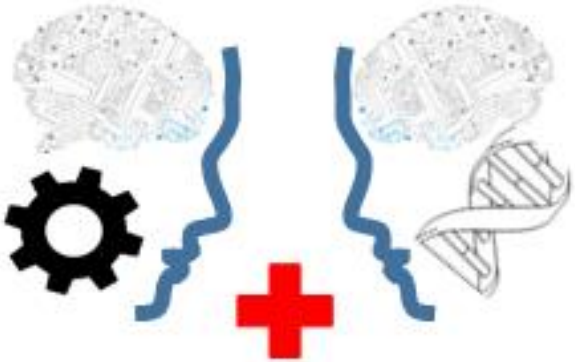
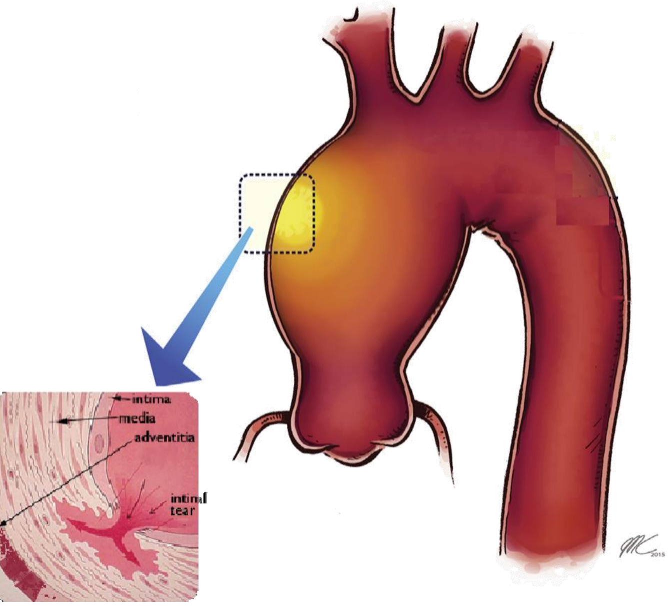


MINES Saint-Étienne

Une école de l'IMT



Links between cell mechanobiology and tissue mechanics in Human Thoracic Aortic Aneurysms

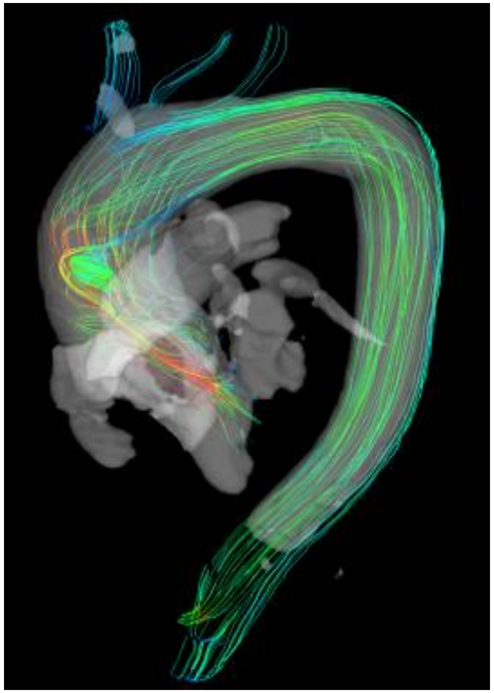
Stéphane AVRIL

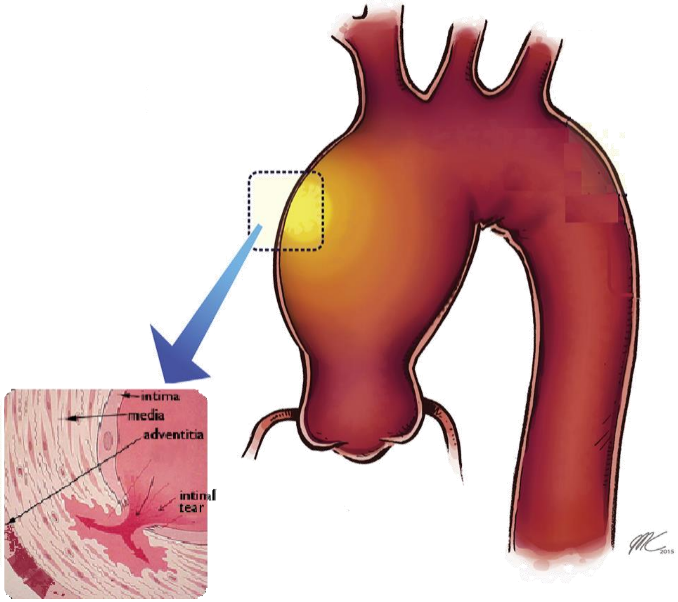
SAINBIOSE
SAnté INgénierie BIOlogie Saint-Etienne
U1059 • INSERM • SAINT-ETIENNE

Inserm
Institut national de la santé et de la recherche médicale

Twitter: @StphaneAvril1

Aneurysms and Dissections of the aorta



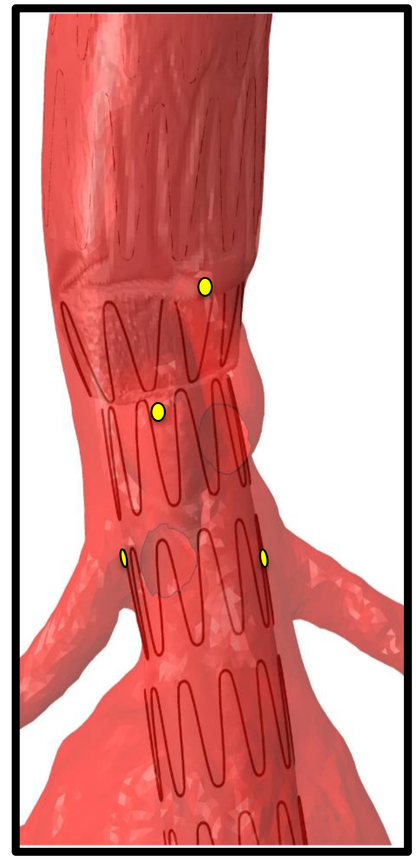


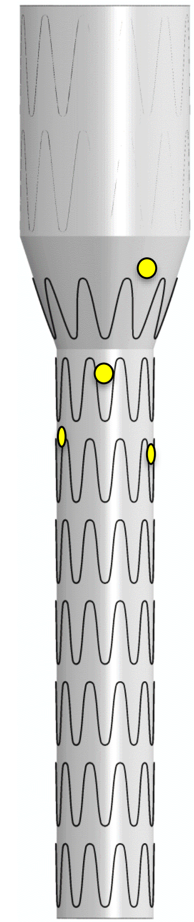
== Devastating complications!

Beyond current industrial applications…

Marie Lannelongue

HÔPITAUX UNIVERSITAIRES
HENRI MONDOR
ALBERT CHENEVIER - JOFFRE-DUPUYTREN
EMILE ROUX - GEORGES CLEMENCEAU





PrediSurge

avril@emse.fr

MINES Saint-Étienne
Une école de l'IMT

OPEN QUESTIONS I AM INTERESTED IN

- ❑ Understand and explain the role of mechanics in the progression of cardiovascular diseases
- ❑ Simulate the progression of cardiovascular diseases using patient-specific computational models
- ❑ Develop predictive models of mechano-regulation by vascular cells in arteries

avril@emse.fr

OUTLINE

- **PART I: Coupling continuum mechanics models and biology to predict aortic aneurysm progression**

- PART II: Towards continuum mechanics of tensional homeostasis down to the subcellular level

avril@emse.fr

Jay D. Humphrey:

From Complexity Comes Simplicity

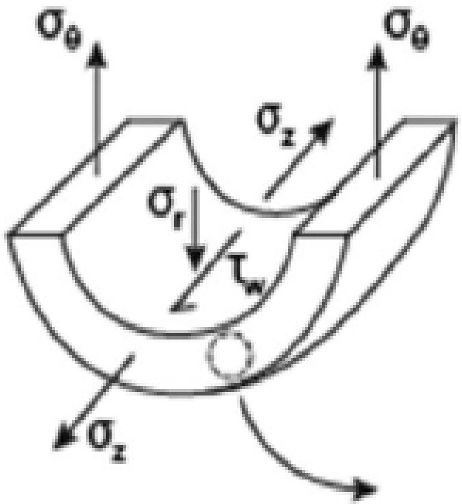
- Nonlinear Material Properties and Large Strain
- Anisotropy (circumferential muscle, axial collagen)
- Residual Stresses
- Smooth Muscle Activation
- Heterogeneity (functionally graded)

→ MECHANOREGULATION

Early Stress Analyses (~1979)

$$\mathbf{t} = -p\mathbf{I} + \tfrac{1}{2} c e^{Q} \mathbf{F} \cdot \frac{\partial Q}{\partial \mathbf{E}} \cdot \mathbf{F}^{T}$$

