BioMechanics
Nonlinear constitutive response of human tissues

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Meccanica dei Materiali e della Frattura
Complementi di Scienza delle Costruzioni
Biomechanics?

“Biomechanics is the study of the structure and function of biological systems by means of the methods of mechanics” (1974)

Gustav Eiffel (1832-1923)

Garabit Viaduct
The railroad engineer Karl Culmann (1821-1881) and the anatomist Hermann von Meyer (1801-1869) analyzed the stress patterns in a human femur.

Julius Wolff (1836-1908) introduced the first law of bone remodeling, opening the door to the modern orthopedic medicine...
Why study BioMechanics
understanding to understand
understanding to enhance environmental health
Multiscale hierarchical mechanics in soft tissues

Soft tissues are throughout the whole human body and they include tendons, ligaments, skin, fibrous tissues, muscles and blood vessels. They link, support, and are part of other bio-structures and organs, playing a key role in the biomechanics of many body systems (e.g., musculo-skeletal, cardiovascular).
Collagen is the most abundant protein of the human body

Stiffness and strength features in soft tissues mainly depend on the arrangement and the amount of collagen, which is organized in agreement with a precise hierarchical multiscale scheme.
Stiffness and strength features in soft tissues mainly depend on the arrangement and the amount of collagen, which is organized in agreement with a precise hierarchical multiscale scheme.
For instance, in the case of a uni-directional tissue subjected to a uni-axial tensile test along the fiber direction, a progressive fiber straightening and the disappearance of nanoscale kinks within molecules are experienced, resulting in an increase of the overall tissue stiffness.
State of the art

At the macroscopic level, several constitutive models for collagen-rich tissues can be found in the specialized literature. Most of them are deduced from phenomenological evidences and generally employ exponential and power-law functions, based on parameters having no direct physical or morphological meaning.

Other approaches, namely structural approaches, aim to link model parameters with structural properties of the tissue, either by micro–macro homogenization techniques, describing effects related to collagen fibers as linearly elastic, or by assuming an orthotropic hyper-elastic macroscopic behavior, accounting for the main constituents of the tissue and for some microscale features.

…… any direct relationship with the molecular scale is usually neglected and the corresponding models are not able to give predictive indications on nanoscale effects, that probably play the most important role in many diseases…..

\[
\Psi(C) = \Psi_m(C) + \Psi_f(C)
\]

Holzapfel et al., 2000

\[\frac{k_1}{2k_2} \{\exp[k_2(J_4^{(a)} - 1)^2] - 1\}\]

Balzani et al., 2006

\[\alpha_1 (J_4^{(a)} - 1)^{\alpha_2}\]

\[S = 2 \frac{\partial \Psi}{\partial C}\]

\[C = F^T F\]

\[M := a \otimes a\]

\[J_4 := \text{tr}[CM]\]
Fibers are assumed to be embedded into a linearly elastic isotropic matrix. Neglecting any fiber–matrix interaction effect, crimped fibers are reduced to equivalent reinforcing straight fibers, exhibiting an elastic transversally isotropic behavior with the symmetry axis coincident to the fiber-chord direction.

A collagen fiber is modeled as a homogeneous beam with a circular cross-section of constant radius and with a periodic planar centerline. The tangent elastic modulus of the fiber material along the direction perpendicular to the fiber cross-section is determined via a variational approach.
Dati sperimentali

$E_c = 0.2 \text{ GPa}$

$E_c = 0.5 \text{ GPa}$

$E_c = 1 \text{ GPa}$

---

Dati sperimentali

- Sintesi: Micro-macro
Experimental data

- $E_c = 0.2 \text{ GPa}$
- $E_c = 0.5 \text{ GPa}$
- $E_c = 1 \text{ GPa}$

Micro-macro

Nanoscale structures and nanoscale mechanisms are fundamental
Multiscale homogenization approach

Crimped fibers model

$\lambda_F$
Collagen fibrils are modelled as long right cylinders. Let \( f \) be the fibril axis direction. From a computational point of view, fibrils are thought as a collection of identical one-dimensional molecules, with axis aligned along \( f \) and mutually interacting through identical cross-links, which connect pairs of adjacent molecules.
Multiscale homogenization approach
Dati sperimentali

\( E_c = 0.2 \) GPa

\( E_c = 0.5 \) GPa

\( E_c = 1 \) GPa

Only microscale effects…
Experimental data and model

nanoscale structures and nanoscale mechanisms are fundamental
Molecular collagen parameters are the same
The puzzle:
“Our understanding of aortic diseases continues to advance as new partnerships between surgeons, biologists, engineers and mathematicians [...].”

