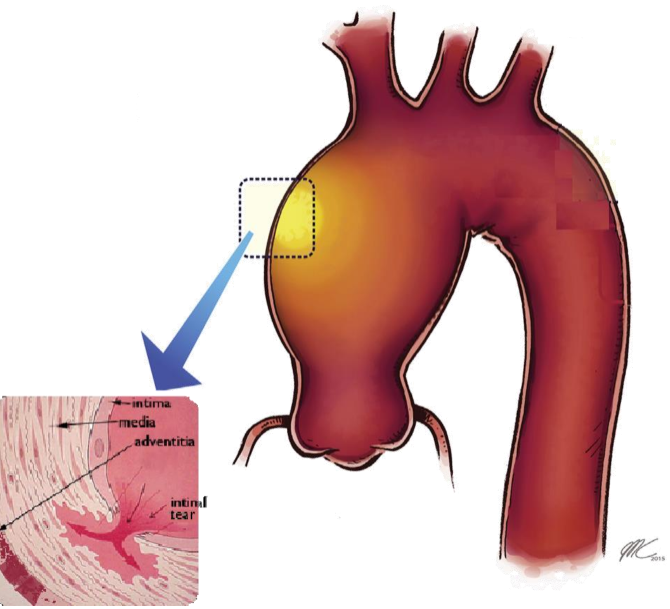
TU Graz

TECHNISCHE UNIVERSITÄT WIEN Vienna | Austria

MINES Saint-Étienne
Une école de l'IMT

Multiscale mechanics of Aneurysms: what can biologists and clinicians learn from engineers?



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

- Autonomic Nervous System Epidemiology, Physiology, Engineering, Health EA 4607

- Thrombosis Research Group, EA3065
- Interdisciplinary Aerosolized Nanoparticles Laboratory, EA 4624

