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

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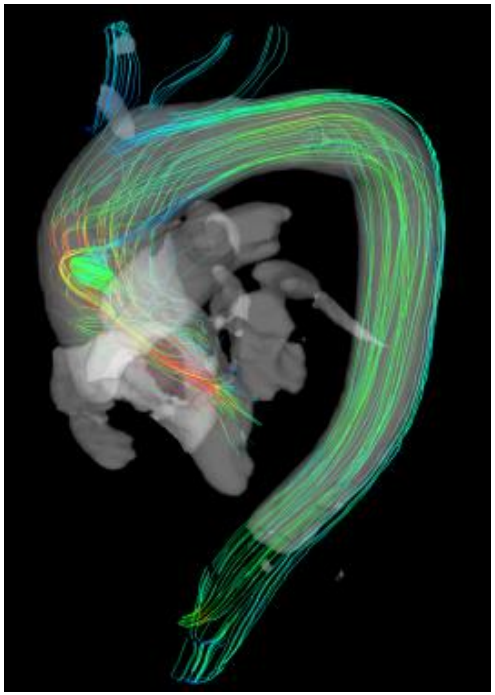
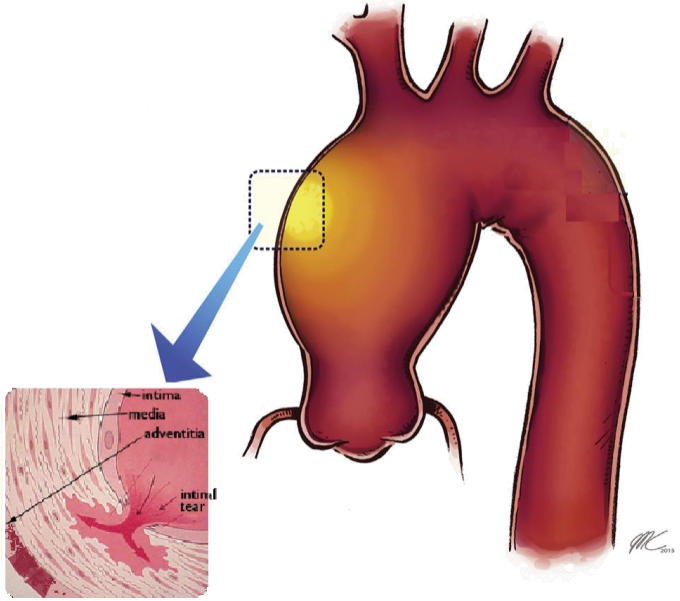
Twitter: @StphaneAvril1

Aneurysms and Dissections of the aorta





== Devastating complications!

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OUTLINE

- PART I: Industrial applications of continuum mechanics models in cardiovascular medicine

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

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

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- **PART I: Industrial applications of continuum mechanics models in cardiovascular medicine**

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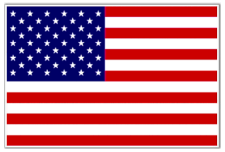
Continuum mechanics can predict health!!
It even enables decisions everyday in healthcare combined with ROM and AI

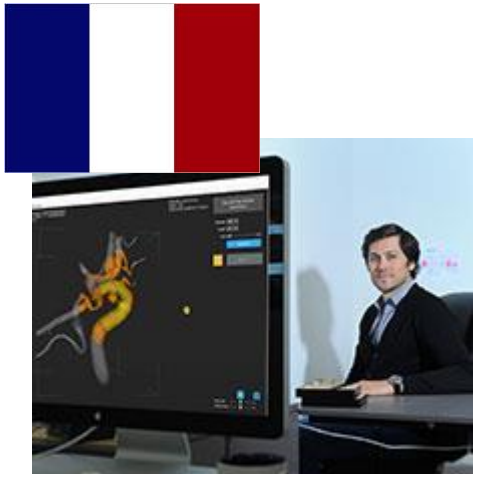


2014: FDA allows marketing of HeartFlow vFFR-CT tool for optimal treatment of coronary stenosis

Gaus S, *et al*, JCCT 2013, 7(5):279-88.

2019: FEops HEARTguide in silico tool for planning transcatheter aortic valve implantation is CE-marked

El Faquir N, *et al* Int J Cardiov Img 2019

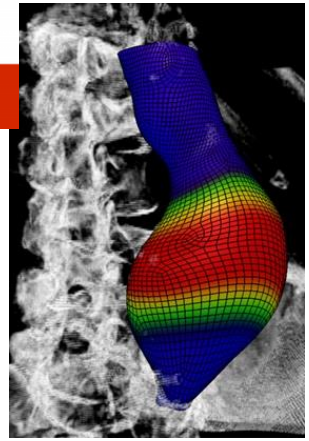


2014: Sim&Cure

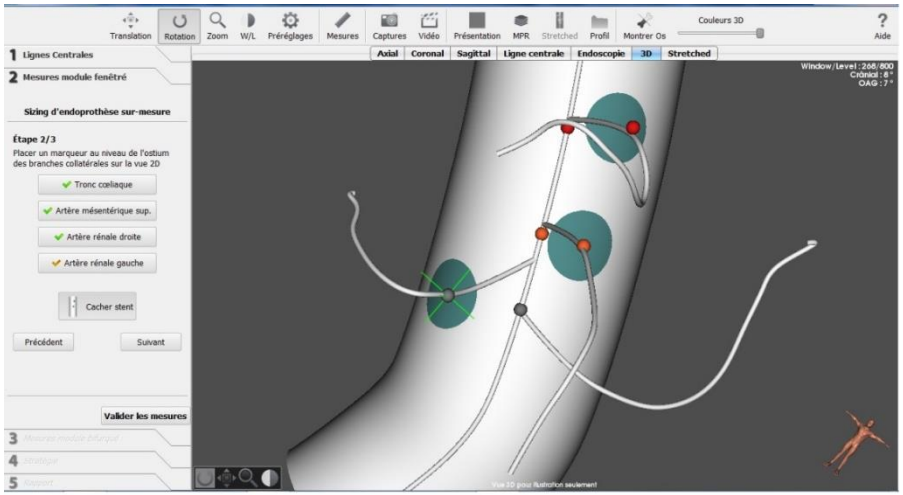
2017: Predisurge

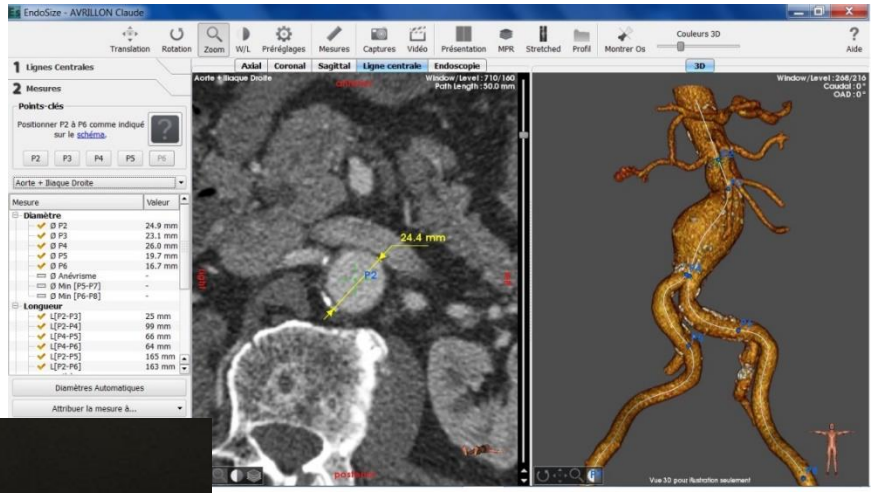
Derycke, *et al* Circulation Img 2021

Vascops

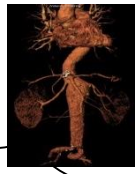


Planification / sizing of fenestrated stent grafts in EVAR procedures





PrediSurge



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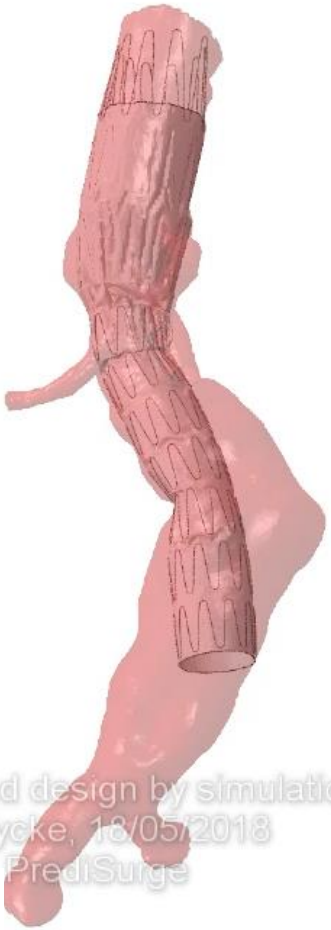
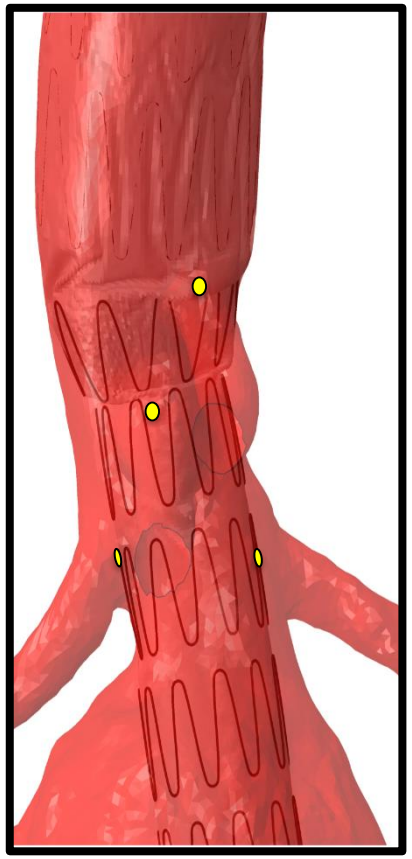
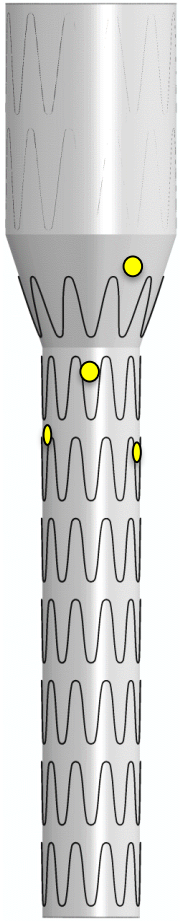
Clinically validated for FEVAR Zenith® Cook Medical







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

OUTLINE

- PART I: Industrial applications of continuum mechanics models in cardiovascular medicine

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

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

Jay D. Humphrey:

From Complexity Comes Simplicity

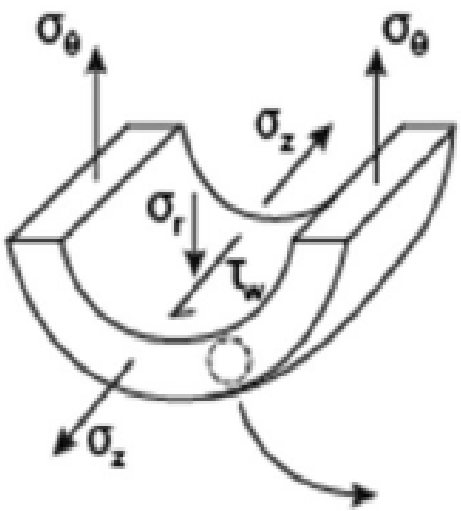
- Nonlinear Material Properties and Large Strain
- Anisotropy (circumferential muscle, axial collagen)
- Residual Stresses
- Smooth Muscle Activation
- Heterogeneity (functionally graded)

→ MECHANOREGULATION

Early Stress Analyses (~1979)

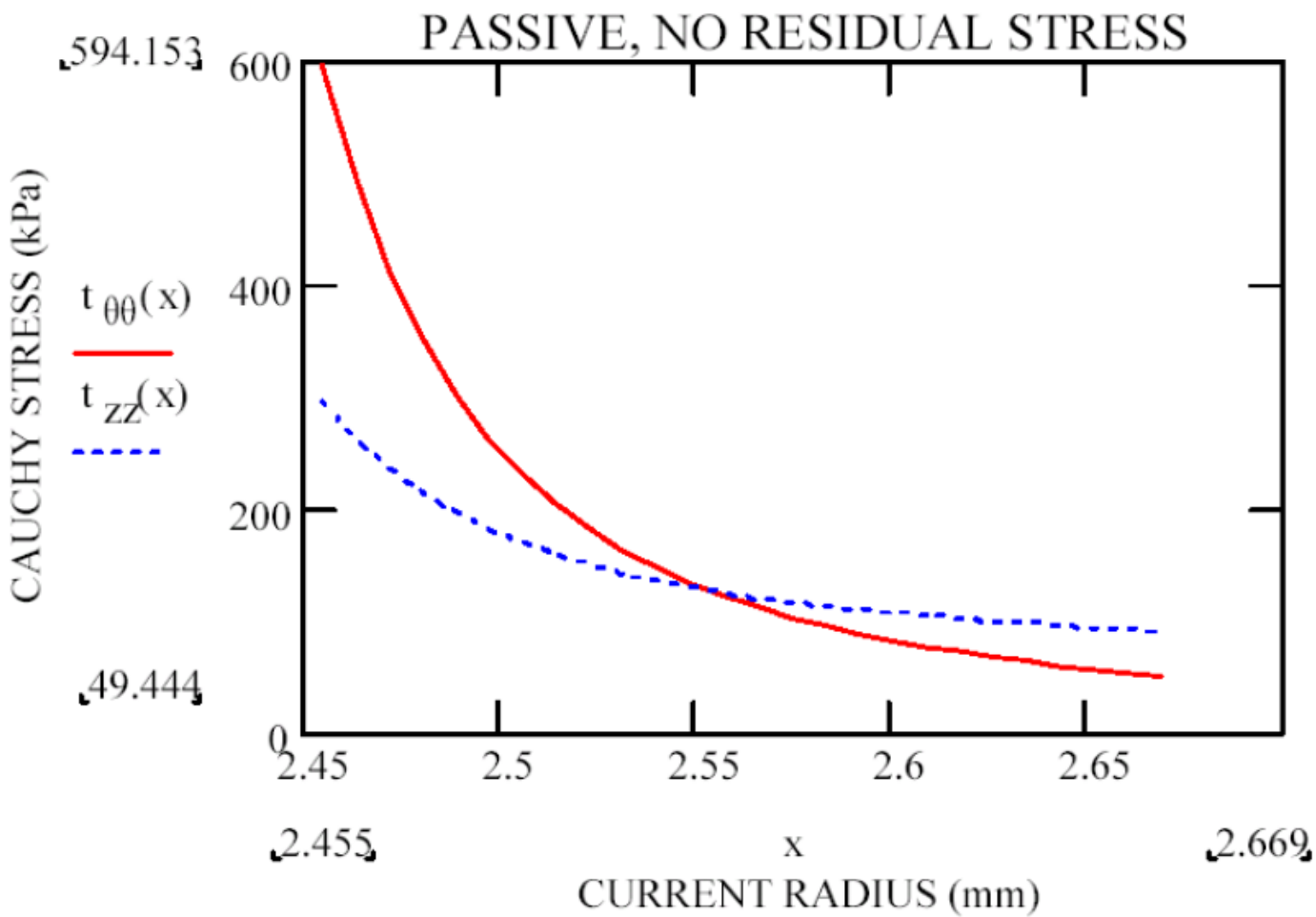
$$\mathbf{t} = -p\mathbf{I} + \tfrac{1}{2} c e^{Q} \mathbf{F} \cdot \frac{\partial Q}{\partial \mathbf{E}} \cdot \mathbf{F}^{T}$$

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



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

Early Stress Analyses (~1979)



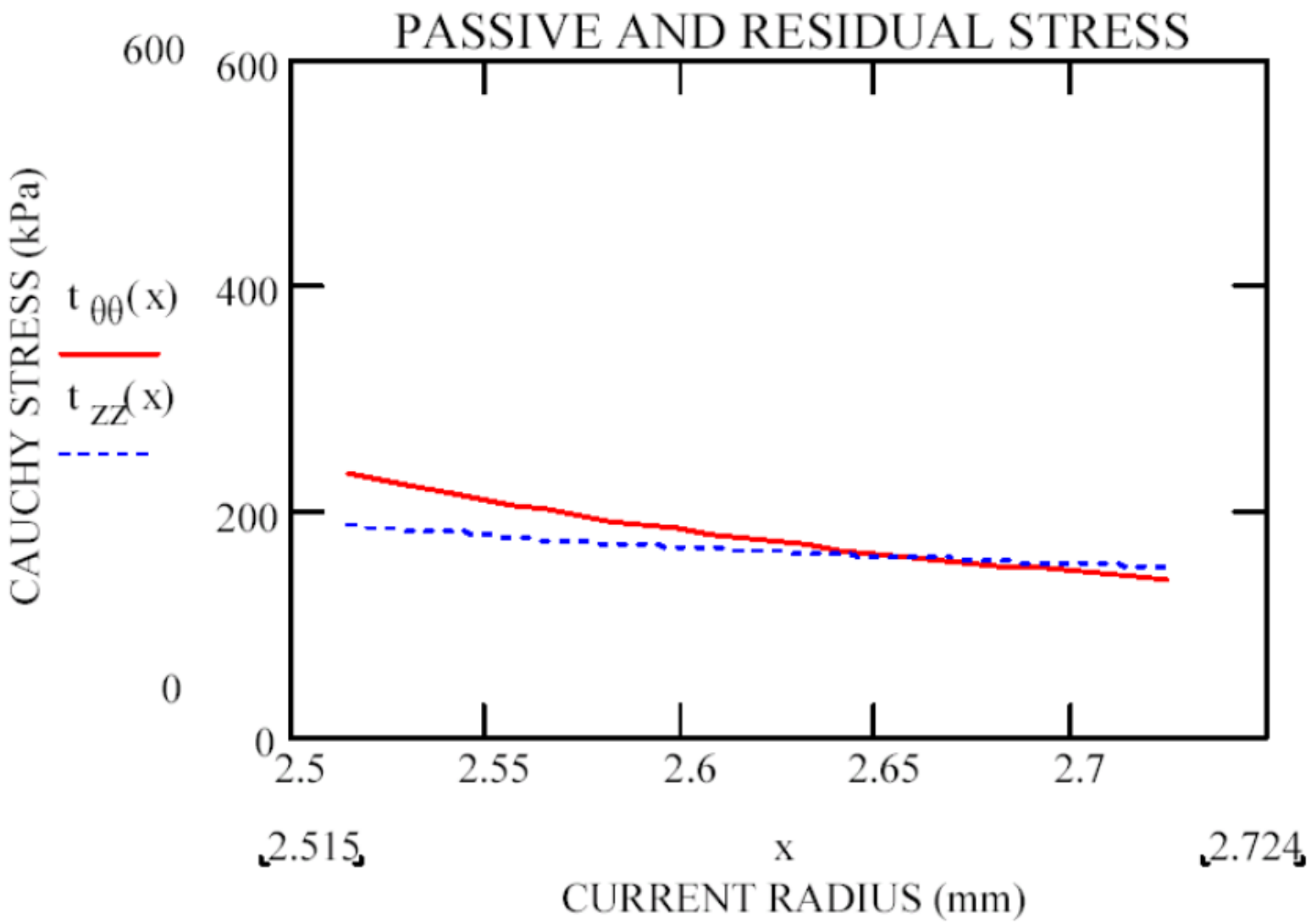
Importance of Residual Stress (~1986)

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

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

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

Importance of Residual Stress (~1986)