From Biomechanics and Pathobiology of Aortic Aneurysms
by J.A. Phillipi, S. Pasta and D.A. Vorp
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
Aim
Understand **physiological** and **pathological** mechanism to improve diagnosis and therapy

Specific target
Instruct the **computational model** of an aneurysmatic arterial segment with histological/biochemical info

How
Development of a computational model with:
- Patient-specific geometry
- Advanced multiscale constitutive description
- Fluid-structure interaction (FSI)
Computational approach

CT Images → Solid Domain → Fluid Domain → Fluid-Structure Interaction → Multiscale homogenisation → Clinical Insights

- Fibrils
- Fibers
- MLU
- Aortic tissue

\[ Q_{IN} \]

\[ \begin{align*}
\dot{p} & = - \frac{1}{R_p} p - \frac{1}{C} p_c + \frac{1}{R_d} (p_c - \bar{p}) \\
\end{align*} \]
Blood flow model

Incompressible Newtonian Fluid

\[
\begin{align*}
\rho_f \frac{\partial \mathbf{v}_f}{\partial t} + \rho_f (\mathbf{v}_f \cdot \nabla) \mathbf{v}_f - \nabla \cdot \sigma_f &= 0, \\
\nabla \cdot \mathbf{v}_f &= 0 \\
\sigma_f &= 2\mu_f \text{Sym} (\nabla \mathbf{v}_f) - p_f \mathbf{I}
\end{align*}
\]

in \( \Omega_f(t) \),

Initial and boundary conditions

\[
\begin{align*}
\mathbf{v}_f(\bar{x}, \bar{t}) &= \bar{\mathbf{v}}_f(\bar{x}) \quad \text{in} \ \Omega_f(t) \\
p_f(\bar{x}, \bar{t}) &= \bar{p}_f(\bar{x}) \quad \text{in} \ \Omega_f(t)
\end{align*}
\]

\[
\begin{align*}
\mathbf{v}_f(\mathbf{x}, t) &= -\frac{Q_{IN}(t)}{A^+} n_{\Sigma_f}(\bar{\mathbf{x}}, \bar{t}) \quad \text{on} \ \Sigma_f^+(t) \\
\mathbf{v}_f(\mathbf{x}, t) &= 0 \quad \text{on} \ \Sigma_f^-(t) \\
p_f(\mathbf{x}, t) &= \hat{p}(t) \quad \text{on} \ \Sigma_f^-(t)
\end{align*}
\]

Three-element Windkessel circuit

\[
\begin{align*}
Q_{OUT}(t) &= \frac{p_c(t)}{R_d} + C \frac{dp_c(t)}{dt} \\
\hat{p}(t) &= Q_{OUT}(t) R_p + p_c(t)
\end{align*}
\]
Computational approach

CT Images → Solid Domain

Multiscale homogenisation

Fibrils → Fibers

MLU

Aortic tissue

Fluid-Structure Interaction

Fluid Domain

Clinical Insights

\( Q_{IN} \)

\( p \)

\( p_c \)

\( R_p \)

\( C \)

\( R_d \)
Structural model

Updated-Lagrangean approach
\[ t_s^k = \bar{t} + (k - 1) d\tau_s, \quad \mathbf{x}_s^k = \mathbf{x}_o + \mathbf{u}_s(\mathbf{x}_o, t_s^k) \]

Incremental structural problem
\[
\begin{align*}
\nabla \cdot d\mathbf{\sigma}_s(\mathbf{x}_s^k, t_s^k) &= 0 \\
\tau(d\mathbf{D}(\mathbf{x}_s^k, t_s^k)) &= \text{Sym}(d\mathbf{H}(\mathbf{x}_s^k, t_s^k)) \quad \text{in } \Omega_s(t_s^k) \\
d\mathbf{\sigma}_s(\mathbf{x}_s^k, t_s^k) &= \mathbf{C}(\mathbf{x}_s^k, t_s^k) d\mathbf{D}(\mathbf{x}_s^k, t_s^k) \\
\mathbf{u}_s(\mathbf{x}_o, t_s^k) &= \mathbf{u}_s(\mathbf{x}_o, \bar{t}) + \sum_{j=1}^{k-1} d\mathbf{u}_s(\mathbf{x}_o^j, t_s^j)
\end{align*}
\]