- Laboratory of Integrative Biology of Bone Tissue INSERM U1059

- Platelet Inflammatory response to stress

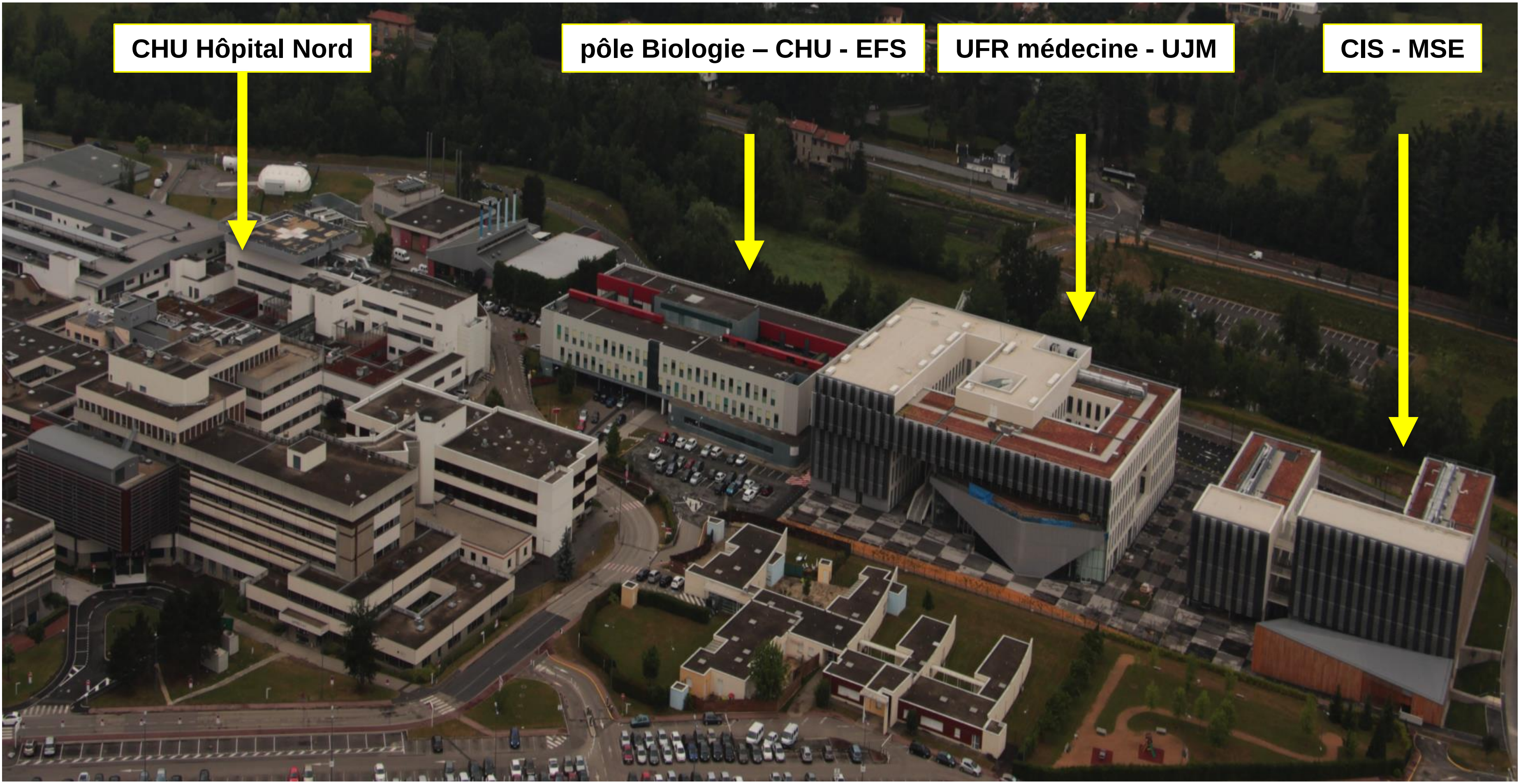
CIS, biomedical engineering centre

- Biomechanics of Soft Tissues, Medical Textiles and Implants
- Engineering of biomaterials and aerosols

SAINBIOSE = 200 people

- Centre d'Investigation Clinique (CIC, INSERM)
- Clinical departments
- Biology
- Medical Imaging

« Where engineers, biologists and physicians meet together to improve health »



Since 2016 - 60 m€ from CPER and other public private sources

BOOSTED BY THE DYNAMISM IN BIOTECH AND HEALTH OF THE LYON AREA

IVTV
INGÉNIERIE ET VIEILLISSEMENT DES TISSUS VIVANTS

Inserm
La science pour la santé
From science to health

IDEX LYON
UNIVERSITÉ DE LYON

Ingénierie Lyon Saint-Etienne
Inge'LySE

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POLE des TECHNOLOGIES MEDICALES
connecting expertise

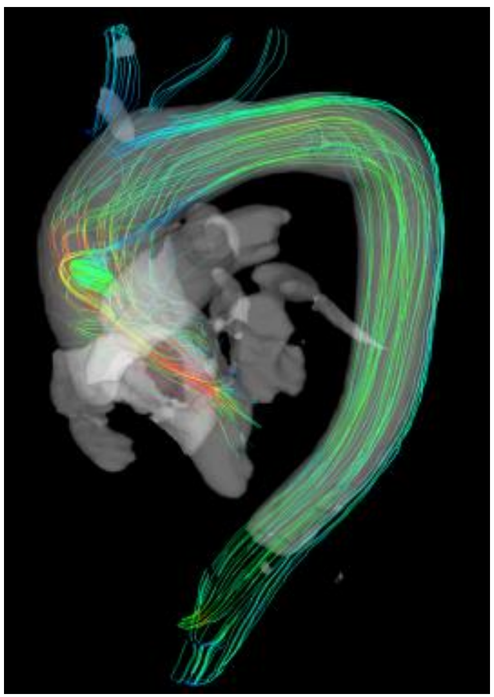
RÉPARER L'HUMAIN
GROUPE DE RECHERCHE NATIONAL

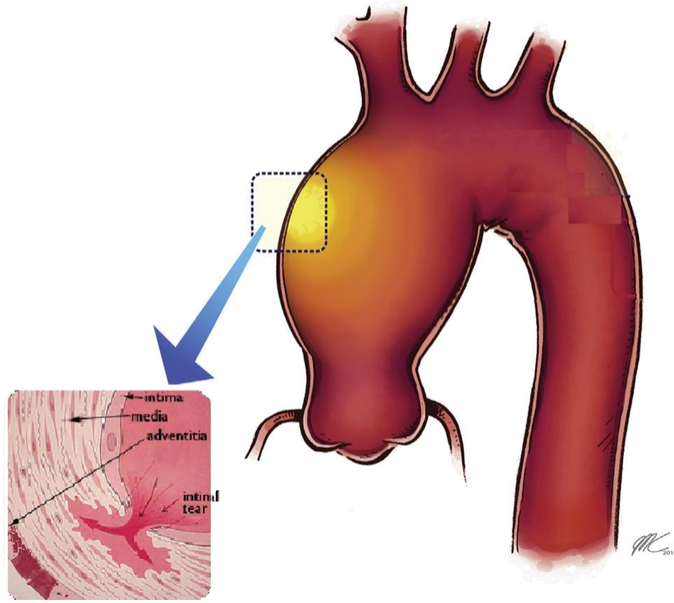
MANUTECH SLEIGHT
Université de Lyon

LYONBIOPOLE
Auvergne - Rhône - Alpes

CHAIRE SANTÉ DES AINÉS
INGÉNIERIE DE LA PRÉVENTION

Aneurysms and Dissections of the aorta





== Devastating complications!