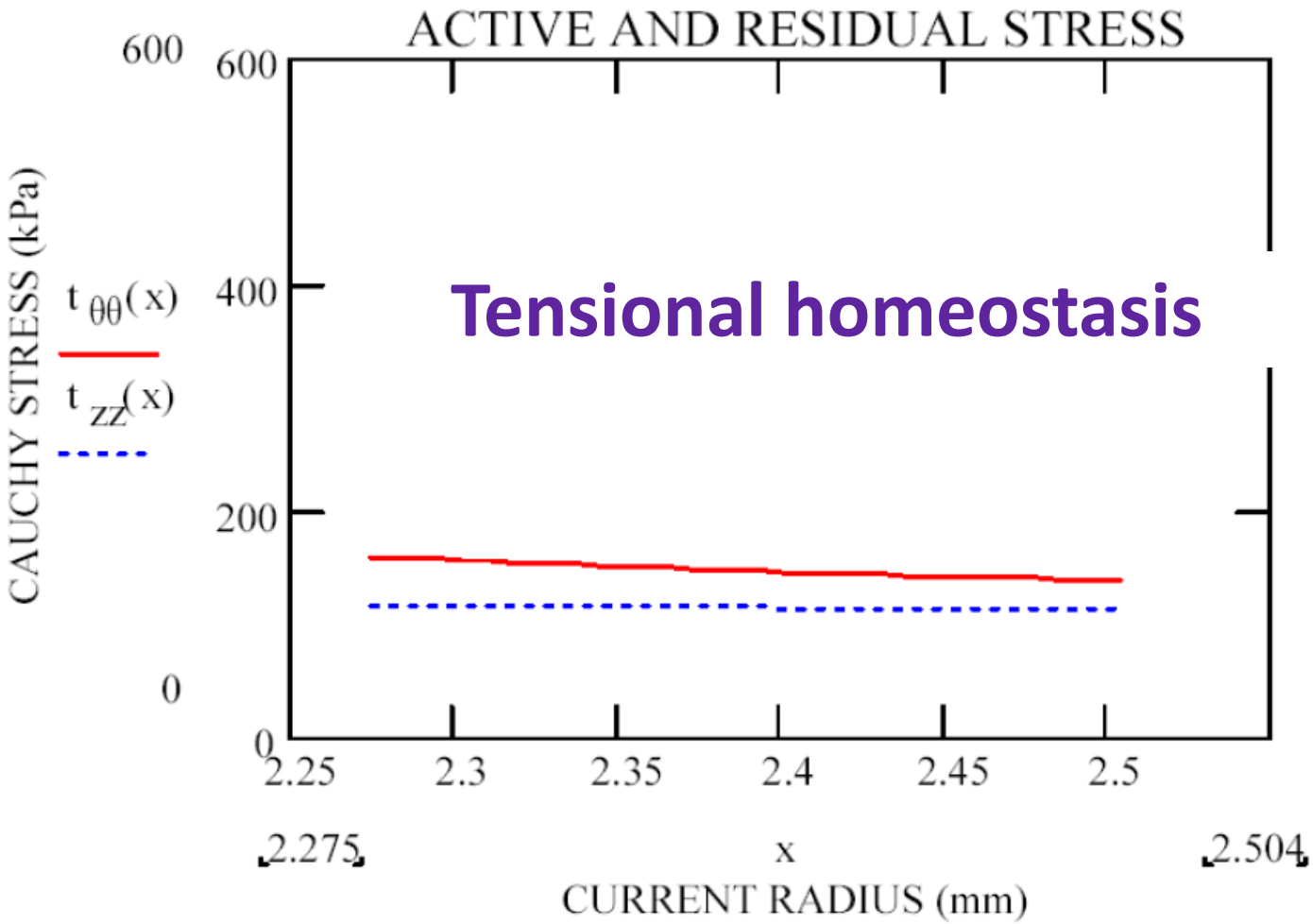
Importance of Smooth Muscle (~1999)

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

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

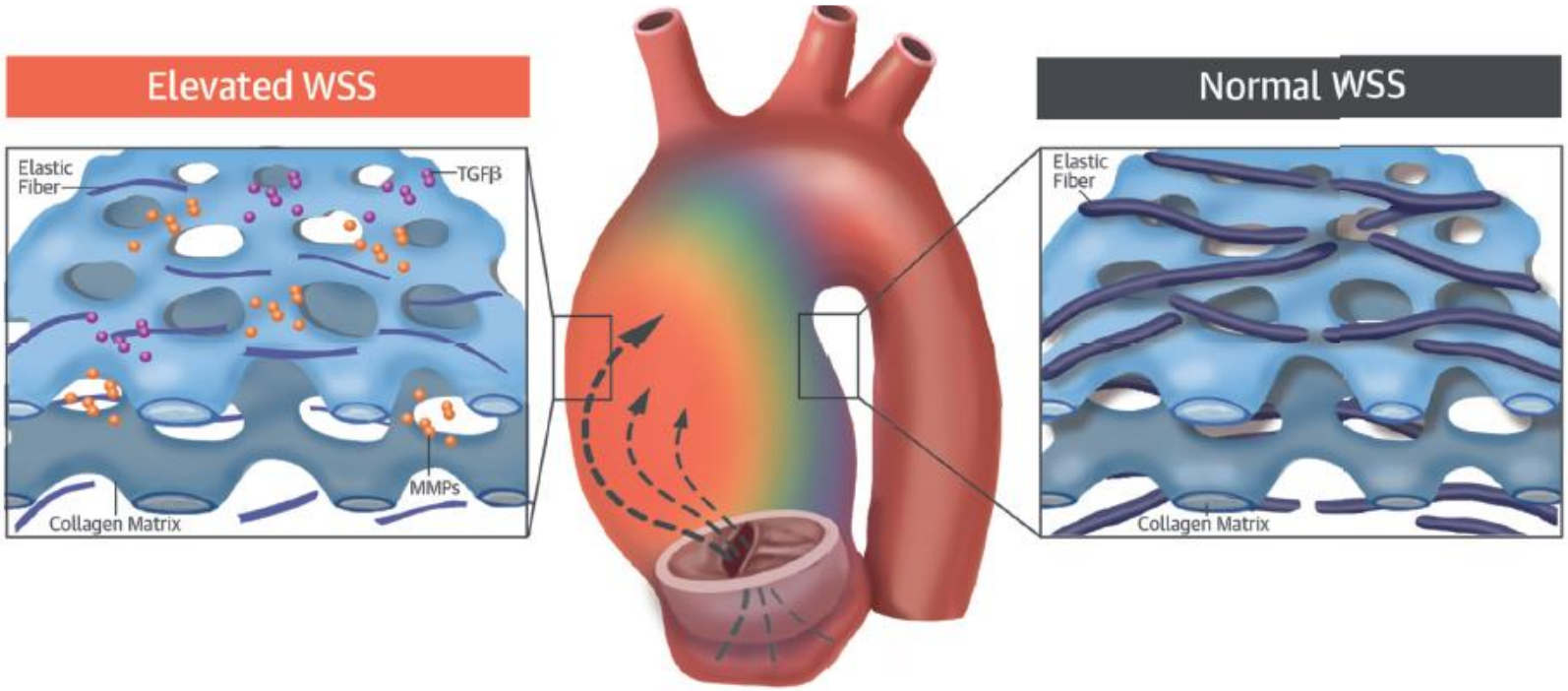
$$\mathbf{F} = \text{diag}\left[\frac{\partial r}{\partial R}, \frac{r\pi}{R\Theta_o}, \lambda\Lambda \right]$$

Importance of Smooth Muscle (~1999)



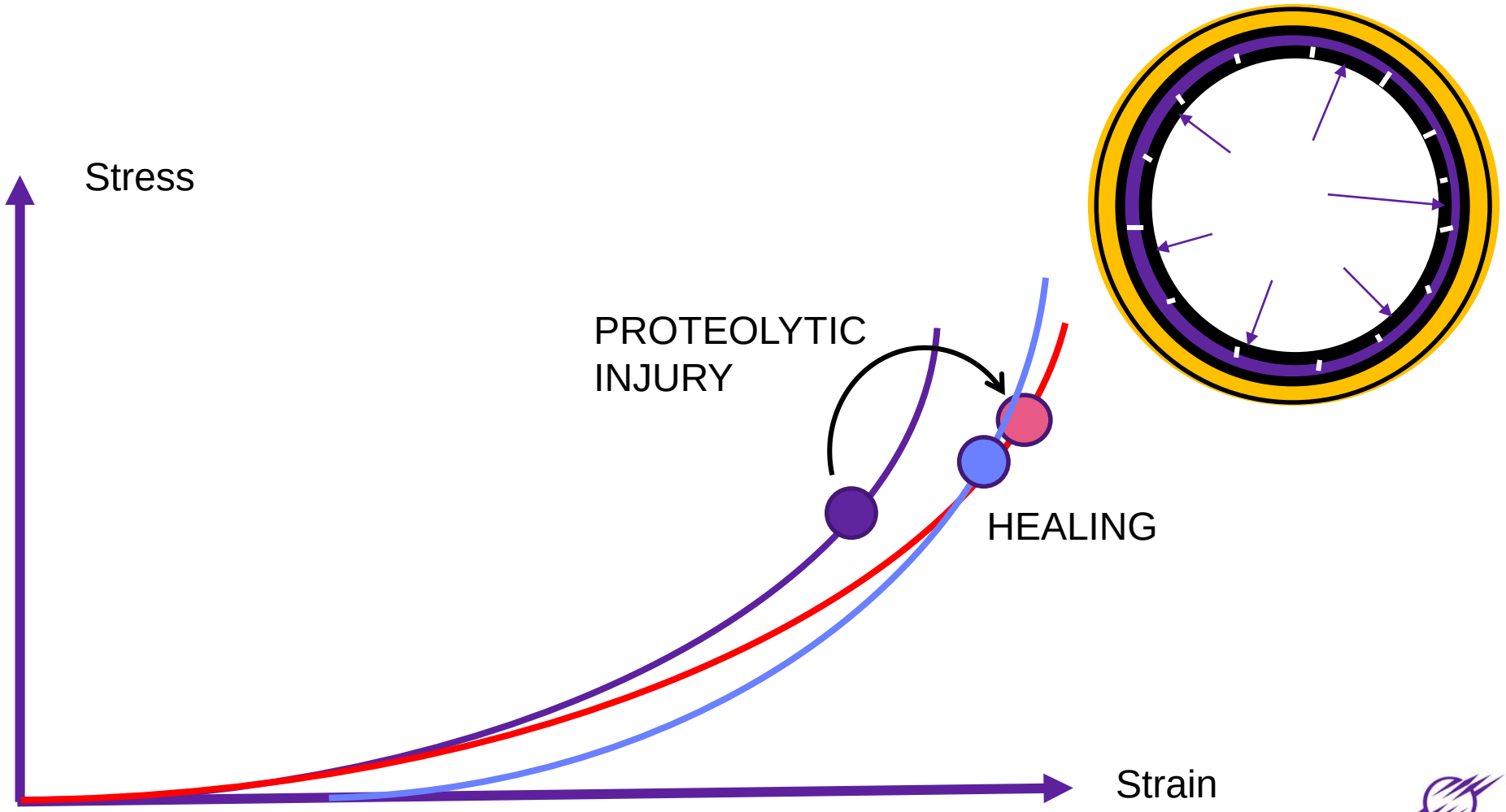
Tensional homeostasis in ATAA?