Boundary conditions
\[
\begin{align*}
\tau(d\mathbf{\sigma}_s(\mathbf{x}_s^k, t_s^k) n_{\Sigma s}(\mathbf{x}_s^k, t_s^k)) &= d\mathbf{p}_s(\mathbf{x}_s^k, t_s^k) \quad \text{on } \Sigma^i(t_s^k) \\
\tau(d\mathbf{\sigma}_s(\mathbf{x}_s^k, t_s^k) n_{\Sigma s}(\mathbf{x}_s^k, t_s^k)) &= \mathbf{K}^e d\mathbf{u}_s(\mathbf{x}_s^k, t_s^k) \quad \text{on } \Sigma^e(t_s^k) \\
\tau(d\mathbf{\sigma}_s(\mathbf{x}_s^k, t_s^k) n_{\Sigma s}(\mathbf{x}_s^k, t_s^k)) &= \mathbf{K}^\pm d\mathbf{u}_s(\mathbf{x}_s^k, t_s^k) \quad \text{on } \Sigma^\pm(t_s^k)
\end{align*}
\]

Constitutive law
\[ \mathbf{C}(\mathbf{x}, t) = \mathbf{C}(\mathbf{x}_\Gamma + s \mathbf{n}(\mathbf{x}_\Gamma, t), t) = \tilde{\mathbf{C}}(\mathbf{x}_\Gamma, \mathbf{D}(\mathbf{x}_\Gamma, t), \mathcal{S}(\mathbf{x}_\Gamma)) \quad \text{Nonlinearly Elastic Anisotropic} \]
Multiscale homogenization approach

\[ \sigma_C(\lambda_4) = \int_1^{\lambda_4} \frac{E_F(\eta)}{\eta} d\eta \]

\[ E_F = \frac{3\mu_F r_F^2 \ell_F (H_F^2 + \ell_F^2) E_f}{H_0^2 + \ell_0^2 (4H_F^4 + 3\ell_F^2 r_F^2 + 4H_F^2 \ell_F^2)} \]

\[ \frac{\partial H_F}{\partial \lambda_F} = -\frac{2H_F \ell_F \ell_o (H_F^2 + \ell_F^2)}{\lambda_F (4H_F^2 + 3\ell_F^2 r_F^2 + 4H_F^2 \ell_F^2)} \]

\[ \lambda_f = \sqrt{\frac{H_F^2 + \ell_F^2}{H_0^2 + \ell_0^2}} \]

**fibers**

\[ E_f(\lambda_f) = \mu_f \left[ \frac{1}{E_m(\lambda_m(\lambda_f))} + \frac{A_m}{\Lambda_c k_c \ell_m o_m} \right]^{-1} \]

\[ \frac{\partial \lambda_m}{\partial \lambda_f} = \frac{E_f(\lambda_f)}{\mu_f E_m(\lambda_m(\lambda_f))} \]

**fibrils**

\[ E_m(\lambda_m) = \frac{E^s_m(\lambda_s^s(\lambda_m))E^h_m(\lambda_h^h(\lambda_m))}{E^s_m(\lambda_s^s(\lambda_m)) + E^h_m(\lambda_h^h(\lambda_m))} \]

\[ E^s_m(\lambda_s^s(\lambda_m)) = \frac{k_B T \ell_{m,o}}{\ell_p \ell_c A_m} \left\{ \frac{\ell_c^3}{2[\ell_c - \ell_{m,o} \lambda_m^s]^3} + 1 \right\} \]

\[ \frac{\partial \lambda_m^s}{\partial \lambda_m} = \frac{E_m(\lambda_m)}{E^s_m(\lambda_s^s(\lambda_m))} \]

\[ \frac{\partial \lambda_m^h}{\partial \lambda_m} = \frac{E_m(\lambda_m)}{E^h_m(\lambda_h^h(\lambda_m))} \]

\[ E^h_m(\lambda_h^h(\lambda_m)) = \frac{\ell_{m,o}}{\ell_c} \left[ \frac{\hat{E}}{1 + e^{-\eta(\ell_{m,o} \lambda_m^h/\ell_c - \lambda_h^h) + \hat{E}_o}} \right] \]