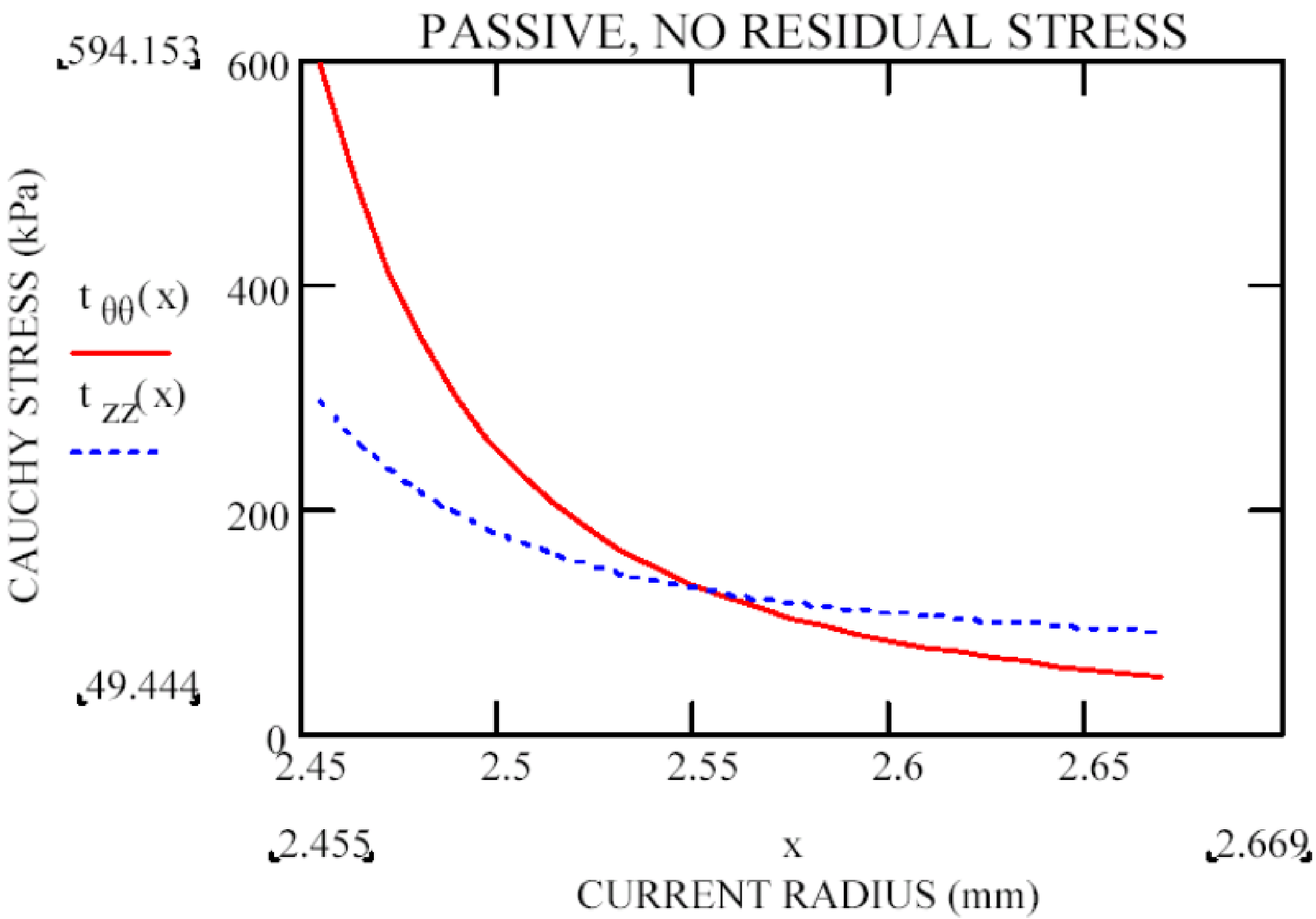
$$\operatorname{div} \ \mathbf{t} = 0$$



$$\mathbf{F} = \operatorname{diag}\left[\frac{\partial r}{\partial R}, \frac{r}{R}, \lambda\Lambda\right]$$

MINES Saint-Étienne

Early Stress Analyses (~1979)



avril@emse.fr

Importance of Residual Stress (~1986)

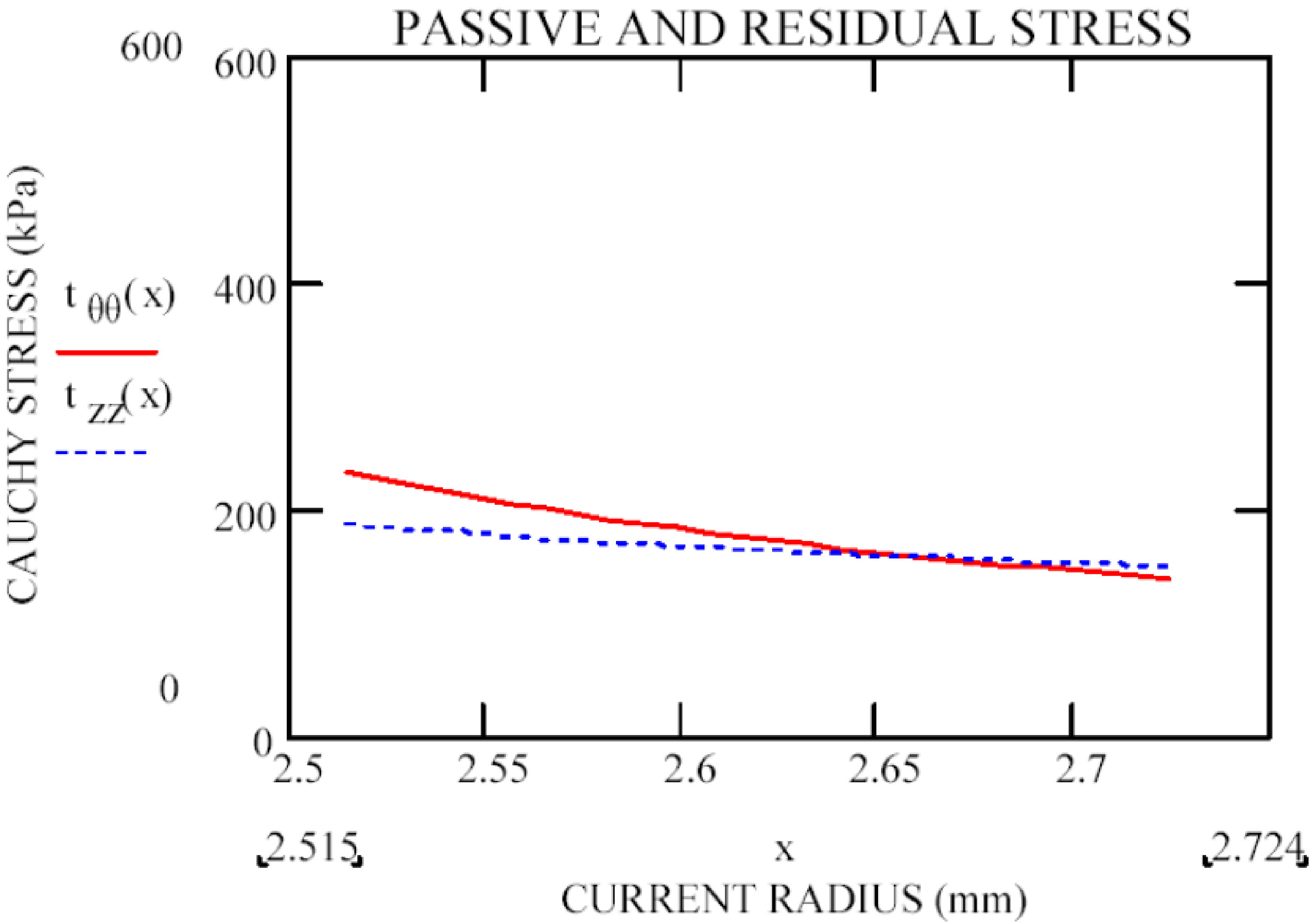
$$\mathbf{t} = -p\mathbf{I} + \tfrac{1}{2} c e^{Q} \mathbf{F} \cdot \frac{\partial Q}{\partial \mathbf{E}} \cdot \mathbf{F}^{T}$$

$$\text{div } \mathbf{t} = 0$$

$$\mathbf{F} = \text{diag}\left[\frac{\partial r}{\partial R}, \frac{r}{R} \quad , \lambda\Lambda \right]$$

avril@emse.fr

Importance of Residual Stress (~1986)



avril@emse.fr

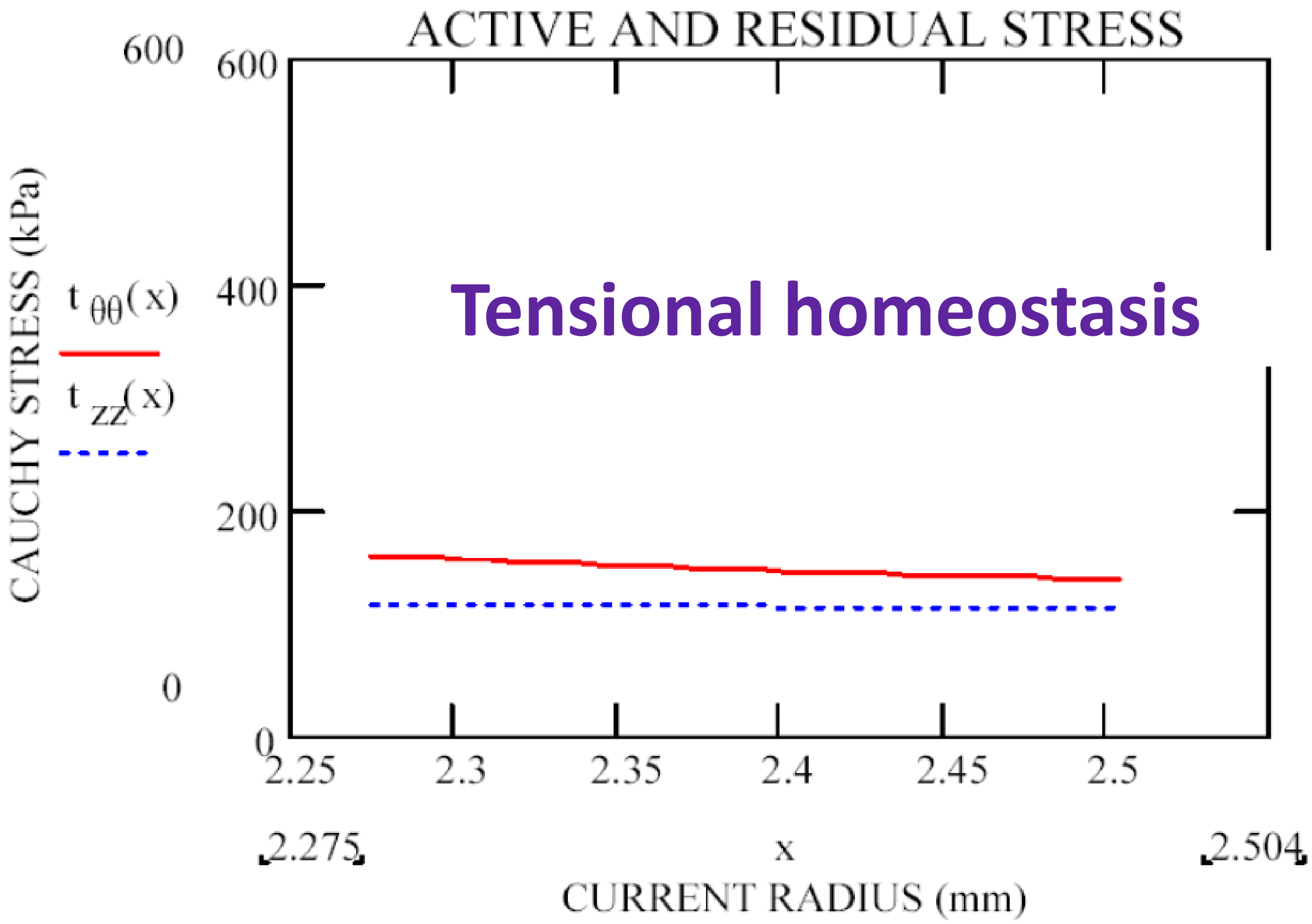
Importance of Smooth Muscle (~1999)

$$\mathbf{t} = -p\mathbf{I} + \tfrac{1}{2} c e^{Q} \mathbf{F} \cdot \frac{\partial Q}{\partial \mathbf{E}} \cdot \mathbf{F}^{T}$$

$$\operatorname{div} \ \mathbf{t} = 0$$

$$\mathbf{F} = \operatorname{diag}\left[\frac{\partial r}{\partial R}, \frac{r\pi}{R\Theta_{o}}, \lambda\Lambda \right]$$

Importance of Smooth Muscle (~1999)