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

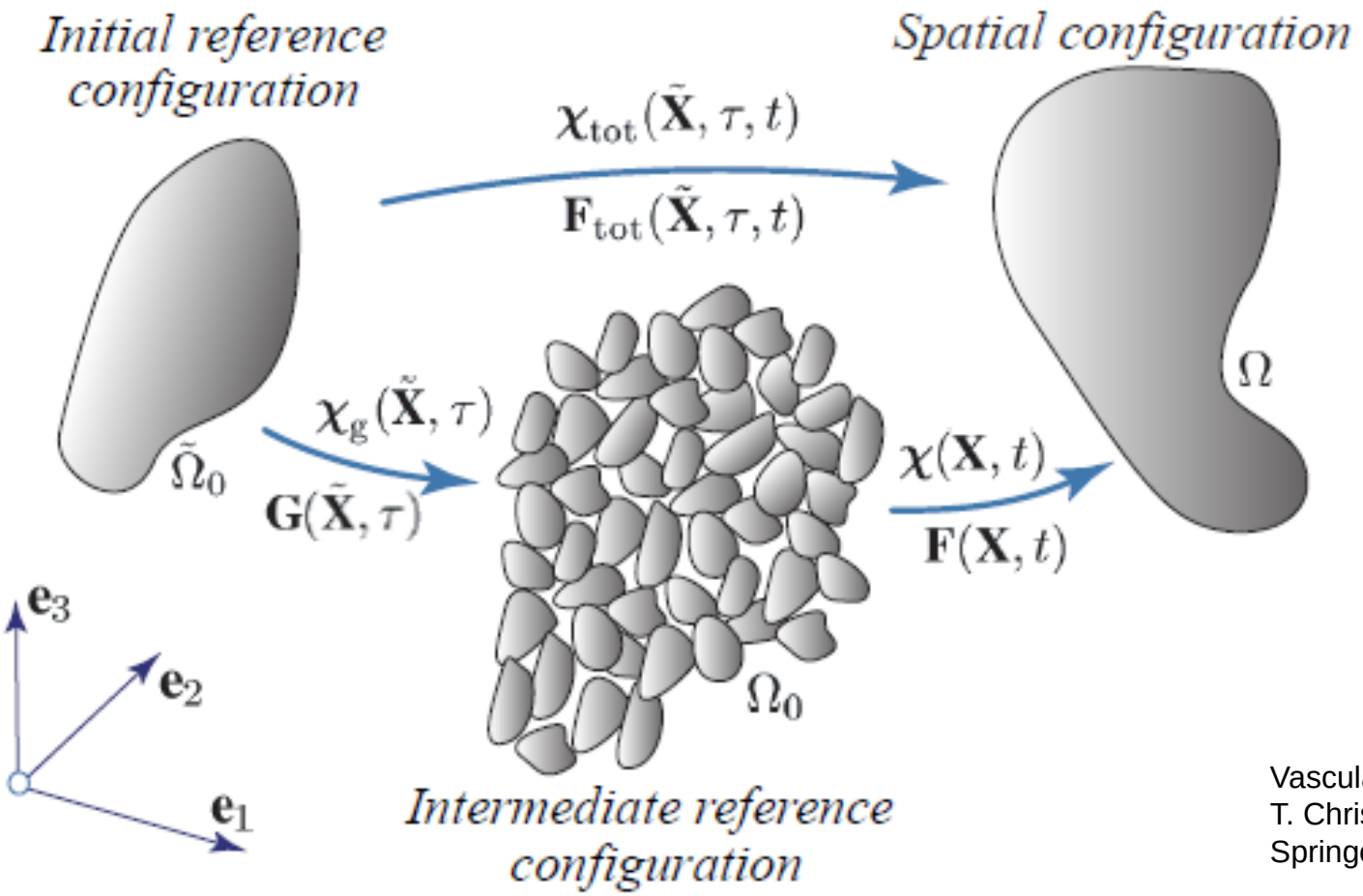


Guzzardi et al, JACC (2014), Condemi et al, IEEE TBME (2019)

Proteolytic injury and tissue adaptation

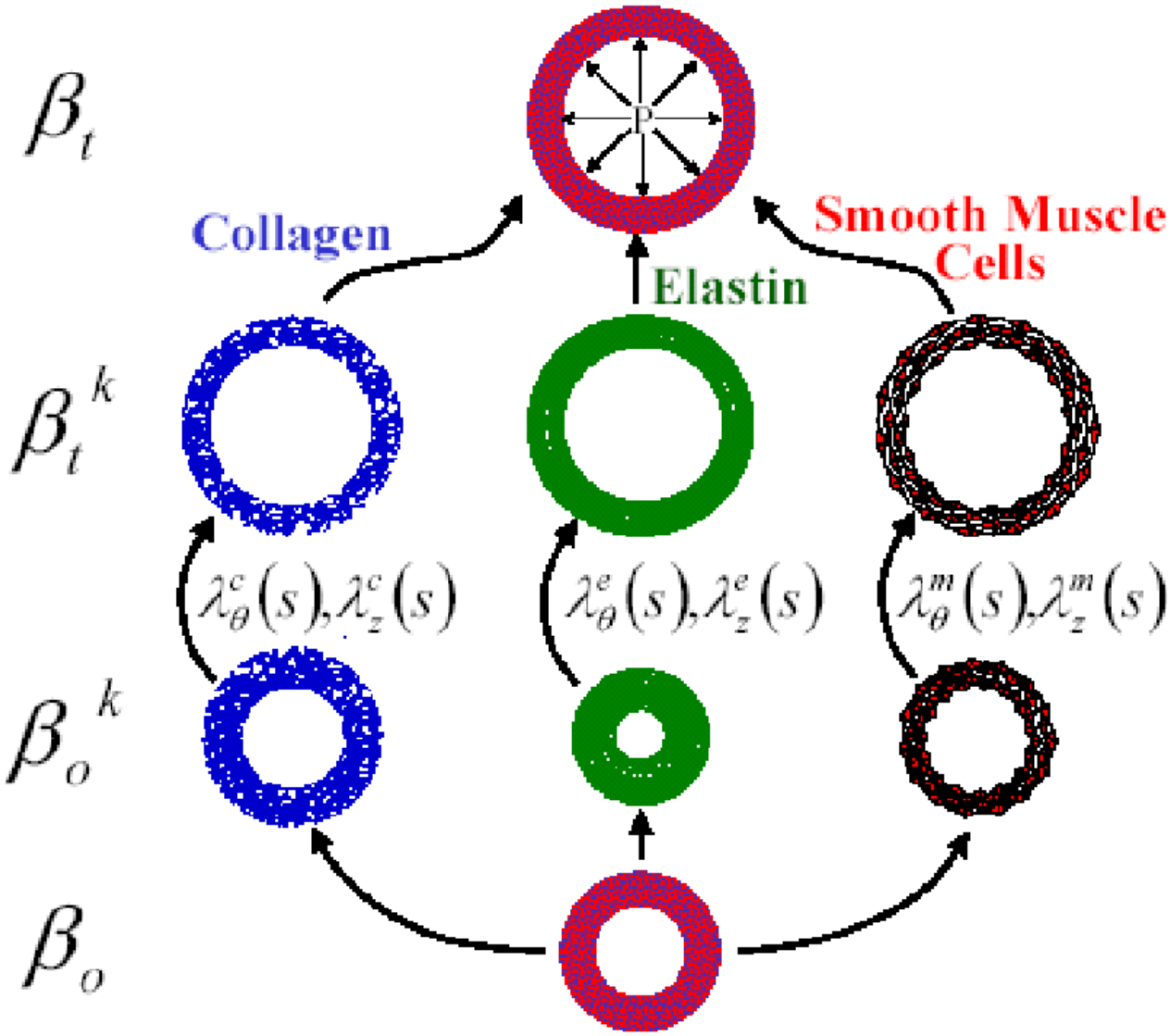


Kinematics-based growth description



Vascular Biomechanics
T. Christian Gasser
Springer

Constrained mixture models



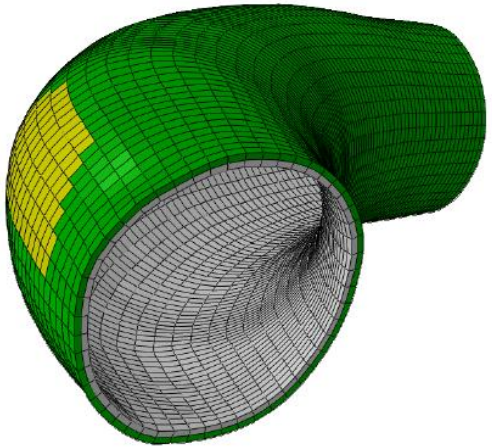
Finite-element simulations

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

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

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

Localization function around the point of TAWSS max



Mousavi et al, BMMB (2019)

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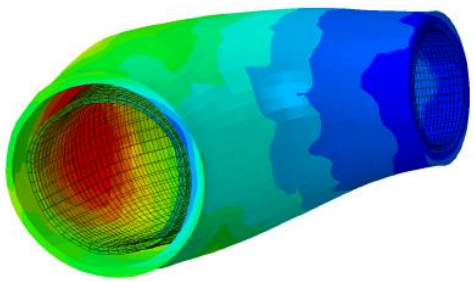
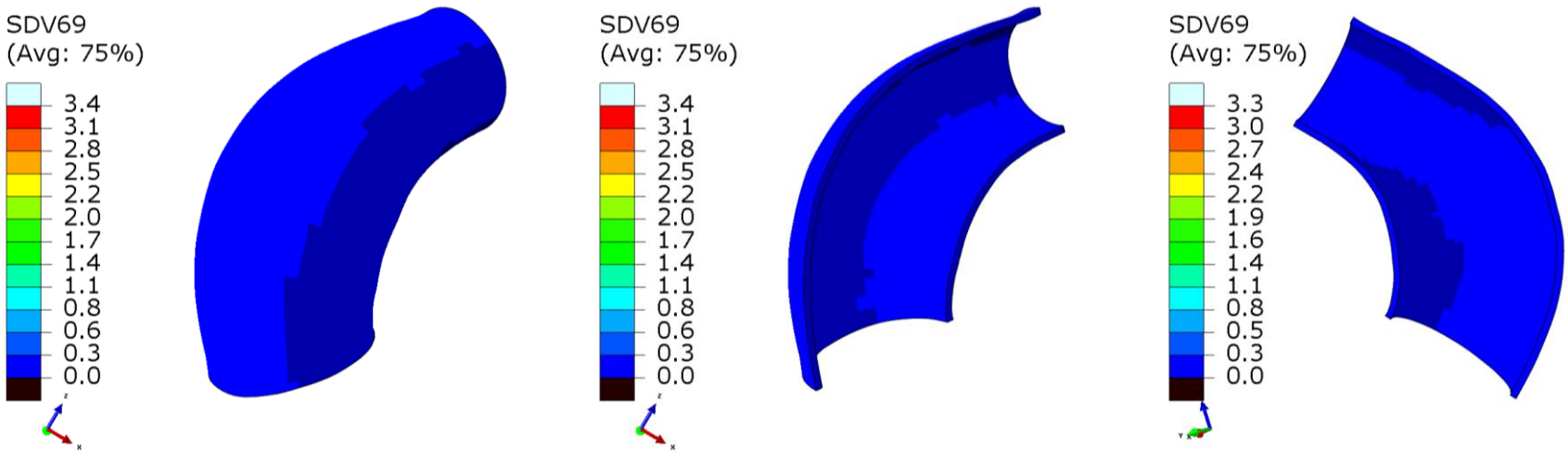
Patient-specific predictions



