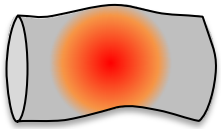
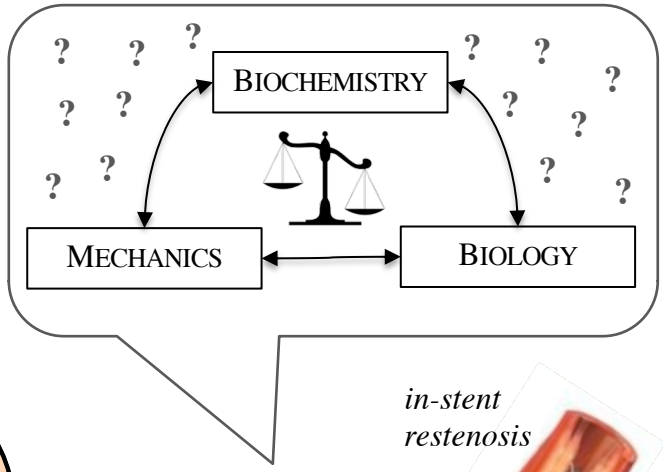
COMPUTATIONAL METHODS
FOR MECHANO-CHEMO-BIOLOGICAL MECHANISMS IN ARTERIES

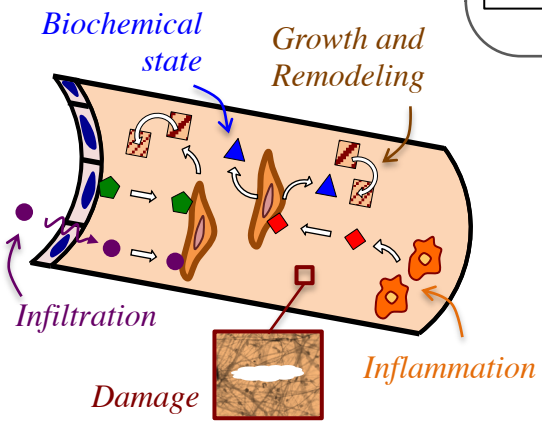


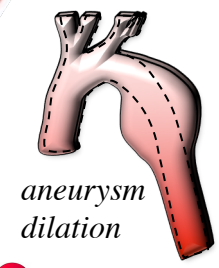


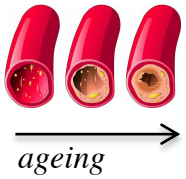
COMETA

- Computational-analytical modelling strategies
- Multiscale and multiphysics mechanisms
- Numerical strategies for coupled problems

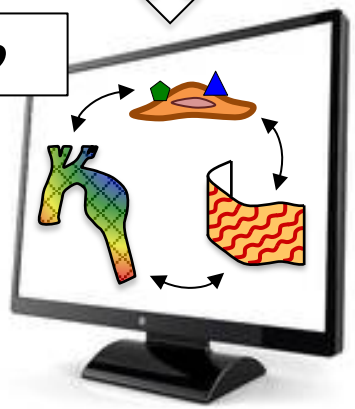
$$\nabla \cdot \boldsymbol{\sigma}(\mathbf{C}, \mathbf{s}) = \mathbf{0}$$
$$\frac{\partial \mathbf{c}}{\partial t} + \nabla \cdot \left(- \mathbb{D} \nabla \mathbf{c} \right) = \mathbf{R}(\mathbf{c}, \mathbf{C})$$
$$\frac{\partial \mathbf{s}}{\partial t} + \nabla \cdot \left(- \mathbb{A} \nabla \mathbf{s} \right) = \mathbf{I}(\mathbf{s}, \mathbf{c})$$







MArCo



Interdisciplinary and industrial applications:

- *In silico* medical research
- Computer-aided design of devices

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Cardiovascular diseases (CVDs) are the leading cause of deaths worldwide, causing 3.9 million deaths in Europe, i.e. 45% of all deaths, and over 1.8 million deaths in the European Union (EU), i.e. 37% of all deaths. Nowadays, CVDs are estimated to cost the EU economy €210 billion a year and these costs are prone to increase with the ageing of the population. Therefore, **novel engineering approaches for personalized medicine arise as urgent needs**.

A major role in the aetiology of CVDs is played by the imbalance of cascades of biochemical reactions involved in cell-cell signalling pathways. The imbalance of these pathways leads to non-physiological concentrations of molecules in tissues. In turn, over- or under-production of active molecules, such as growth factors or enzymes, determine non-functional growth and remodelling (G&R) of tissue constituents. Therefore, **chemo-biological** mechanisms highly affect the **mechanics** of cardiovascular tissues in terms of stiffness, strength and anisotropic properties. In turn, tissue stresses and strains pave the way to biochemical reactions, closing the loop of a refined feedback control system.

Computational approaches have reached limited results in the understanding of the aetiology of CVDs diseases, since reliable only in terms of mechanical quantities (i.e., stresses and strains) in biological structures at a given pathological state. As a consequence, *in silico* analyses are nowadays far from being used in medical research and clinical practice. The term "digital twin" in a biomechanical context is indeed abused, since current approaches do not manage to reproduce the living properties of biological structures. In this context, **COMETA** is motivated by the high need for **renewing the perspective of *in silico* approaches** in biomechanics, which are to-date not effective in accounting for coupled mechano-chemo-biological effects. **COMETA** will contribute in shedding a light on **how arteries evolve in health and disease.**

Challenges are related to the need of coupling very different physical mechanisms, as well as length and time scales:

(i) loads affecting the **mechanics** of arteries (millimetres) vary with the cardiac cycle (seconds);

(ii) the **biochemical environment**, determined by inter-cellular molecular diffusion (micrometres), reaches the steady-state within hours;

(iii) **biological mechanisms in G&R** occur within several days and affect arterial geometry (millimetres), histological features (micrometres) and molecular properties (nanometres).