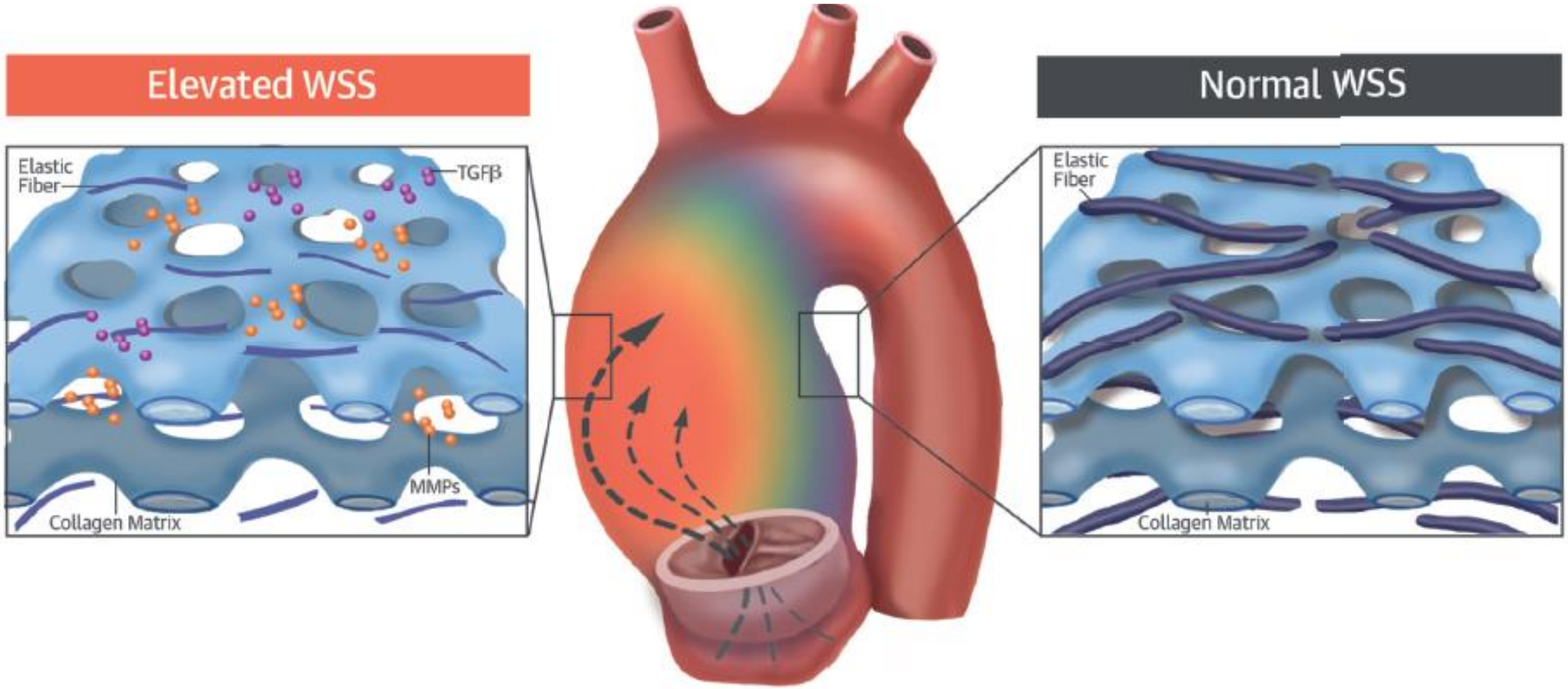


avril@emse.fr

MINES Saint-Étienne

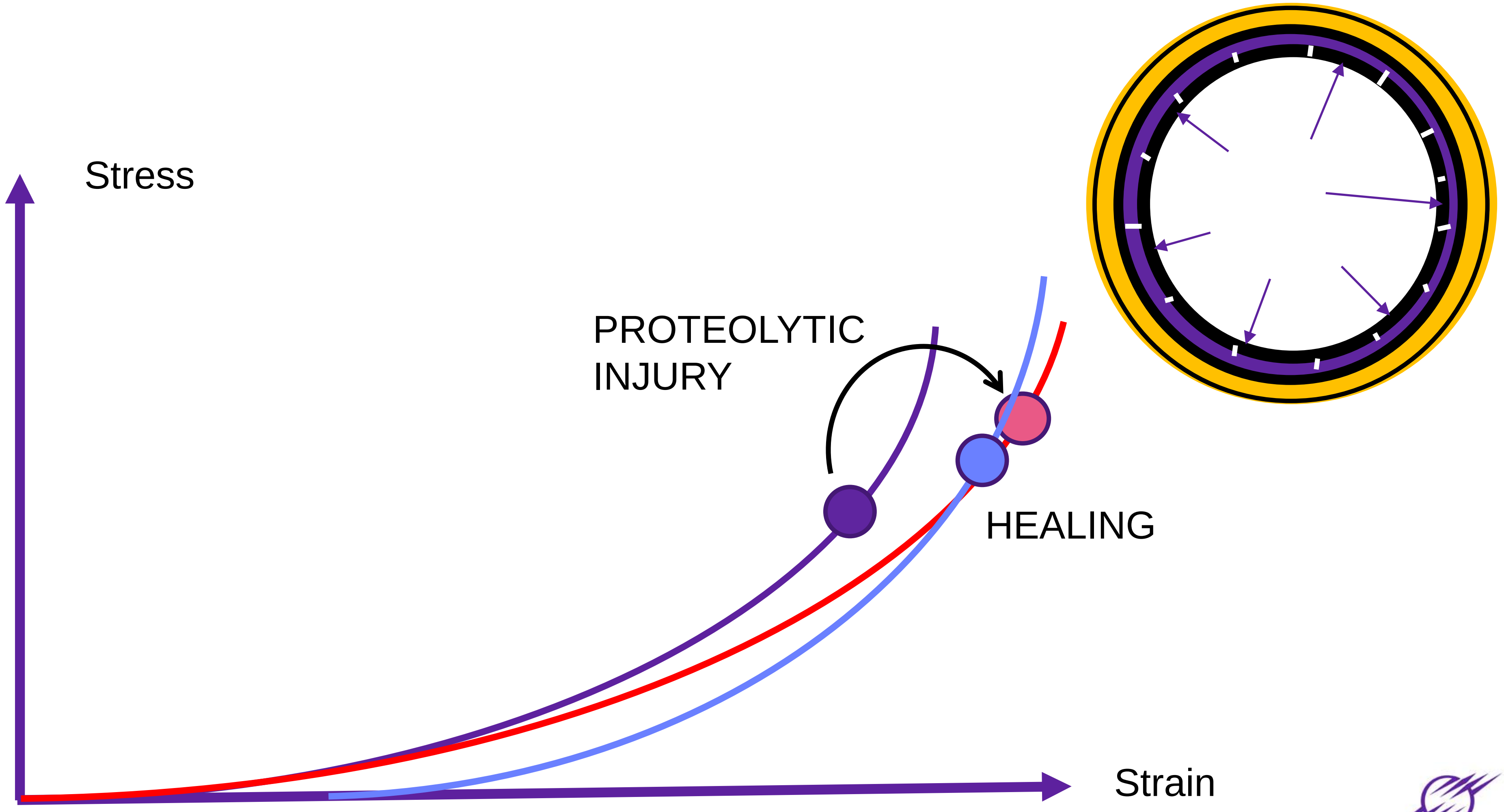
Tensional homeostasis in ATAA?

ATAAs are triggered by local proteolytic injury, which induce adaptation in the ascending thoracic aorta



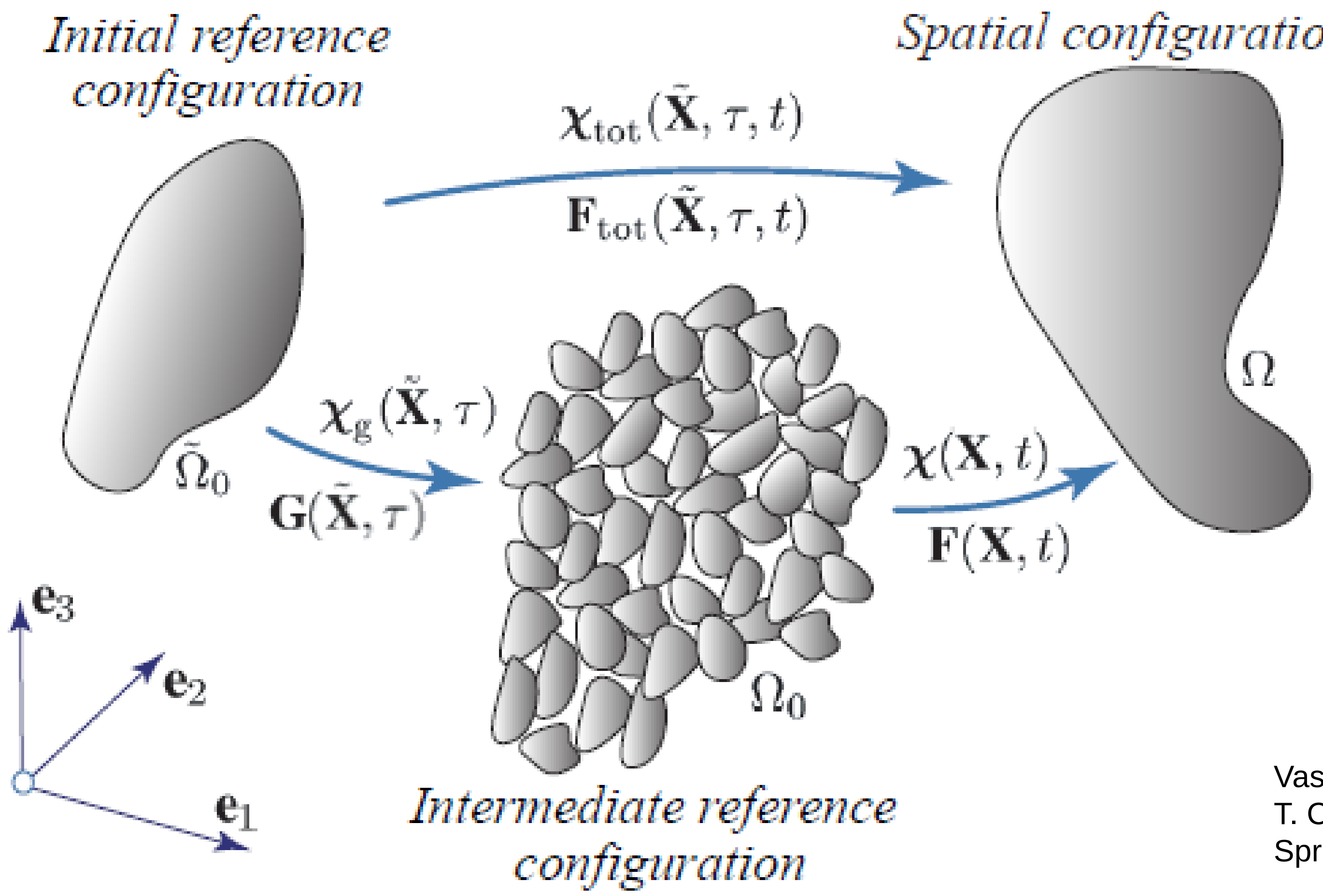
Guzzardi et al, JACC (2014), Condemi et al, IEEE TBME (2019)