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

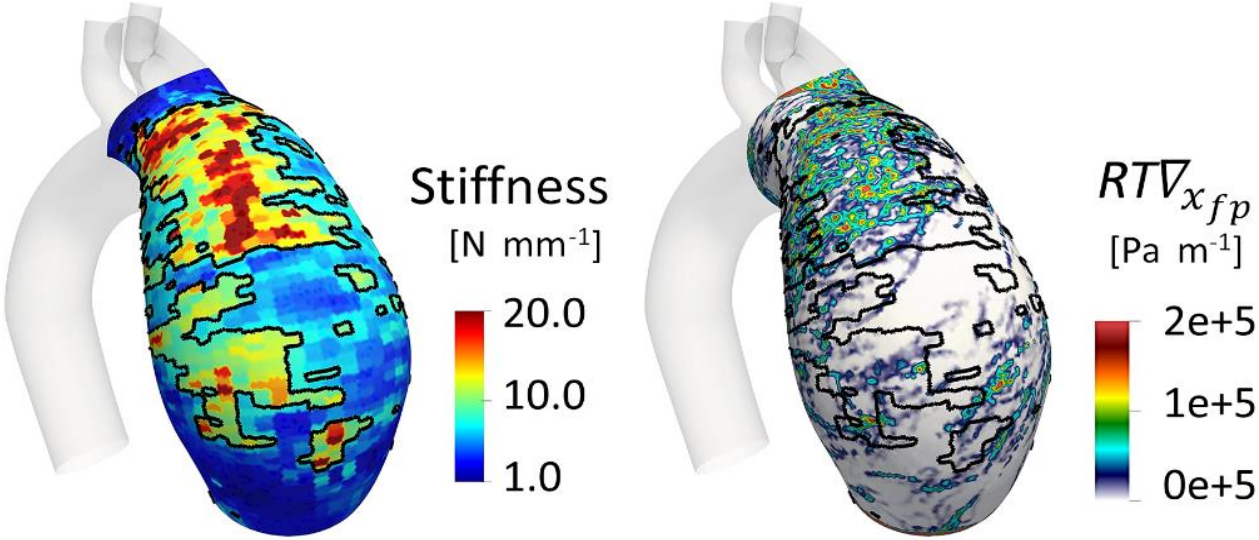
Small growth parameter



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

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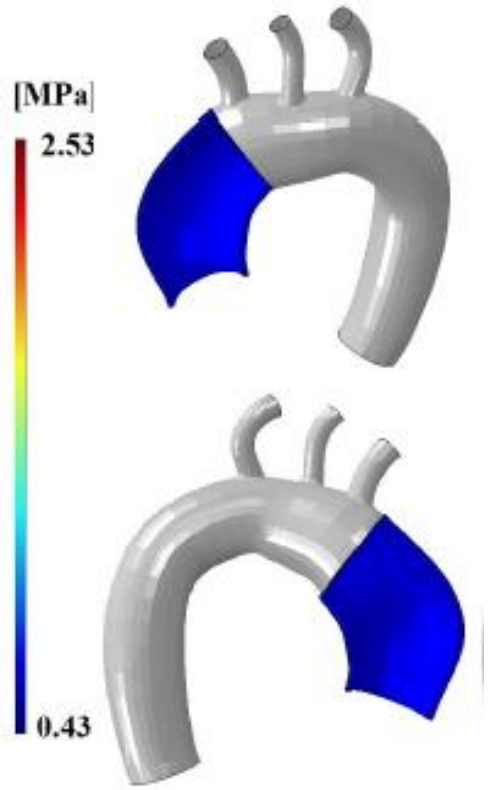
Patient-specific vascular adaptation

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

$$\chi = 1$$

Tangent stiffness after 10 years

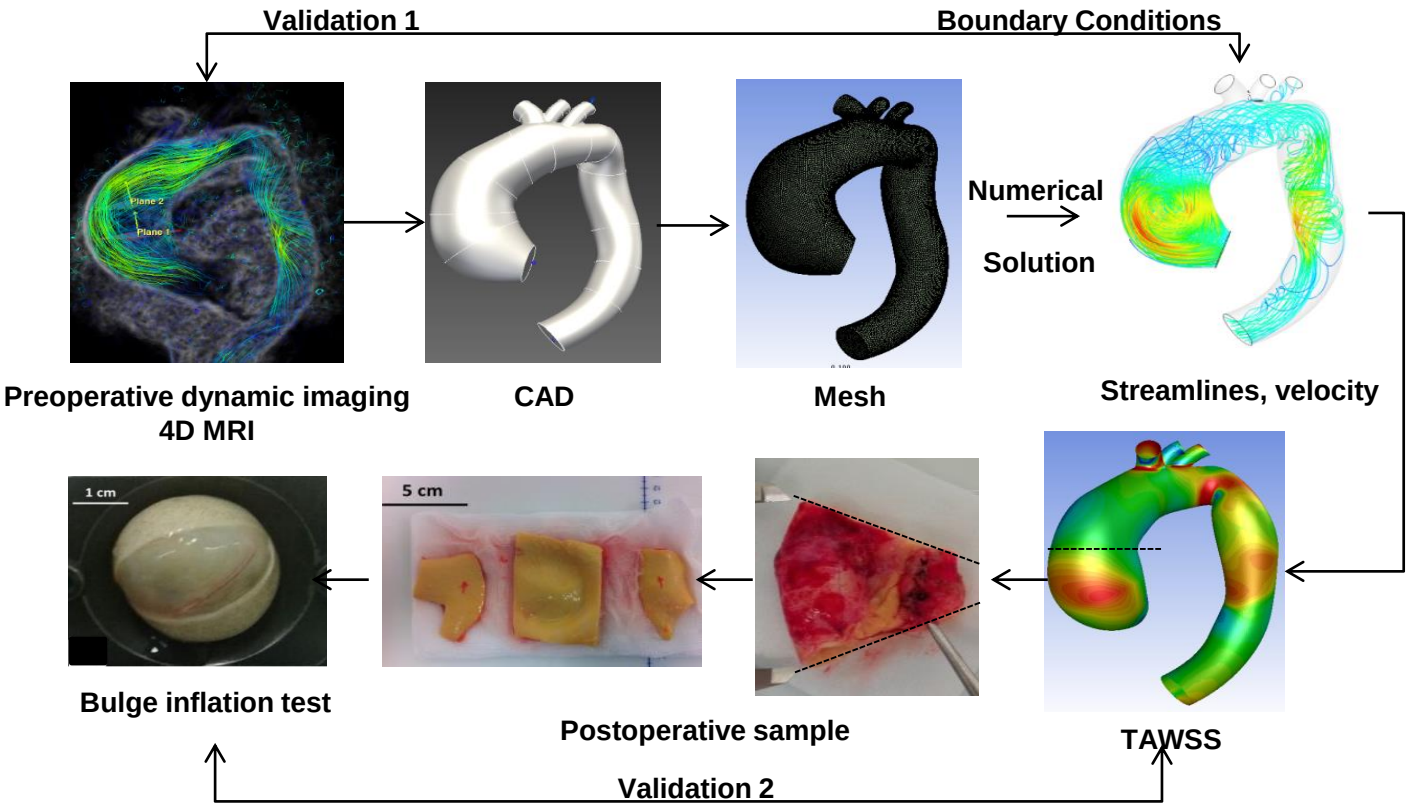


$$\dot{\varrho}^j(t) = \varrho^j(t) k_\sigma^j \frac{\sigma^j(t) - \chi * \sigma_h^j}{\chi * \sigma_h^j}$$

Mousavi et al, CMPB (2021)

TOWARDS INDUSTRIAL APPLICATIONS: AUGMENTED MEDICAL IMAGING

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



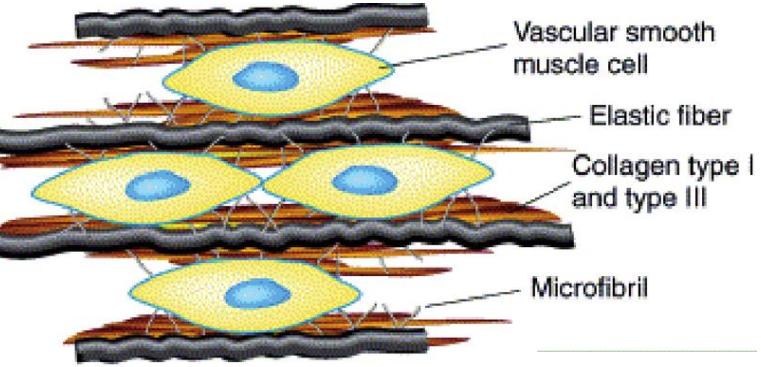
OUTLINE

- PART I: Industrial applications of continuum mechanics models in cardiovascular medicine

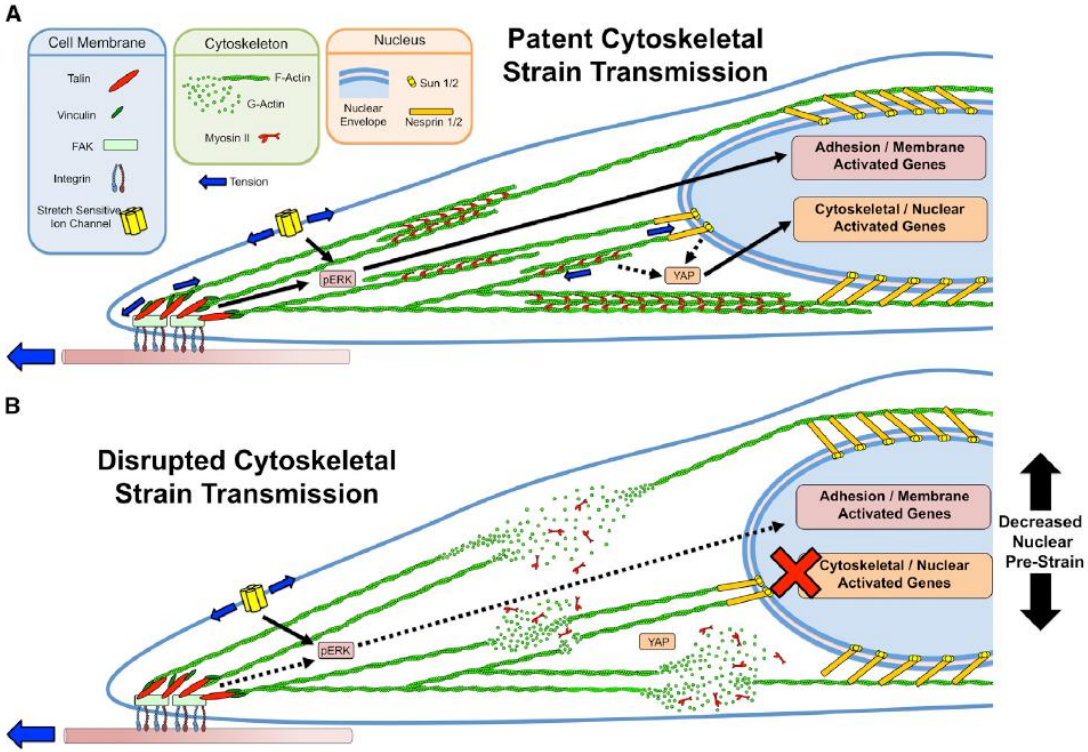
- PART II: The need of combining data driven and continuum mechanics models in cardiovascular mechanobiology