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

OUTLINE

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

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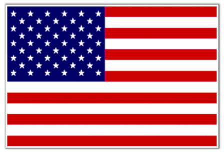
- PART III: Towards continuum mechanics of tensional homeostasis down to the subcellular level

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

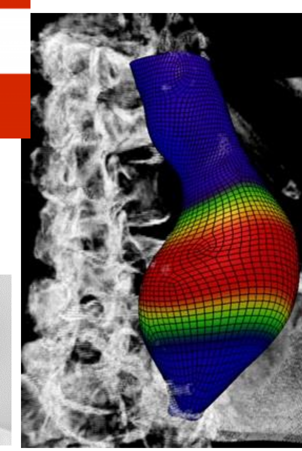
El Faquir N, *et al* Int J Cardiov Img 2019

2014: Sim&Cure

2017: Predisurge

Derycke, *et al* Circulation Img 2021

Vascops



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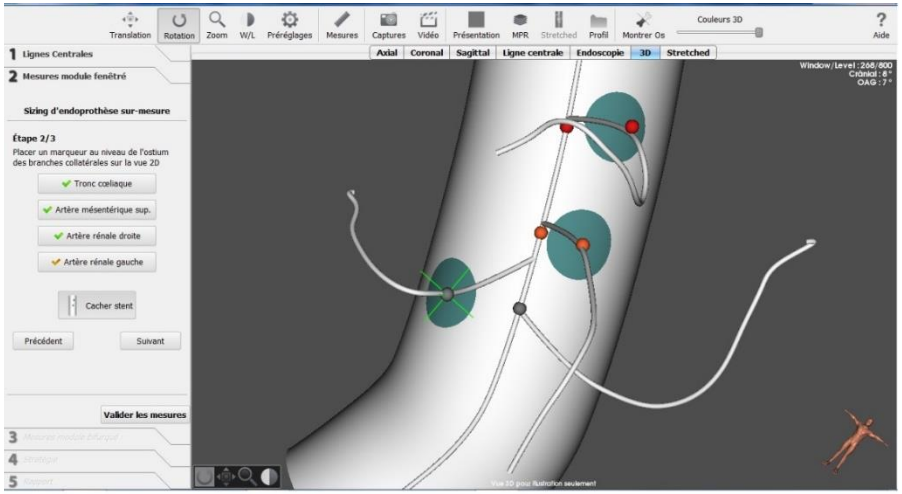
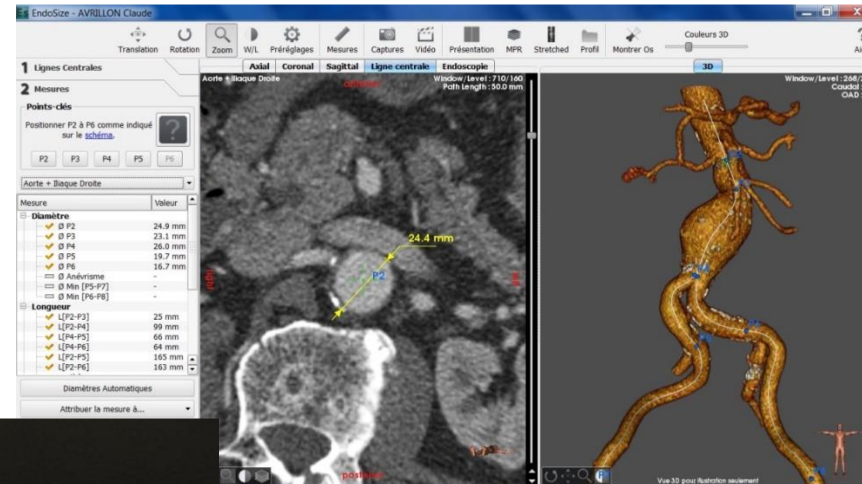
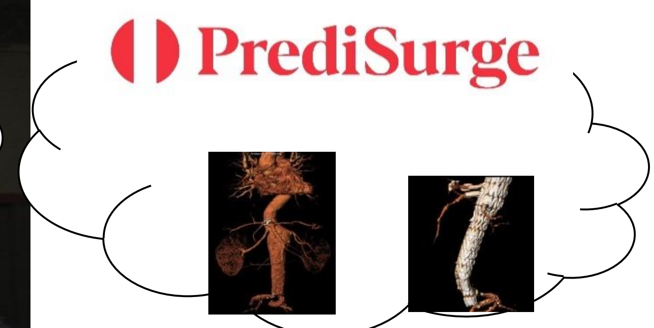
Planification / sizing of fenestrated stent grafts in EVAR procedures