Proteolytic injury and tissue adaptation



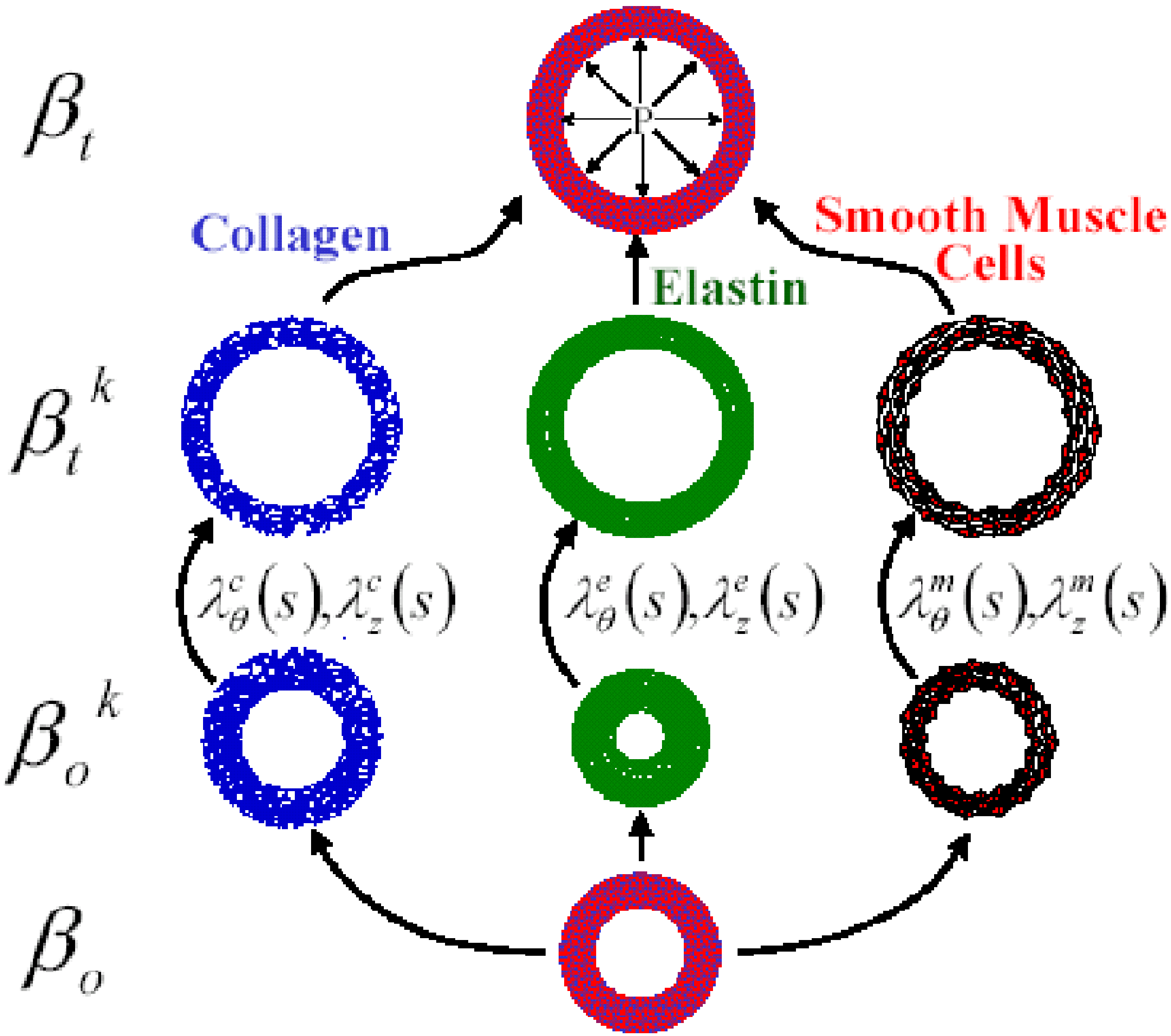
avril@emse.fr

Kinematics-based growth description



Vascular Biomechanics
T. Christian Gasser
Springer

Constrained mixture models



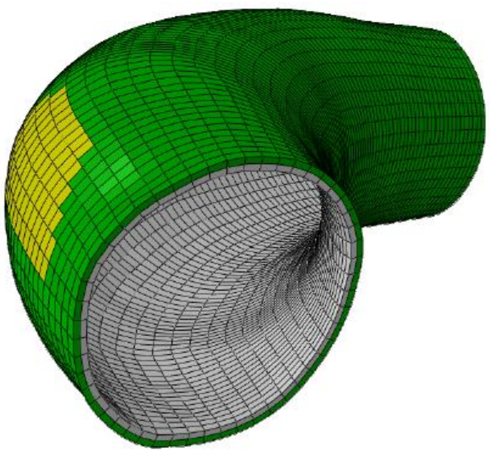
Finite-element simulations

Growth and remodeling of a two–layer patient–specific human ATAAs due to elastin loss

$$W = \varrho_t^{\mathrm{e}}\left(\overline{W}^{\mathrm{e}}(\overline{I}_1^{\mathrm{e}}) + U(J_{\mathrm{el}}^{\mathrm{e}})\right) + \sum_{j=1}^{n} \varrho_t^{\mathrm{c}_j} W^{\mathrm{c}_j}(I_4^{\mathrm{c}_j}) + \varrho_t^{\mathrm{m}} W^{\mathrm{m}}(I_4^{\mathrm{m}})$$

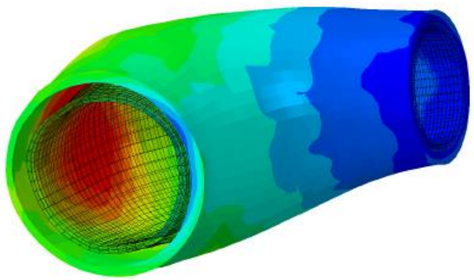
$$\dot{\varrho}^{\mathrm{e}} = -\frac{\varrho^{\mathrm{e}}(\mathbf{X},t)}{T^{\mathrm{e}}} - \frac{D_{\max}}{t_{\mathrm{dam}}}\varrho^{\mathrm{e}}(\mathbf{X},0)\, e^{-0.5\left(\frac{X_3}{L_{\mathrm{dam}}}\right)^2 - \frac{t}{t_{\mathrm{dam}}}}$$

Localization function around the point of TAWSS max



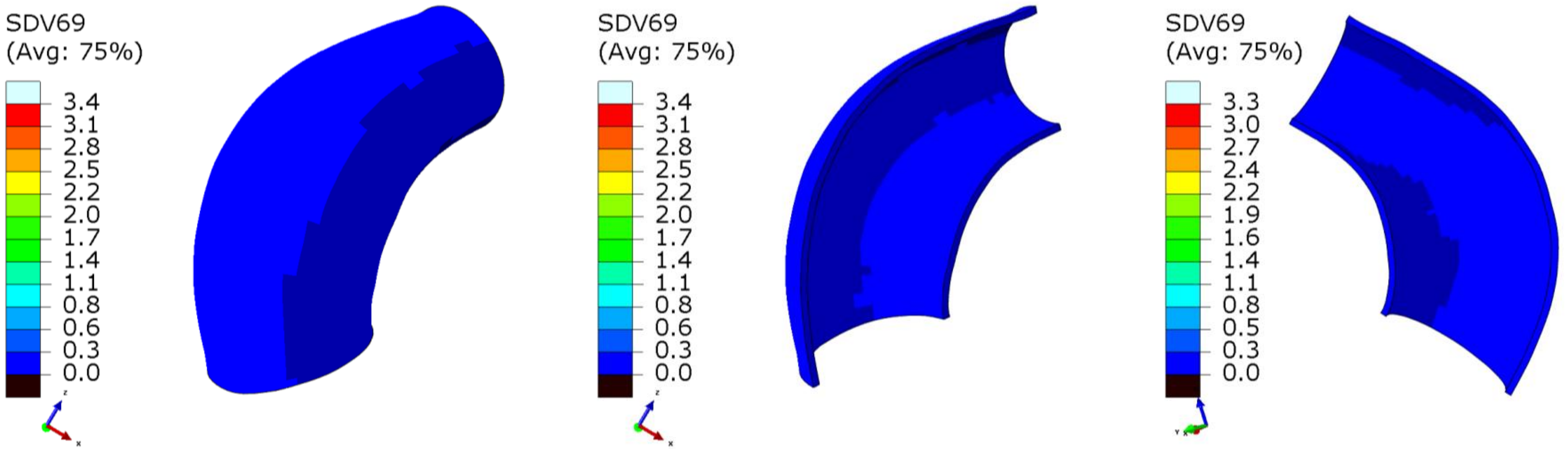
Mousavi et al, BMMB (2019)

Patient-specific predictions



Growth and remodeling of a two–layer patient–specific human ATAAs due to elastin loss

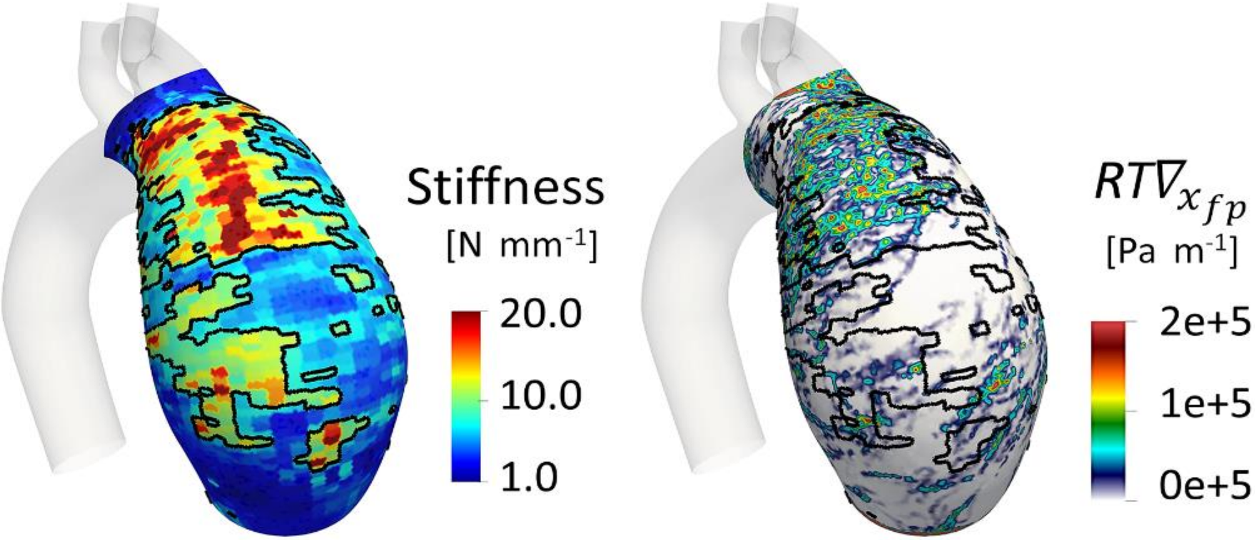
Small growth parameter



Normalized Thickness

Mousavi et al, BMMB (2019)

Some patients show local stiffness increase correlated with local hemodynamics



De Nisco, G., ... & Morbiducci, U. (2020). Medical Engineering & Physics, 82, 119-129.