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

Introduction to mechanobiology



Driscoll et al, Biophysical Journal, 2015



Major role of smooth muscle cells in mechanoregulation

Primary SMC cultures

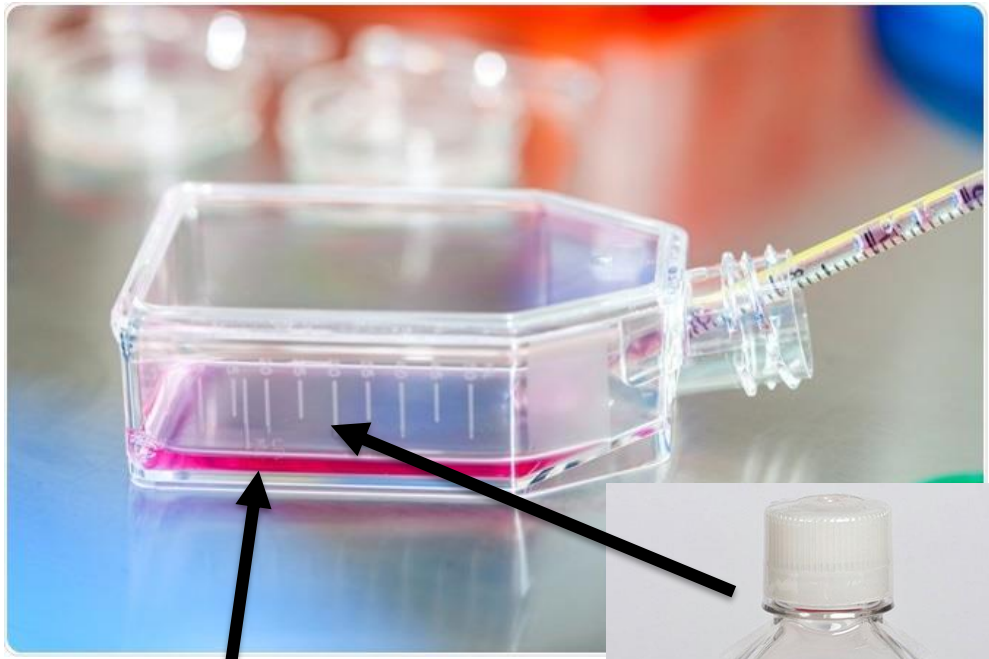
AoSMC lineage

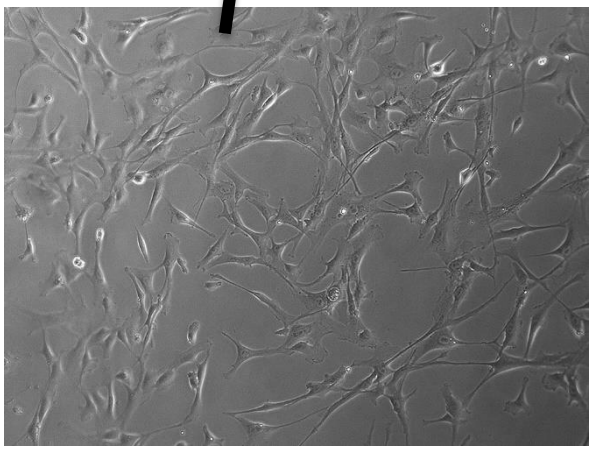
Thawing

Growing (SmGM-2)

Differenciation (SmBM)

Sample preparation



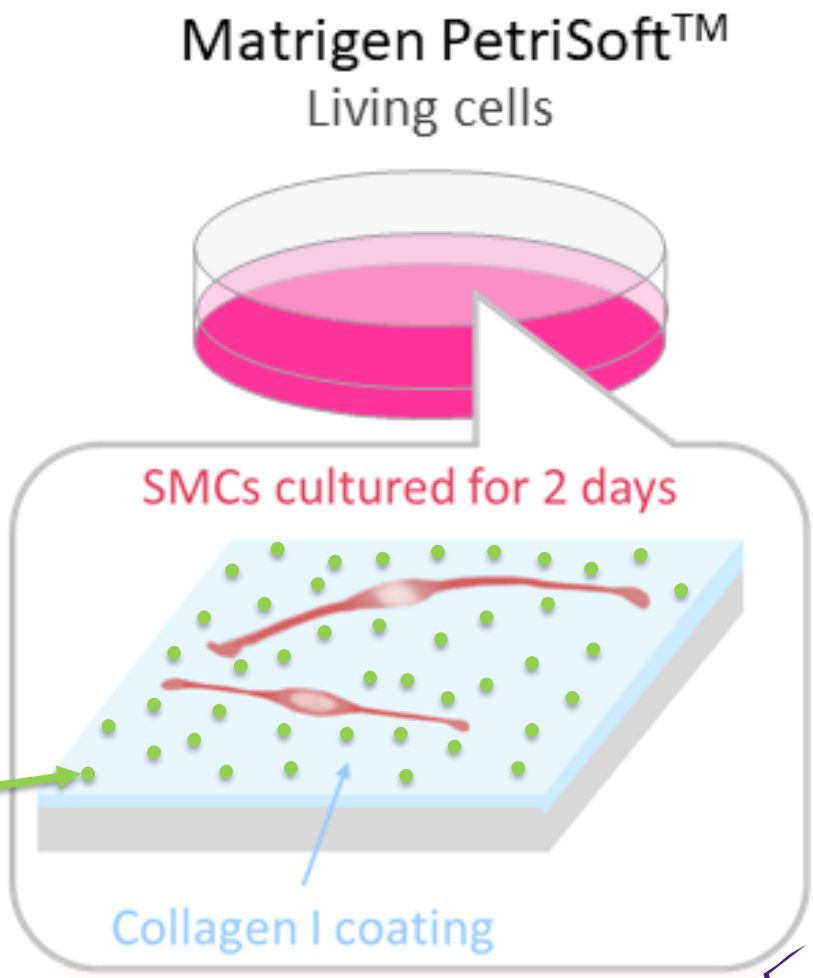


Traction force microscopy

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

Age

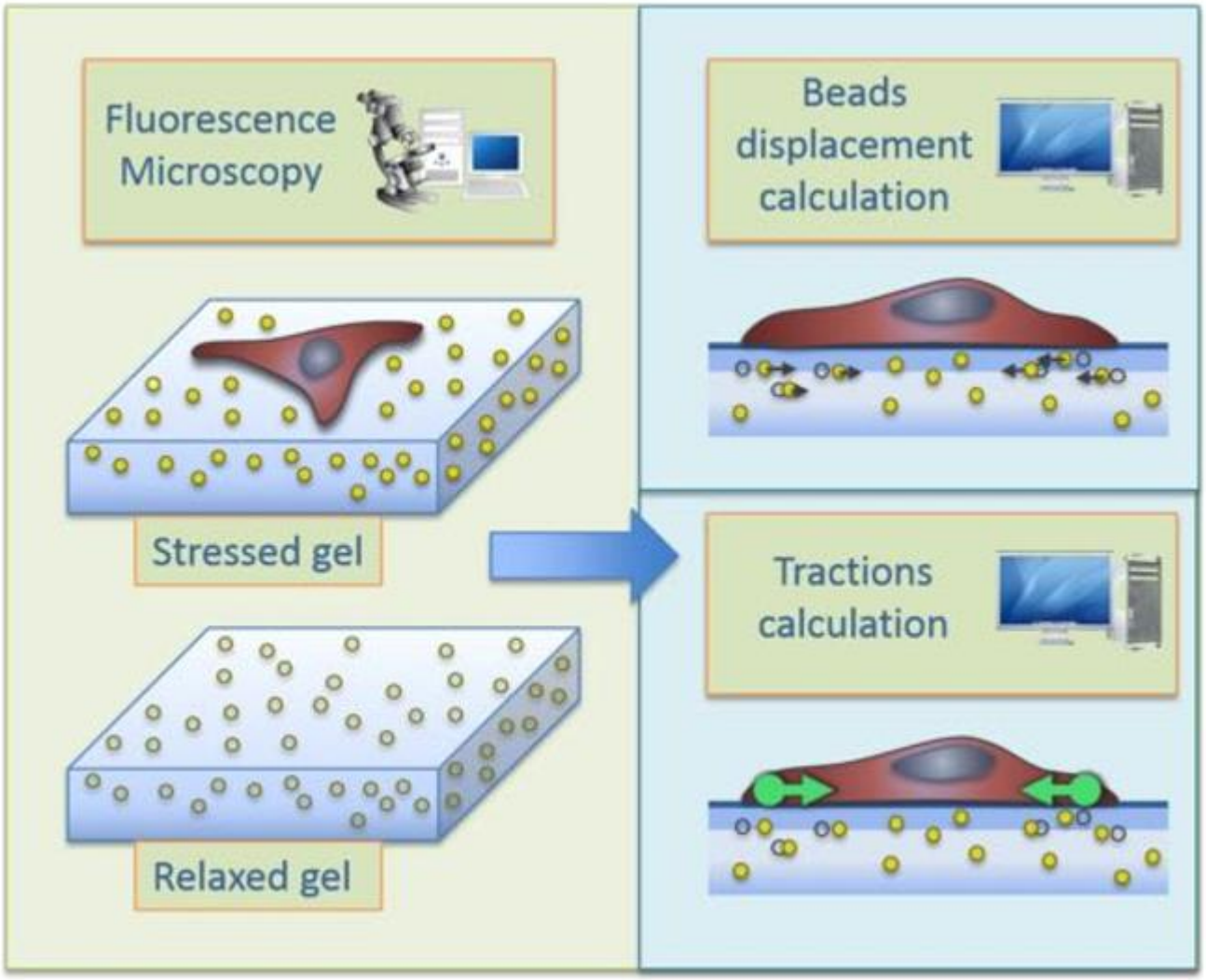
Pathology



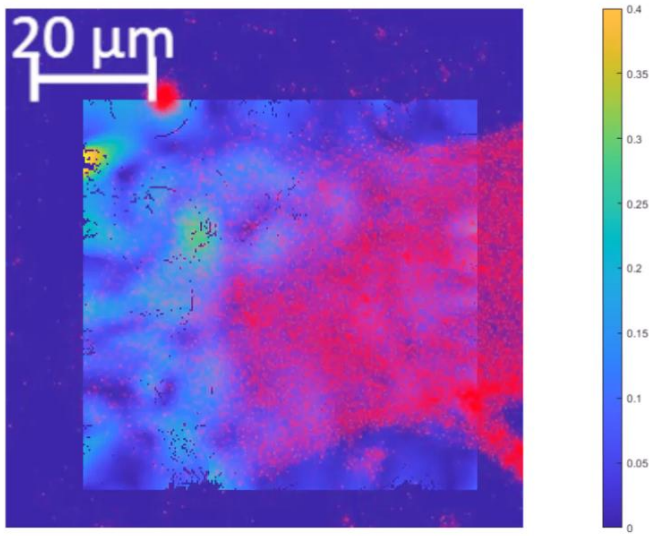
Fluorescent microbeads (yellow-green, 0,2µm φ)