**molecules**

**Constitutive law**

\[ \mathbb{C}(\mathbf{x}, t) = \mathbb{C}(\mathbf{x}_T + s \mathbf{n}(\mathbf{x}_T, t), t) = \tilde{\mathbb{C}}(\mathbf{x}_T, \mathcal{D}(\mathbf{x}_T, t), S(\mathbf{x}_T)) \] Nonlinearly Elastic Anisotropic
Computational approach

CT Images → Solid Domain → Fluid Domain → Clinical Insights

- Fluid-Structure Interaction
- Multiscale homogenisation
  - Molecules
  - Fibrils
  - Fibers
  - MLU
- Aortic tissue

$p$, $p_c$, $R_p$, $C$, $R_d$
Computational approach

Fluid-structure interaction:
- Internal pressure to the solid domain is computed from the fluid problem
- Fluid domain is updated from displacements computed from the solid problem
Case study

d = 15 cm
\(d_A = 5 \text{ cm}\)
\(\delta = 1 \text{ mm}\)
\(\Delta t = 0.1 s\)
\(\Delta t_f \in [5^{-6}, 10^{-3}] \text{ s}\)
\(\Delta t_s = 0.01 \text{ s}\)

# theraedal element \(\approx 4 \times 10^5\)
average element size \(\leq 1.5 \text{ mm}\)

Computational cost:
20GB of RAM for \(\approx 9\) hours
## Parameter employed in simulation

### Blood flow model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood viscosity</td>
<td>$\mu_f$ [Pa-s]</td>
<td>0.0035</td>
</tr>
<tr>
<td>Blood density</td>
<td>$\rho_f$ [Kg/m$^3$]</td>
<td>1050</td>
</tr>
<tr>
<td>Capacitance left common iliac artery</td>
<td>$C^l$ [cm$^5$/dyne]</td>
<td>$1 \cdot 10^{-4}$</td>
</tr>
<tr>
<td>Distal resistance left common iliac artery</td>
<td>$R^l_d$ [dyne-s/cm$^5$]</td>
<td>$1.35 \cdot 10^4$</td>
</tr>
<tr>
<td>Proximal resistance left common iliac artery</td>
<td>$R^l_p$ [dyne-s/cm$^5$]</td>
<td>600</td>
</tr>
<tr>
<td>Capacitance right common iliac artery</td>
<td>$C^r$ [cm$^5$/dyne]</td>
<td>$1 \cdot 10^{-4}$</td>
</tr>
<tr>
<td>Distal resistance right common iliac artery</td>
<td>$R^r_d$ [dyne-s/cm$^5$]</td>
<td>$1.65 \cdot 10^4$</td>
</tr>
<tr>
<td>Proximal resistance right common iliac artery</td>
<td>$R^r_p$ [dyne-s/cm$^5$]</td>
<td>800</td>
</tr>
</tbody>
</table>