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MECHANO-CHEMO-BIOLOGICAL METHODOLOGICAL APPROACH

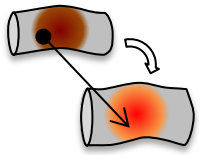
SCALES	*mm*	*μm*	*nm*
seconds	**M**		**C****
hours	**B***	**C**	
days	**B**	**B**	**B**

* Acute inflammations

** Transvascular transport

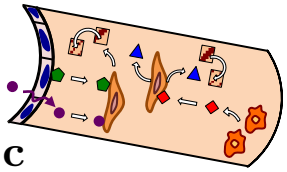
Mechanics

Displacement field **u**



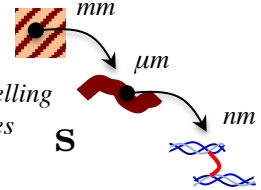
Chemical environment

Molecular concentrations **c**

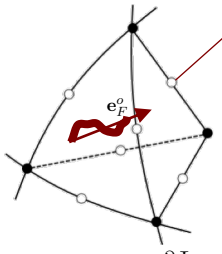


Biological mechanisms

Growth and remodelling of structural features **s**

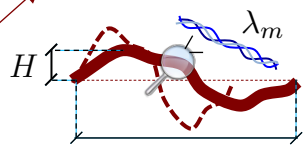


T1) *bioFE*



$$J\boldsymbol{\sigma} = -p\mathbf{I} + 2\mathbf{F}\frac{\partial \Psi_T}{\partial \mathbf{C}}\mathbf{F}^T$$

Analytical Core



$$L = \lambda L_o$$

$$\frac{d}{d\lambda}\begin{pmatrix}\lambda_m \\ H\end{pmatrix} = \mathbf{N}(\lambda_m, H)^*$$

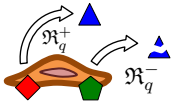
$$\Psi_T = \underline{\alpha_M}\Psi_M(\mathbf{C}) + \underline{\alpha_F}\Psi_F(\lambda_m, H) \Rightarrow \lambda_m(\lambda),\ H(\lambda)$$

Damage variables

*Marino and Wriggers (2017)

T2) *multiT&G&R*

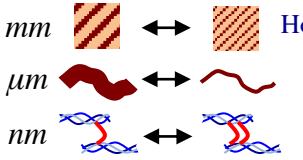
Transport problem



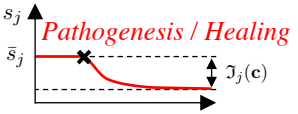
$$\frac{\partial c_q}{\partial t} + \nabla \cdot (-\mathbf{D}_q \nabla c_q + \mathbf{v} c_q) = \mathfrak{R}_q(\mathbf{c}, \mathbf{C})$$

G&R of structural feature s_j

$$\frac{\partial s_j}{\partial t} - \nabla \cdot [\mathbf{A}_j \nabla (s_j - \bar{s}_j)] = -\left(\frac{s_j}{\bar{s}_j + \mathfrak{I}_j(\mathbf{c})} - 1\right)\frac{s_j}{\nu_j}$$



Homeostasis Cell imbalance



T3) *MArCo:* simulation tool

Arterial multiphysics coupled formulation

Displacements
Concentrations
Structure
$\begin{pmatrix}\mathbf{u}\\ \mathbf{c}\\ \mathbf{s}\end{pmatrix}$ ⇨ Balance laws $\begin{pmatrix}\mathcal{L}_u(\mathbf{u},\mathbf{c},\mathbf{s})\\ \mathcal{L}_c(\mathbf{u},\mathbf{c},\mathbf{s})\\ \mathcal{L}_s(\mathbf{u},\mathbf{c},\mathbf{s})\end{pmatrix} = \mathbf{0}$

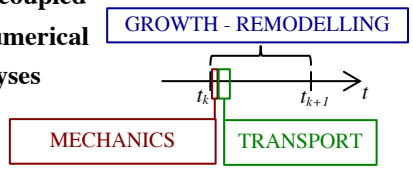
Solution strategies:

fully vs loosely coupled

analytical vs numerical

sensitivity analyses

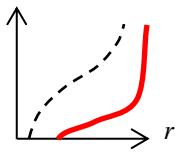
Separation of time scales



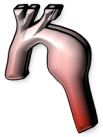
RESULTS

MArCo for…

AGEING



ANEURYSMS



IN-STENT RESTENOSIS

Pathogenesis

Parametric campaigns of *in silico* analyses:

- micro/nano defects
- inflammatory states
- wound healing
- transvascular alterations

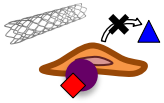
Medical devices

DIAGNOSIS

Radiolabeled imaging

TREATMENTS

Healing pathways



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Department of Civil Engineering and Computer Science

- Funded by Minister of Education, University and Research
- Rita Levi Montalcini Program for Young Researchers
- Availability of **Bachelor** and **Master Theses** projects
- Availability of PhD projects
- International network of research partners:

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Assistant Professor - Rita Levi Montalcini tenure-track Professorship

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