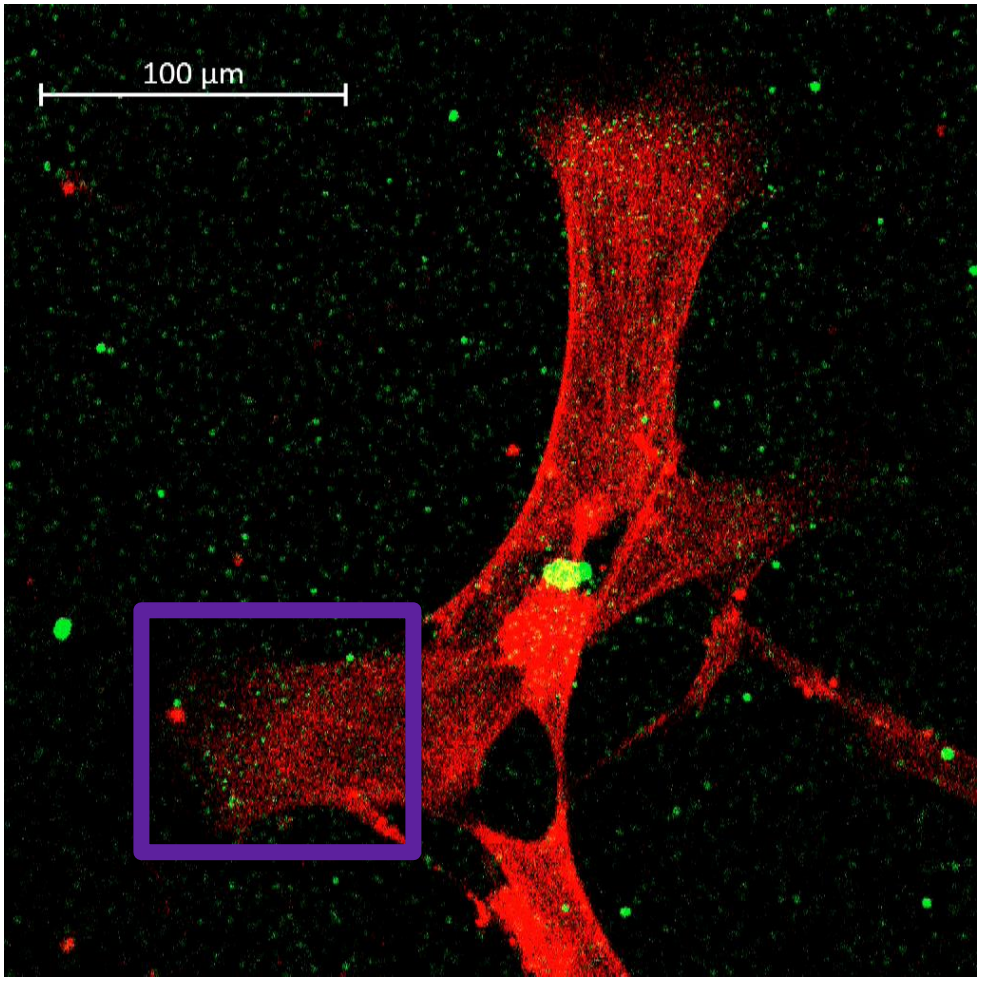
Traction force microscopy

Petit et al, BMMB, 2021



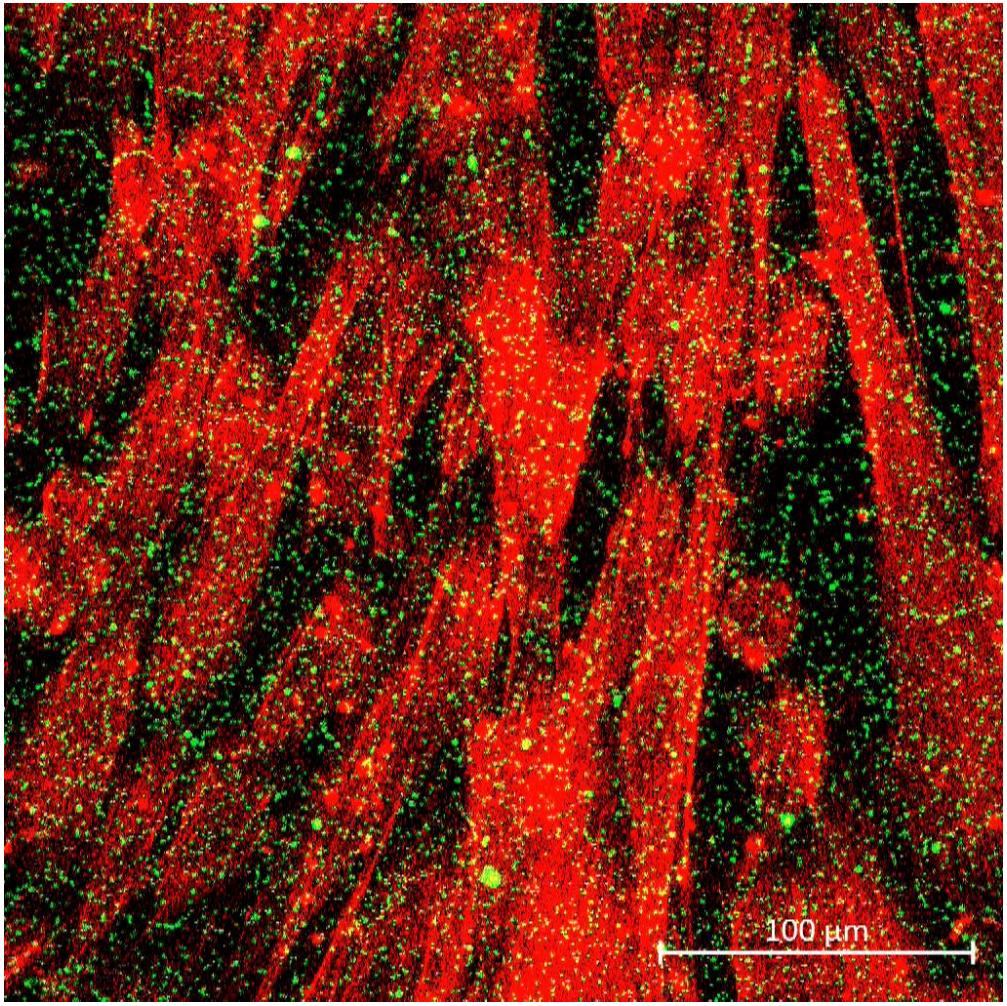
Monitoring mechanobiology of live SMCs





Confocal microscopy + DIC combined with Siractin staining on living cells

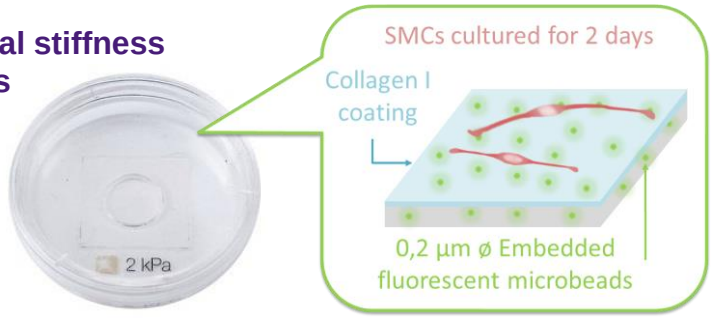
Isolated SMCs versus confluent SMCs



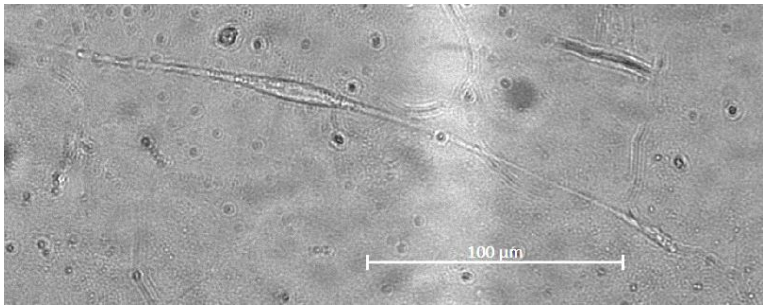
avril@emse.fr

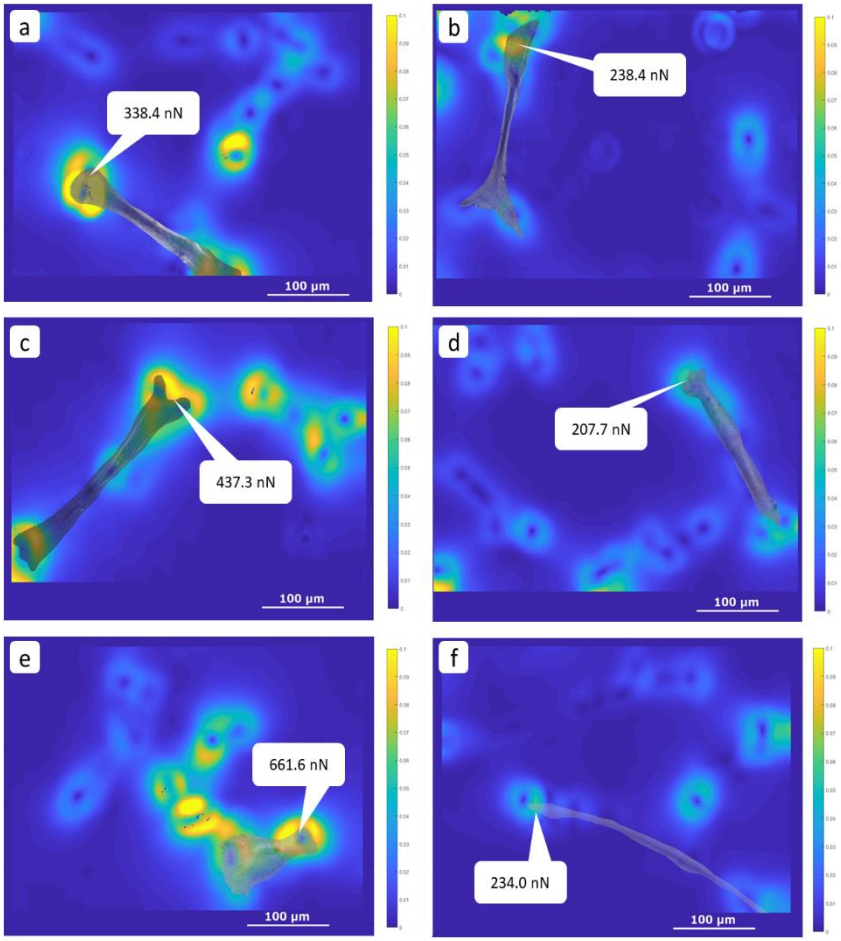
Monitoring mechanobiology *in vivo*

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

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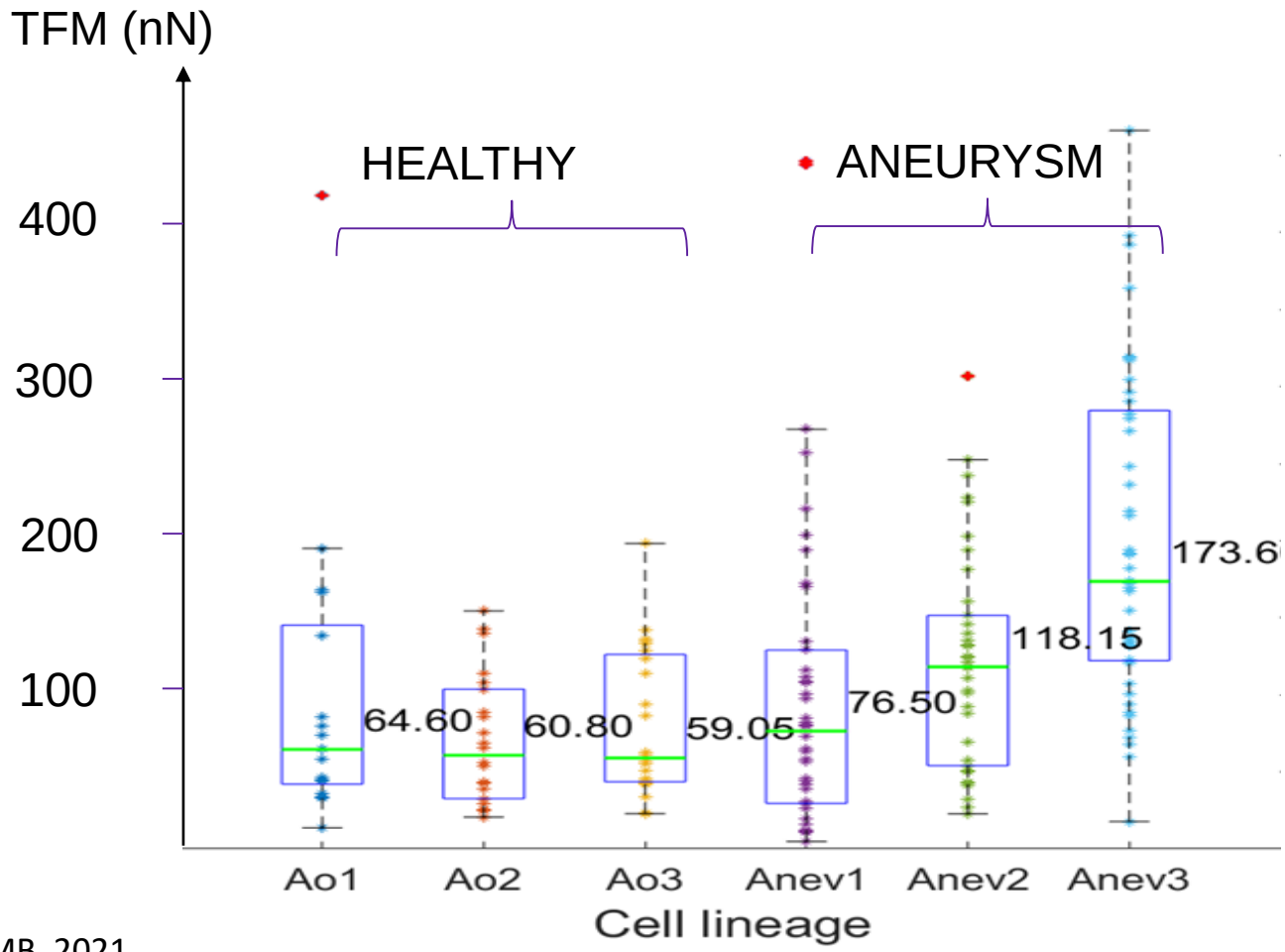
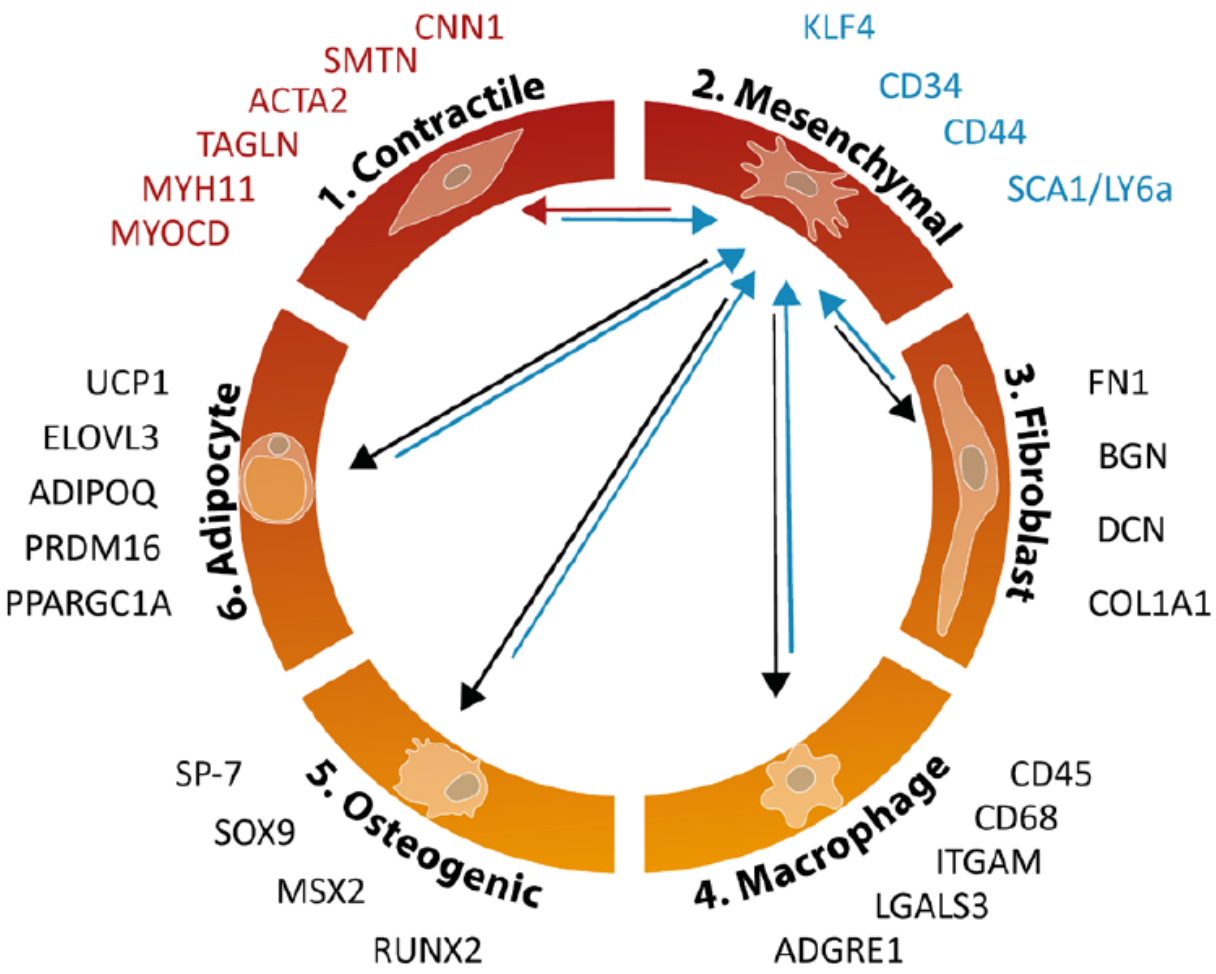
Aneurysmal SMCs tend to apply larger traction forces



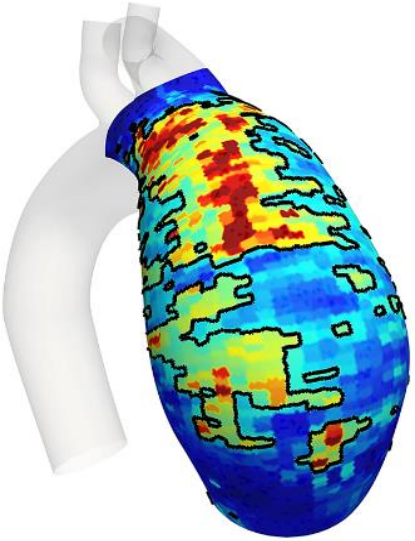
Petit et al, BMMB, 2021

Variety of SMC phenotypes

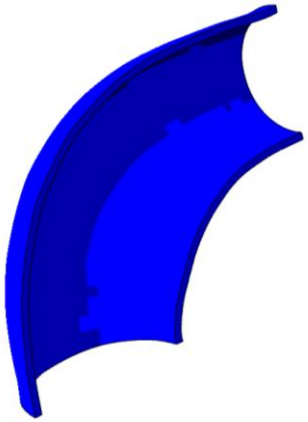


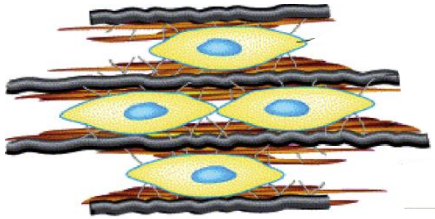
Yap et al, ATVB. 2021; 41:2693–2707

TOWARDS DIGITAL TWINS