### Structural model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surrounding tissues stiffness constant</td>
<td>$\bar{k}^e$ [N/cm$^3$]</td>
<td>0.1</td>
</tr>
<tr>
<td>End boundaries stiffness constant</td>
<td>$k^\pm$ [N/cm$^3$]</td>
<td>1</td>
</tr>
<tr>
<td>MLUs number</td>
<td>$N$</td>
<td>60</td>
</tr>
<tr>
<td>Number of IL sub-layers per MLU</td>
<td>$N_{IL}$</td>
<td>6</td>
</tr>
<tr>
<td>Aortic thickness</td>
<td>$\delta$ [mm]</td>
<td>1</td>
</tr>
<tr>
<td>Collagen volume fraction</td>
<td>$V_F$ [%]</td>
<td>20.0</td>
</tr>
<tr>
<td>MLU fiber orientation vector</td>
<td>$\theta_F$ [°]</td>
<td>${0, 20, 40, 0, -40, -20}$</td>
</tr>
<tr>
<td>Fiber period</td>
<td>$L_o$ [μm]</td>
<td>5.0</td>
</tr>
<tr>
<td>Fiber radius</td>
<td>$r_F$</td>
<td>$0.04 \cdot L_o$</td>
</tr>
<tr>
<td>Fiber crimp amplitude</td>
<td>$H_o$</td>
<td>$0.3 \cdot L_o$</td>
</tr>
<tr>
<td>Cross-link stiffness density</td>
<td>$\lambda_c k_c$ [pN/nm]</td>
<td>10.0</td>
</tr>
<tr>
<td>Matrix Young modulus</td>
<td>$E_M$ [MPa]</td>
<td>1.0</td>
</tr>
<tr>
<td>Matrix Poisson ratio</td>
<td>$\nu_M$</td>
<td>0.49</td>
</tr>
<tr>
<td>Body temperature</td>
<td>$\theta$ [K]</td>
<td>310</td>
</tr>
<tr>
<td>Molecular cross-sectional area</td>
<td>$A_m$ [nm$^2$]</td>
<td>1.41</td>
</tr>
<tr>
<td>Molecular persistence length</td>
<td>$\ell_p$ [nm]</td>
<td>14.5</td>
</tr>
<tr>
<td>Molecular contour length</td>
<td>$\ell_c$ [nm]</td>
<td>287.0</td>
</tr>
<tr>
<td>Molecular kinks length</td>
<td>$\ell_k$ [nm]</td>
<td>14.0</td>
</tr>
<tr>
<td>Molecular high-strain modulus</td>
<td>$\bar{E}$ [GPa]</td>
<td>80.0</td>
</tr>
<tr>
<td>Molecular low-strain modulus</td>
<td>$\bar{E}_o$ [GPa]</td>
<td>1.0</td>
</tr>
<tr>
<td>Molecular uncoiling resistance</td>
<td>$\eta$</td>
<td>22.5</td>
</tr>
<tr>
<td>Molecular uncoiling strain</td>
<td>$\varepsilon^h_o$</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Computational approach

CT Images

Solid Domain

Fluid Domain

Clinical Insights

Multiscale homogenisation

Fluid-Structure Interaction

Molecules

Fibres

MLU

Aortic tissue
Results

Spatial distribution of:

Fluid pressure
Blood streamline
Displacement norm
Tangent circumferential stiffness

at systolic peak
Results:
Hemodynamics Clinical Quantities - WSS

\[ S(x, t) = - [\sigma_f(x, t) n_{\Sigma_f}(x, t)] \cdot t(\bar{x}_\Gamma(x, t), t) \]  
Wall Shear Stress in the mean direction of the fluid flow
oscillatory shear index

\[
\text{OSI}(\mathbf{x}) = \frac{1}{2} \left( 1 - \frac{\left| \int_0^T S(\mathbf{x}, t) \, dt \right|}{\int_0^T |S(\mathbf{x}, t)| \, dt} \right)
\]
Risk Analysis

\[
TBD_{\Delta T}(x) = \frac{\sum_{j=0}^{J} \hat{S}_j T^{-}(\hat{S}_j)}{\sum_{j=0}^{J} \hat{S}_j \left[ T^{-}(\hat{S}_j) + T^{+}(\hat{S}_j) + T^{0}(\hat{S}_j) \right]}
\]

\[
TBD_N(x) = \frac{\sum_{j=0}^{J} \hat{S}_j N^{-}(\hat{S}_j)}{\sum_{j=0}^{J} \hat{S}_j \left[ N^{-}(\hat{S}_j) + N^{+}(\hat{S}_j) + N^{0}(\hat{S}_j) \right]}
\]
Results:

Structural Mechanics Clinical Quantities - Circumferential strain

\[ \Delta \varepsilon_{\varphi}(x_\Gamma, t) = \frac{1}{\delta(x_\Gamma, t)} \int_0^t \int_{-\delta(x_\Gamma, t)/2}^{\delta(x_\Gamma, t)/2} dD(x_\Gamma + s n(x_\Gamma, t), t) : [k(x_\Gamma, t) \otimes k(x_\Gamma, t)] \, ds \, dt \]

Differential Circumferential Strain
Results

Risk Analysis

Average along-the-thickness amplitude of collagen fibers (normalized to diastolic value)
Conclusions


Conclusions
thank you