POLITECNICO DI TORINO

avril@emse.fr

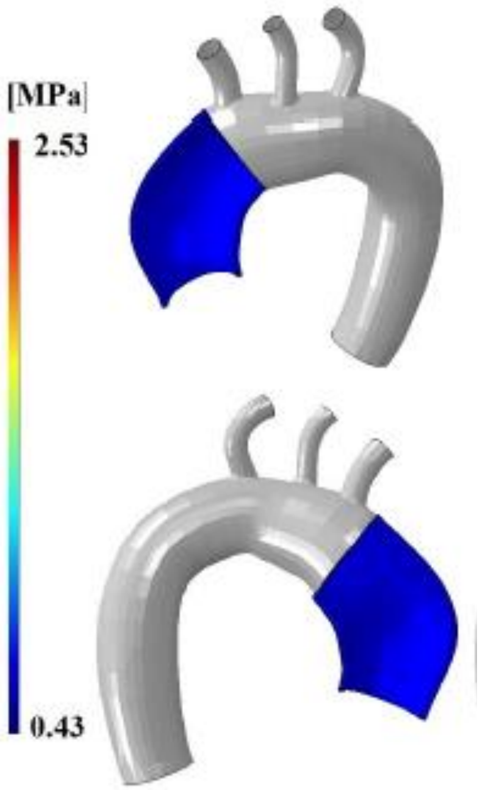
MINES Saint-Étienne

Patient-specific vascular adaptation

$$\dot{\varrho}^{j}(\mathrm{t}) = \varrho^{j}(\mathrm{t}) k_{\sigma}^{j} \frac{\sigma^{j}(t) - \chi * \sigma_{\mathrm{h}}^{j}}{\chi * \sigma_{\mathrm{h}}^{j}}$$

$$\chi = 1$$

Tangent stiffness after 10 years

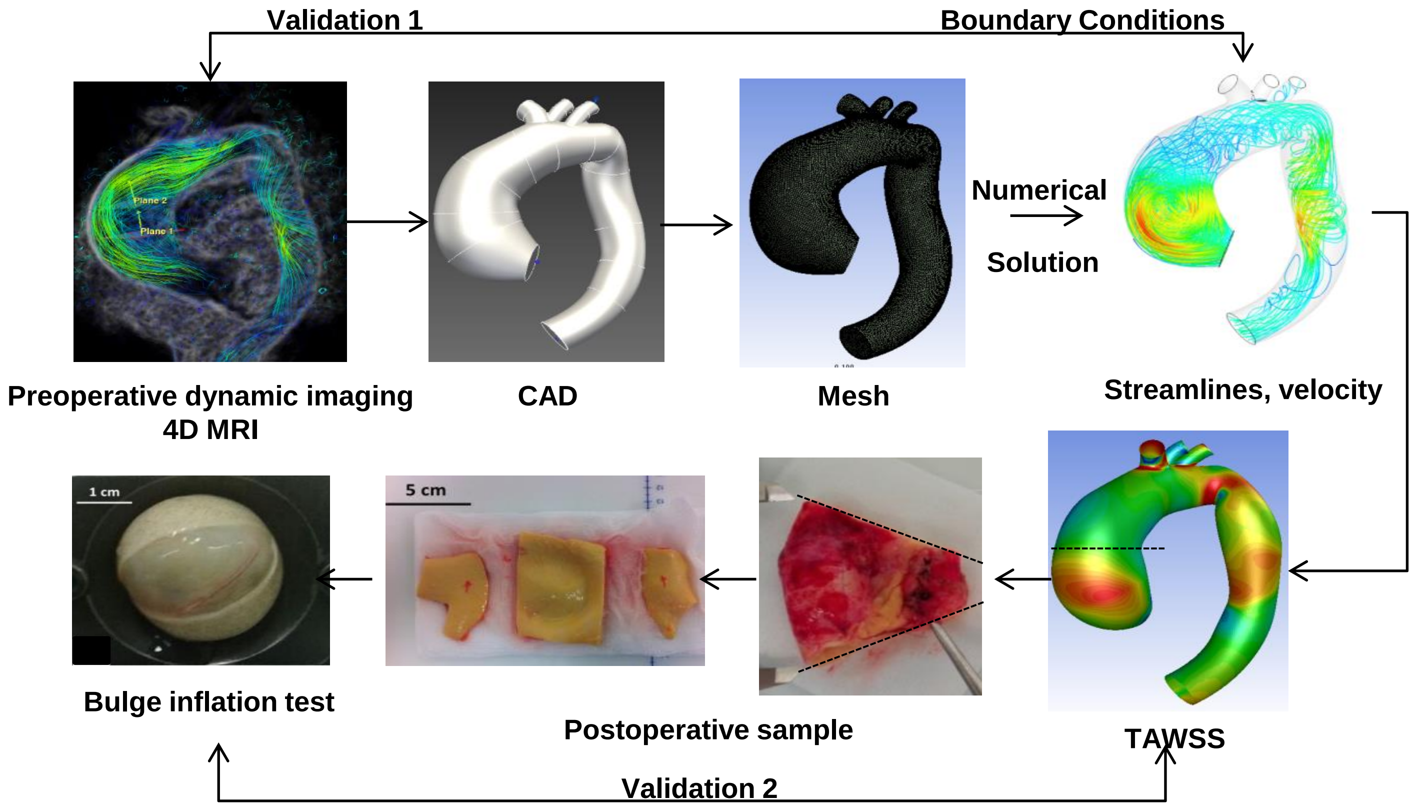


$$\dot{\varrho}^{j}(\mathrm{t}) = \varrho^{j}(\mathrm{t}) k_{\sigma}^{j} \frac{\sigma^{j}(t) - \chi * \sigma_{\mathrm{h}}^{j}}{\chi * \sigma_{\mathrm{h}}^{j}}$$

Mousavi et al, CMPB (2021)

TOWARDS CLINICAL VALIDATION

The maintenance of tensional homeostasis in the tissue is critical but also patient-specific



avril@emse.fr

MINES Saint-Étienne

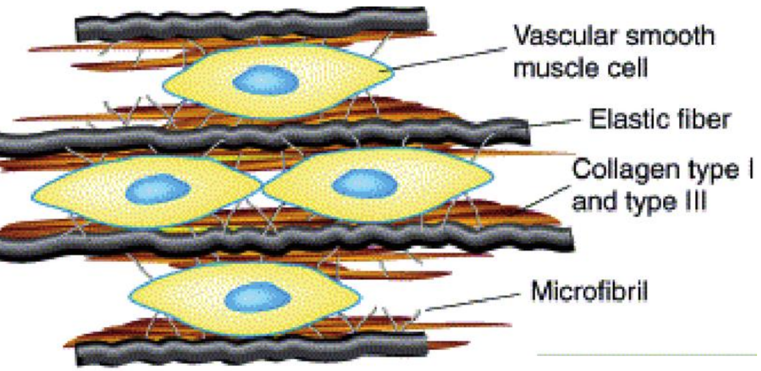
OUTLINE

- PART I: The need of combining data driven and continuum mechanics models in cardiovascular mechanobiology

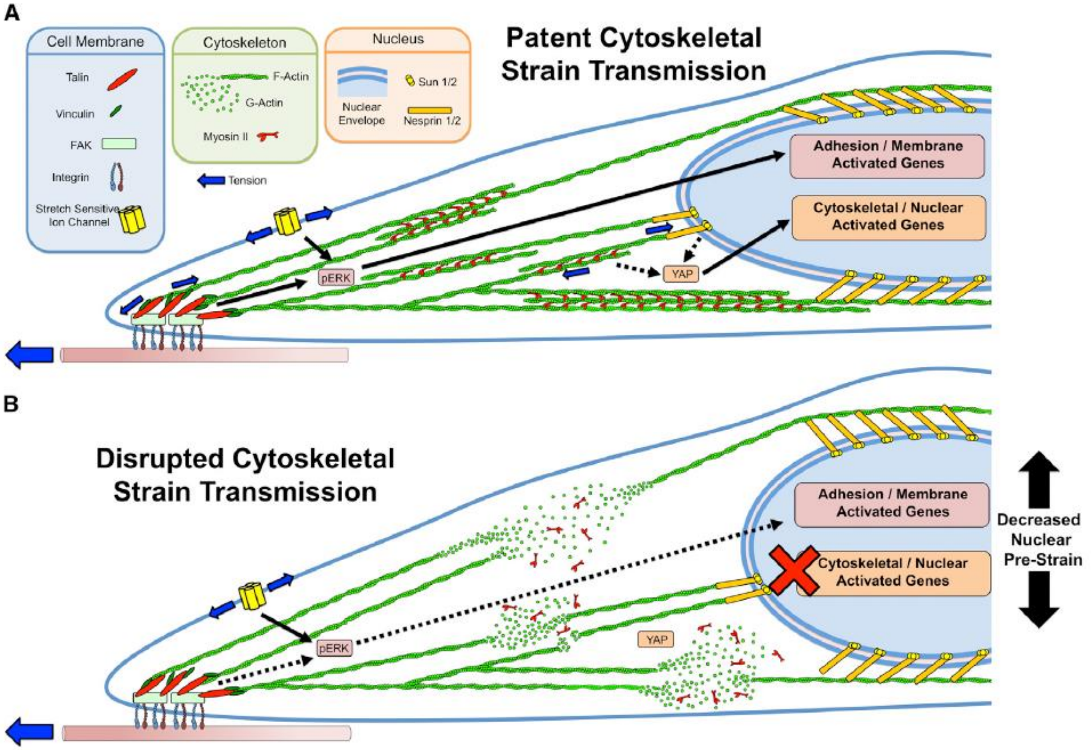
- **PART II: Towards continuum mechanics of tensional homeostasis down to the subcellular level**

