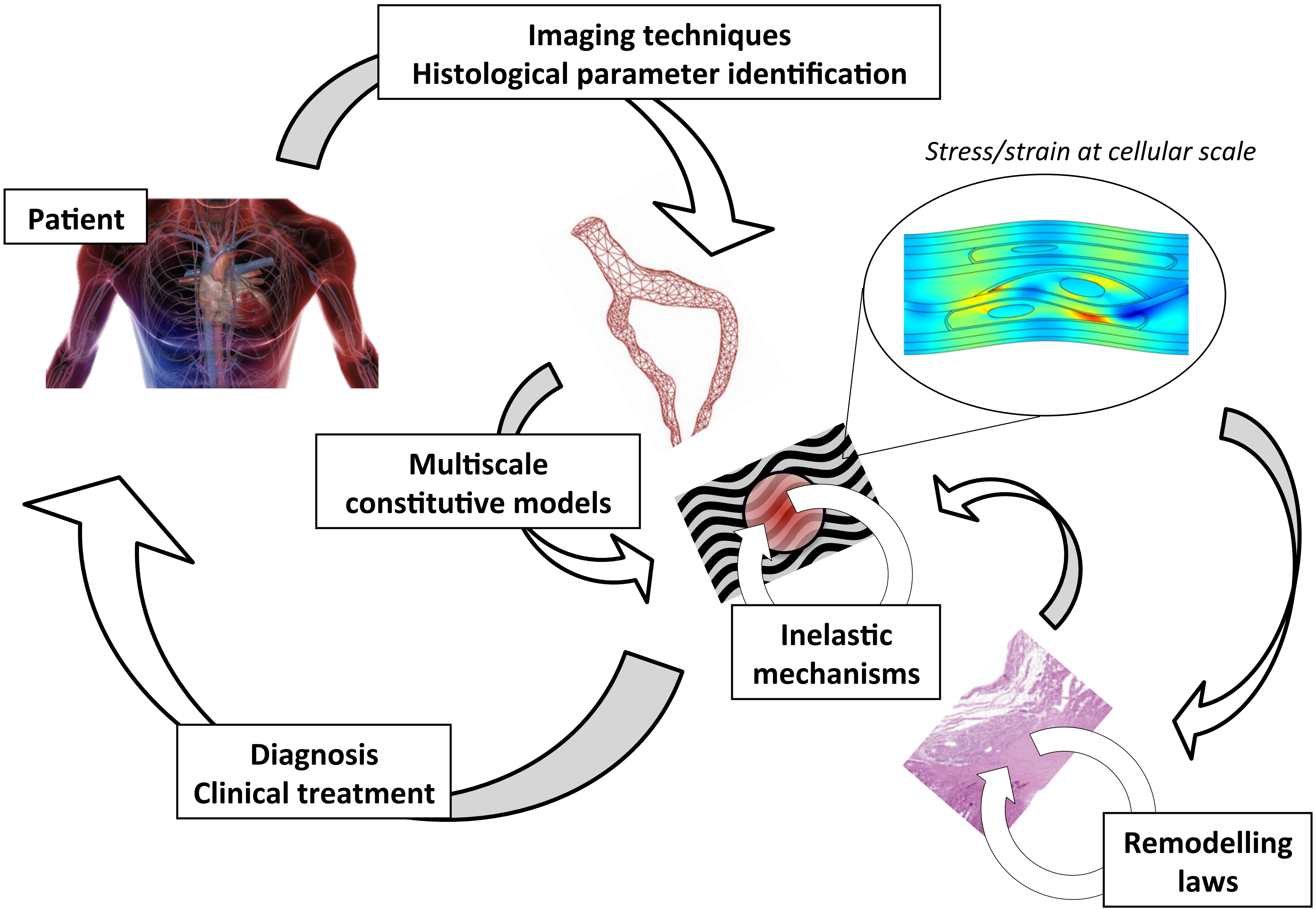
INELASTIC MECHANISMS

Loading-unloading test



Residual strain




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

PRIN Project: Advanced mechanical modeling of new materials and technologies for the solution of 2020 European challenges

Target problem: *Health care devices to treat cardiovascular pathologies* (UNIROMA2 research unit)

Contacts: *Michele MARINO*, PhD, MSc
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University of Rome “Tor Vergata”
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Tel: +39 06 7259 7016