Monitoring gene expressions, tissue stiffness
and hemodynamics





Predicting mechanical regulation,
tissue deformations, stresses and stiffness

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Acknowledgements

- Marta Bracco
- Maria Nicole Antonuccio
- Federica Galbiati
- Francesco Bardi
- Francesca Condemi
- Beatrice Bisighini
- Cristina Cavinato
- Salvatore Campisi
- Simona Celi
- Marco Biancolini
- Michele Marino
- Umberto Morbiducci
- Diego Gallo
- Salvatore Pasta
- Marzio Di Giuseppe
- Joan Laubrie
- Chloé Techens
- Jérôme Molimard
- Baptiste Pierrat
- Fanette Chassagne
- Claire Morin
- Miquel Aguirre
- Jamal Mousavi
- Shaojie Zhang
- Felipe Sempertegui
- Di Zuo
- Yiqian He
- Victor Acosta
- Felipe Sempertegui
- Solmaz Farzeneh
- Claudie Petit
- Ali Akbar Karkhaneh
- Amira Ben Hacine
- Jay Humphrey
- Christian Cyron
- Fabian Braeu
- Jean-Noël Albertini
- Magalie Viallon
- Pierre Croisille
- Joannes Kalliauer
- Christian Hellmich
- Selda Sherifova
- Gerhard Holzapfel