avril@emse.fr

Introduction to cell mechanobiology



Driscoll et al, Biophysical Journal, 2015



Major role of smooth muscle cells in mechanoregulation

Primary SMC cultures

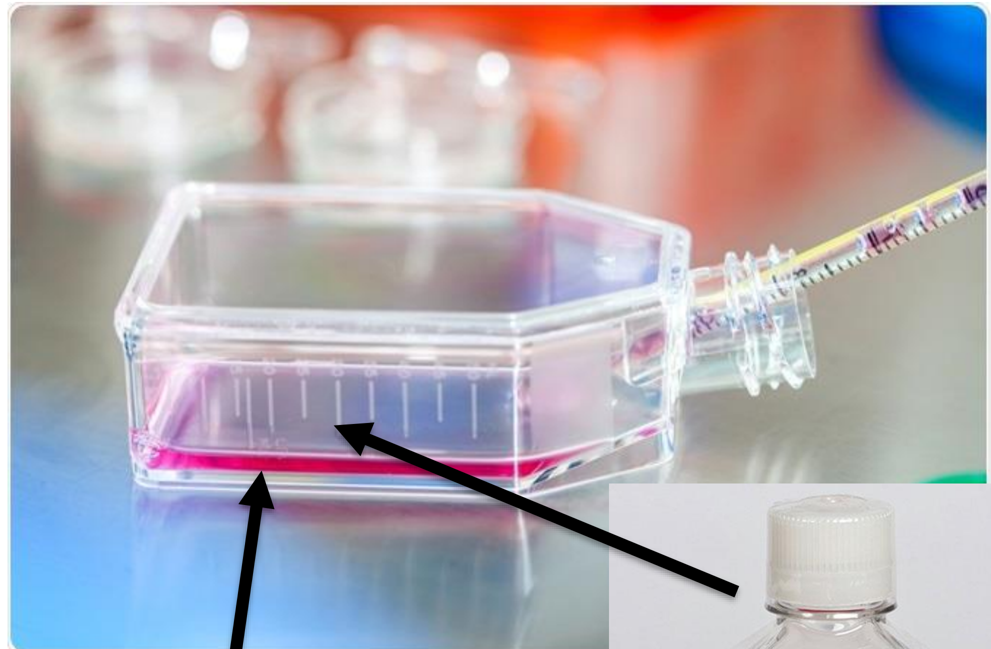
AoSMC lineage

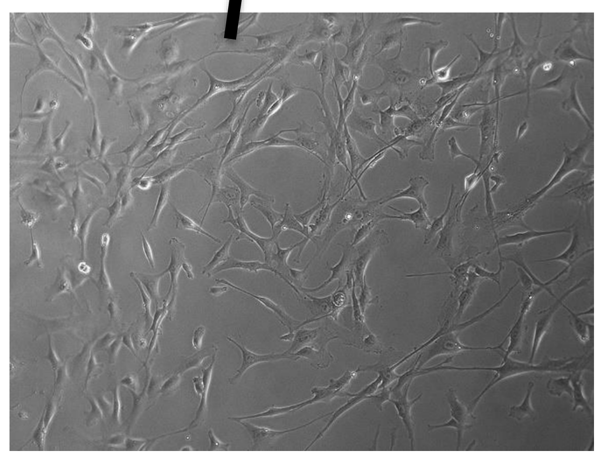
Thawing

Growing (SmGM-2)

Differenciation (SmBM)

Sample preparation





avril@emse.fr

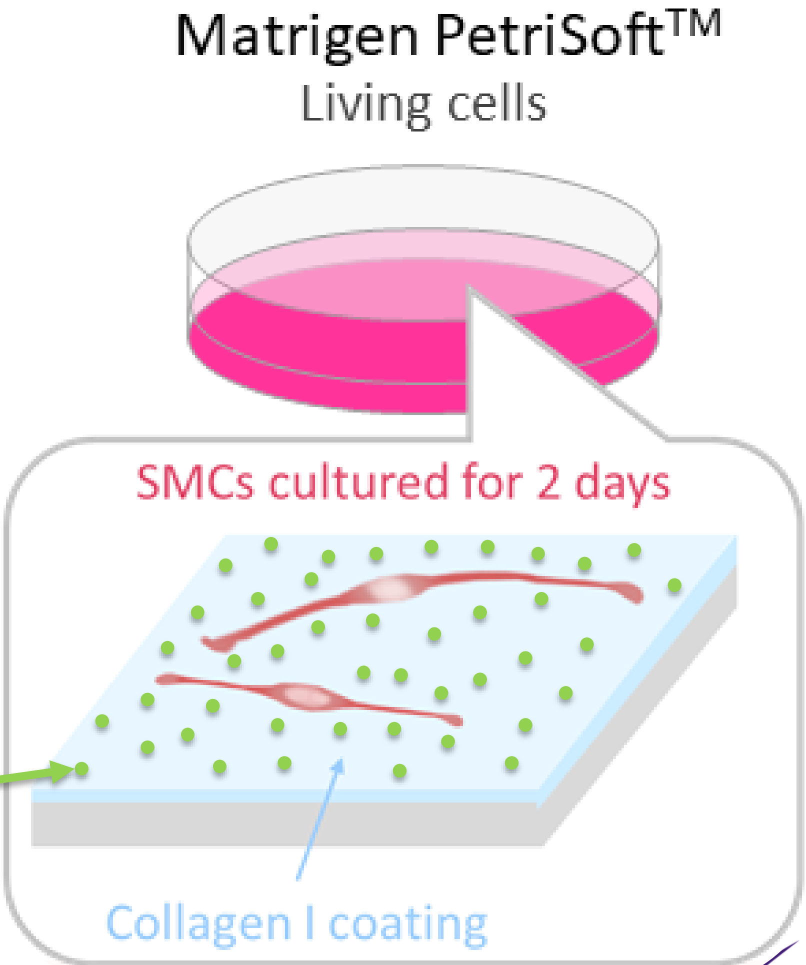
Saint-Étienne

Traction force microscopy

3 groups
Lonza, F, 24 y.o.
Healthy, AoPrim4, F, 60 y.o.
Pathological AnevPrim4, F, 60 y.o.

Age

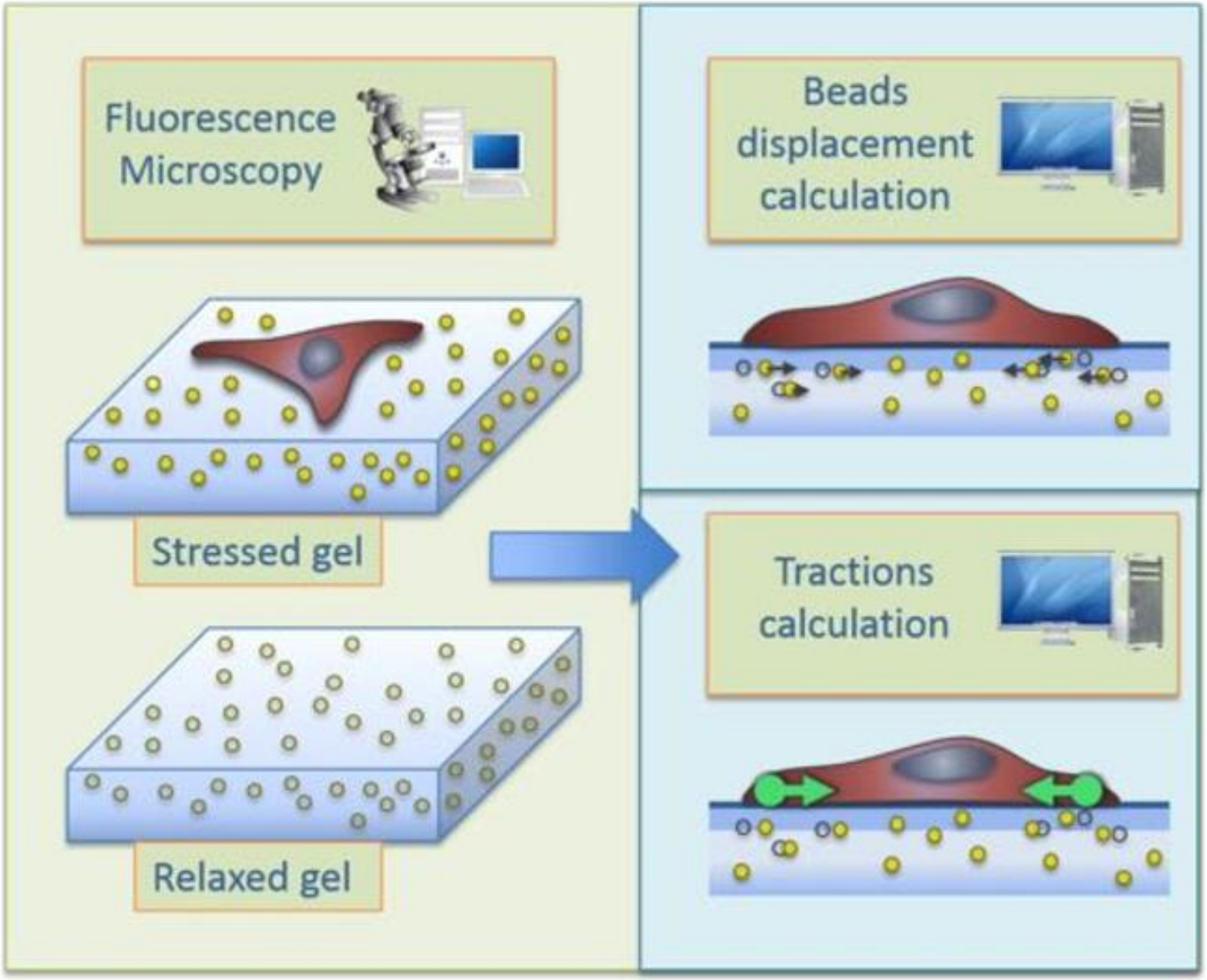
Pathology



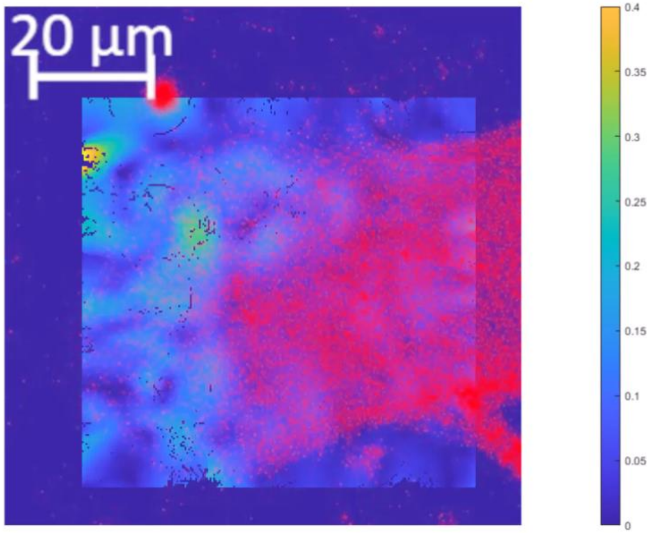
Fluorescent microbeads (yellow-green, 0,2µm φ)

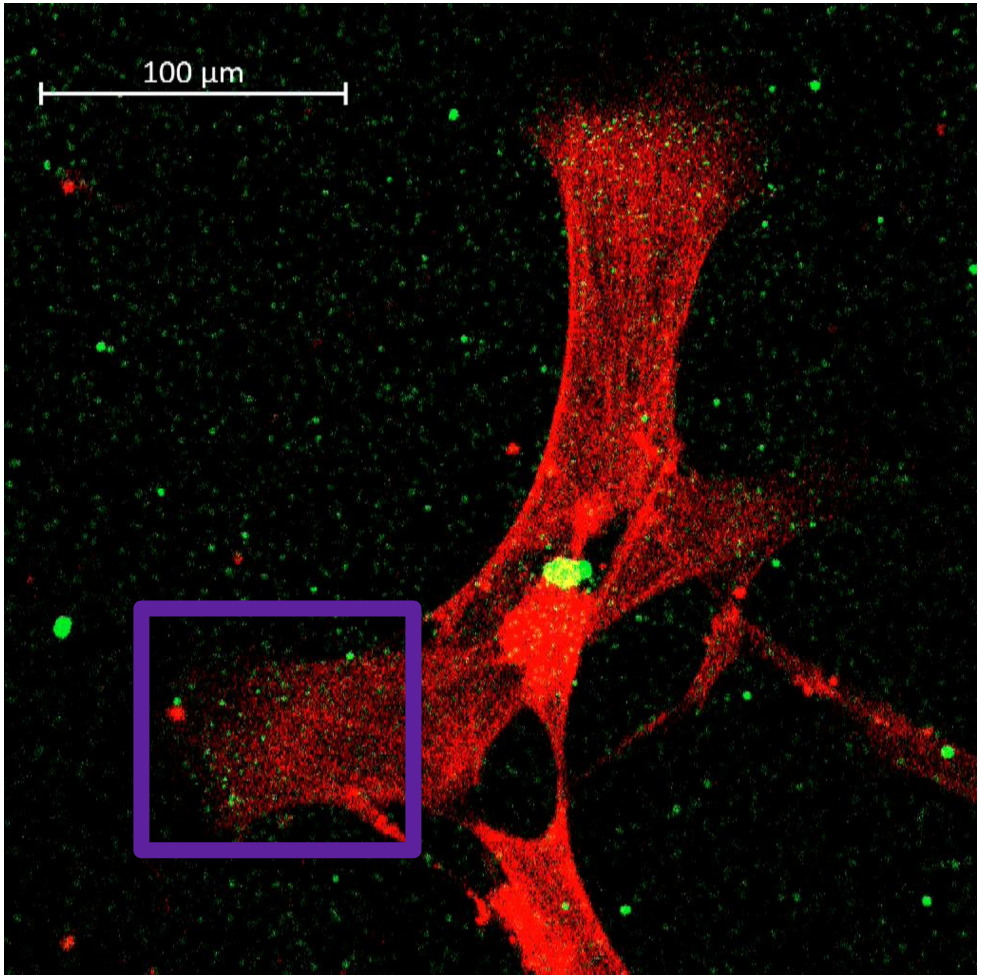
Traction force microscopy

Petit et al, BMMB, 2021



Monitoring mechanobiology of live SMCs



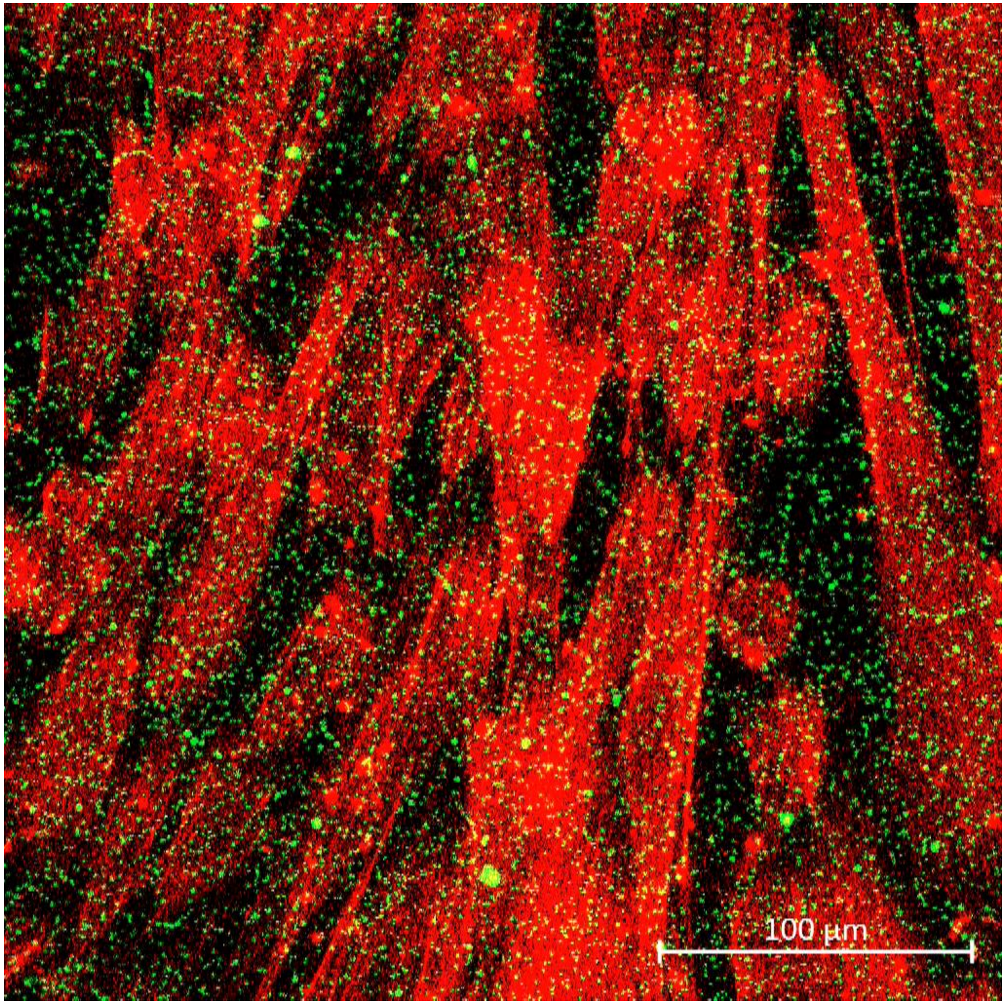


Confocal microscopy + DIC combined with Siractin staining on living cells

avril@emse.fr

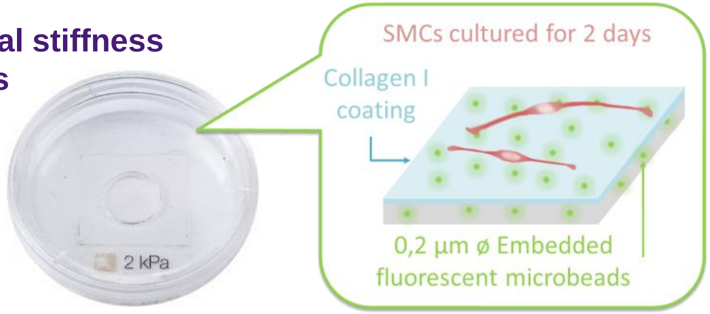
MINES Saint-Étienne
Une école de l'IMT

Isolated SMCs versus confluent SMCs

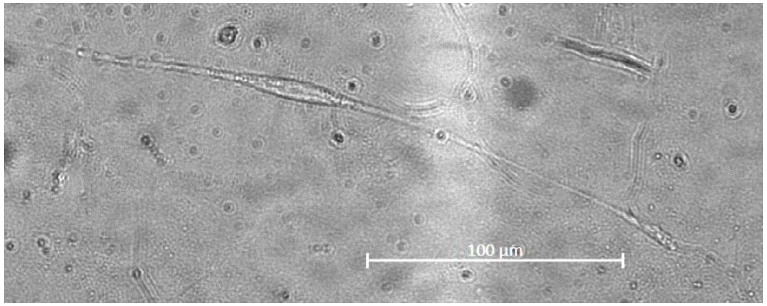


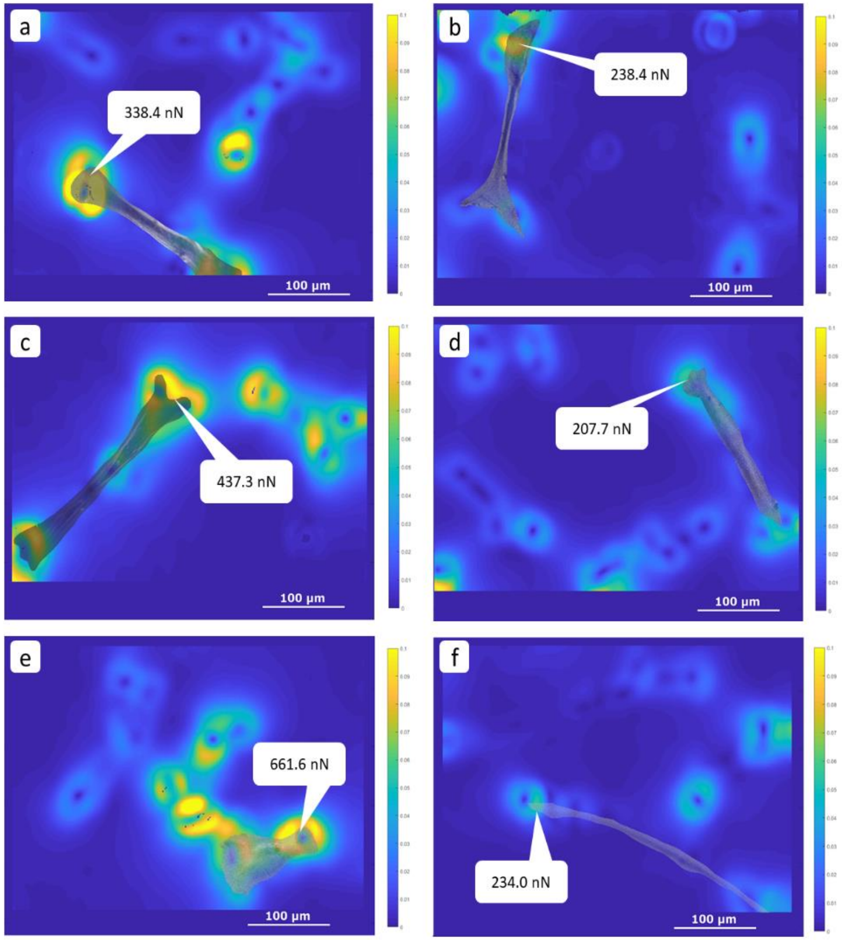
Monitoring mechanobiology *in vivo*

Several stiffness values



Aortic SMCs from human primary culture (AoSMC, Lonza), passages 5-7, cultured in a **differenciating medium** (SmBM, Lonza)





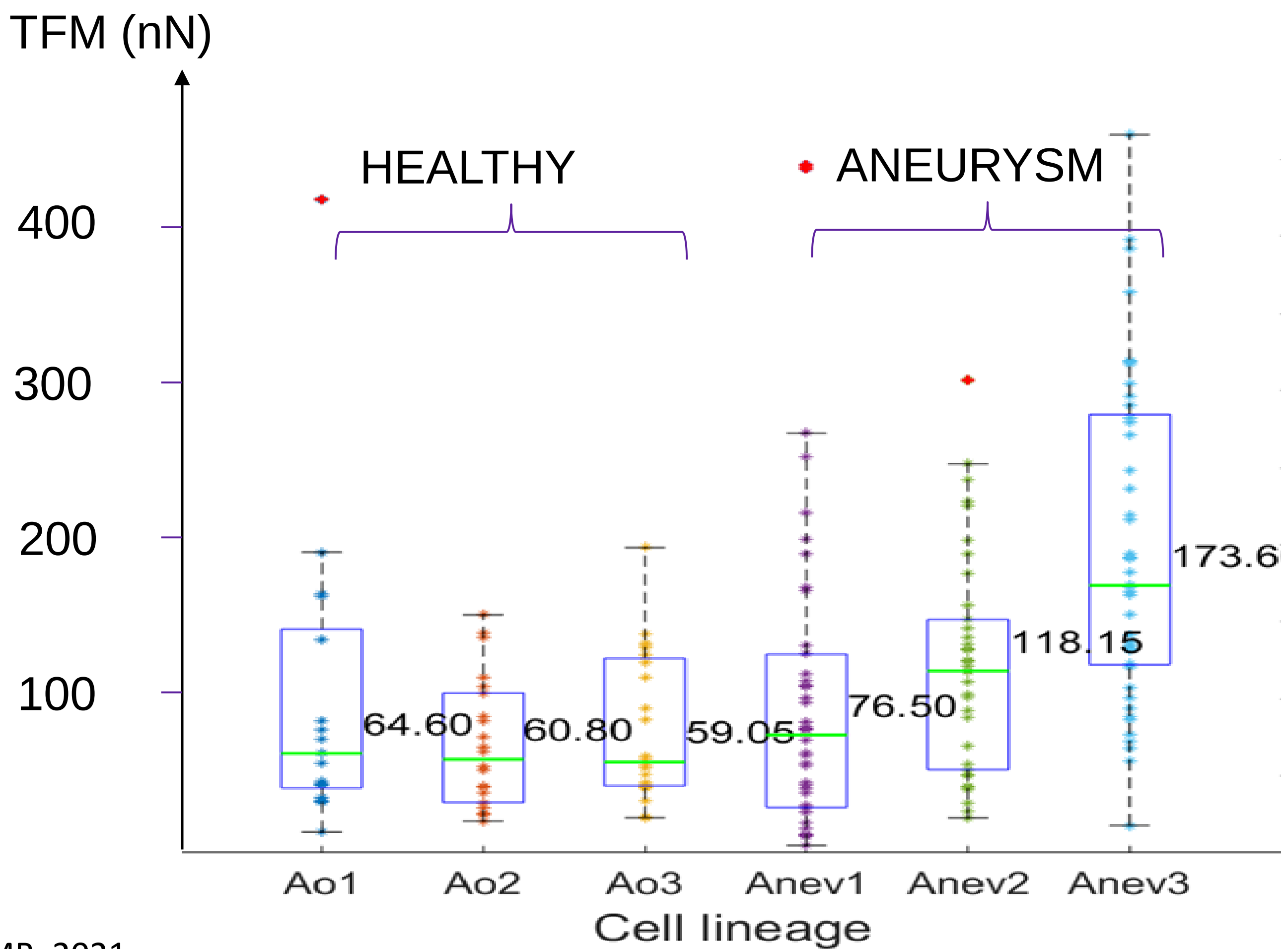
- **Fluorescent microscopy + DIC :** track the displacement of fluorescent microbeads
- **Cell unbinding method (with trypsin) :** assess the homeostatic state of single SMCs

Petit et al, BMMB, 2021

avril@emse.fr

MINES Saint-Étienne
Une école de l'IMT

Aneurysmal SMCs tend to apply larger traction forces

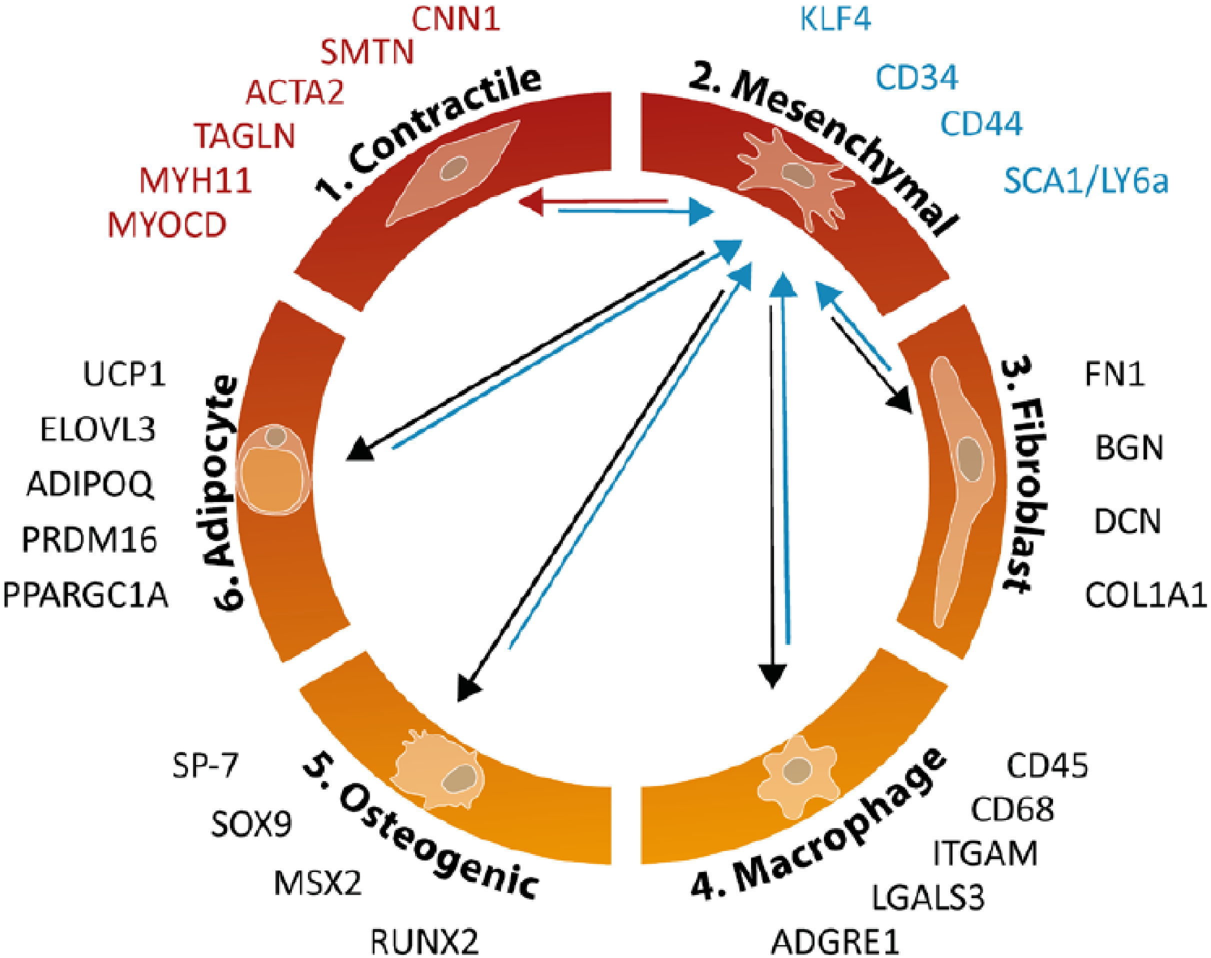


Petit et al, BMMB, 2021

avril@emse.fr

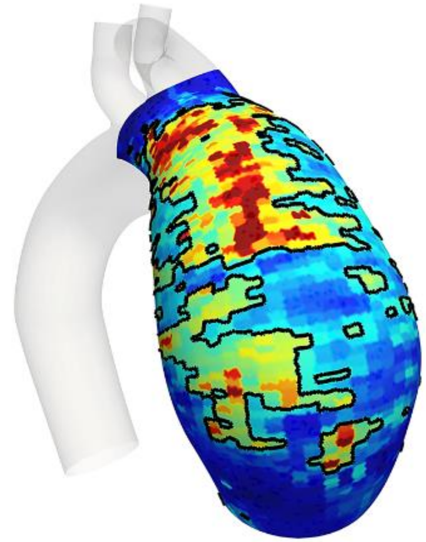
MINES Saint-Étienne
Une école de l'IMT

Variety of SMC phenotypes

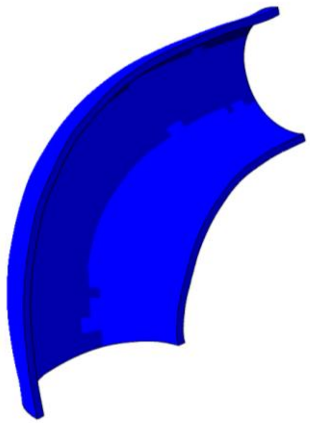


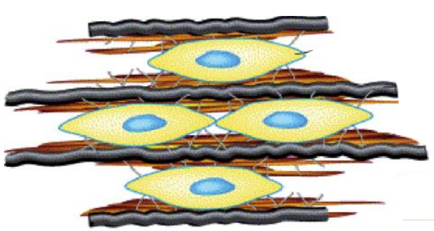
Yap et al,
ATVB. 2021;
41:2693–2707

TOWARDS DIGITAL TWINS



Monitoring gene expressions, tissue stiffness
and hemodynamics





Predicting mechanical regulation,
tissue deformations, stresses and stiffness

avril@emse.fr

Acknowledgements

- Felipe Sempertegui
- Alvaro Navarette
- Joan Laubrie
- Jamal Mousavi
- Shaojie Zhang
- Di Zuo
- Yiqian He
- Victor Acosta
- Marta Bracco
- Maria Nicole Antonuccio
- Federica Galbiati
- Francesco Bardi
- Solmaz Farzeneh
- Francesca Condemi
- Cristina Cavinato
- Jérôme Molimard
- Baptiste Pierrat
- Claudie Petit
- Marzio Di Giuseppe
- Jay Humphrey
- Christian Cyron
- Fabian Braeu
- Ambroise Duprey
- Jean-Pierre Favre
- Jean-Noël Albertini
- Salvatore Campisi
- Magalie Viallon
- Pierre Croisille
- Lauranne Maes
- Nele Famaey

anr

erc European Research Council

HORIZON 2020

MEDITATE

MINES Saint-Étienne
Une école de l'IMT