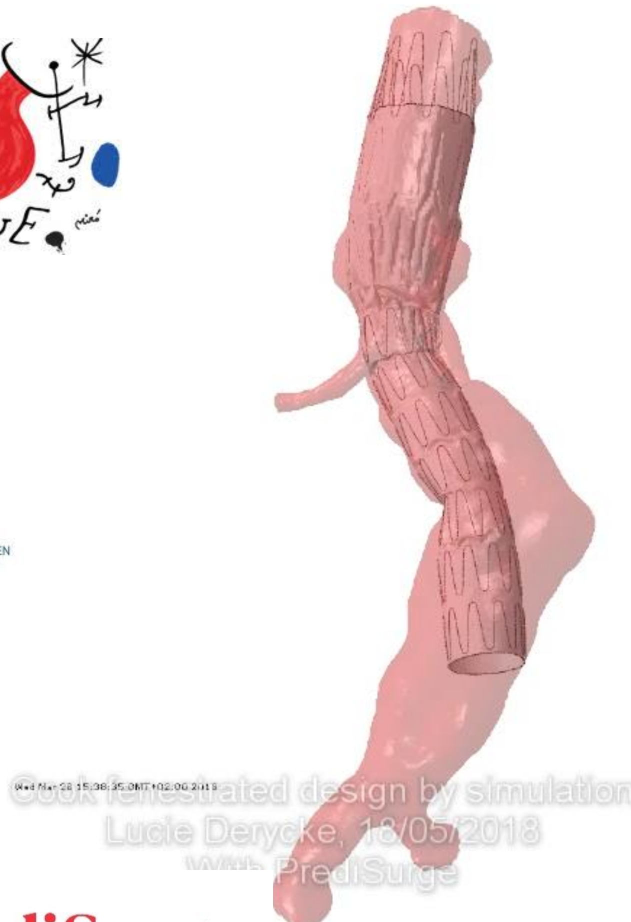


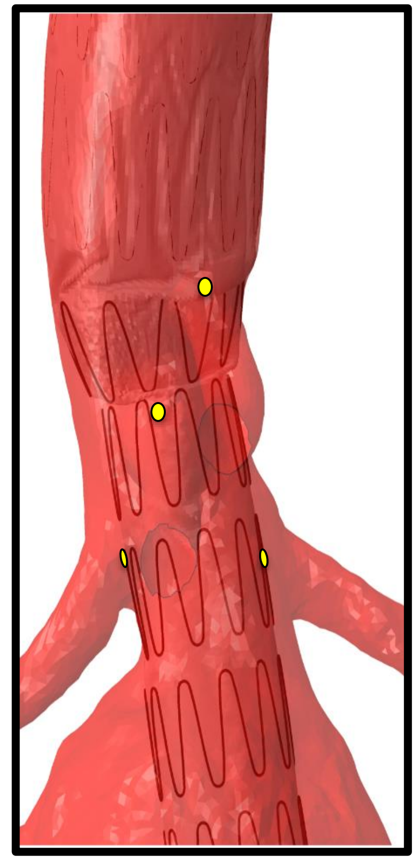


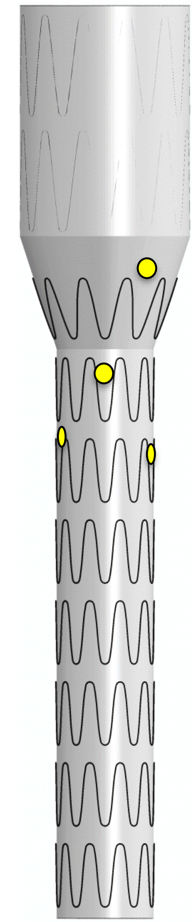
Clinically validated for FEVAR Zenith® Cook Medical

Marie Lannelongue

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







PrediSurge

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Une école de l'IMT

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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

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Jay D. Humphrey:

From Complexity Comes Simplicity

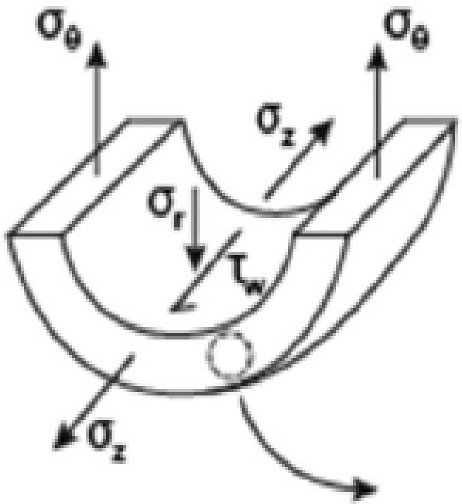
- Nonlinear Material Properties and Large Strain
- Anisotropy (circumferential muscle, axial collagen)
- Residual Stresses
- Smooth Muscle Activation
- Heterogeneity (functionally graded)

→ MECHANOREGULATION

Early Stress Analyses (~1979)

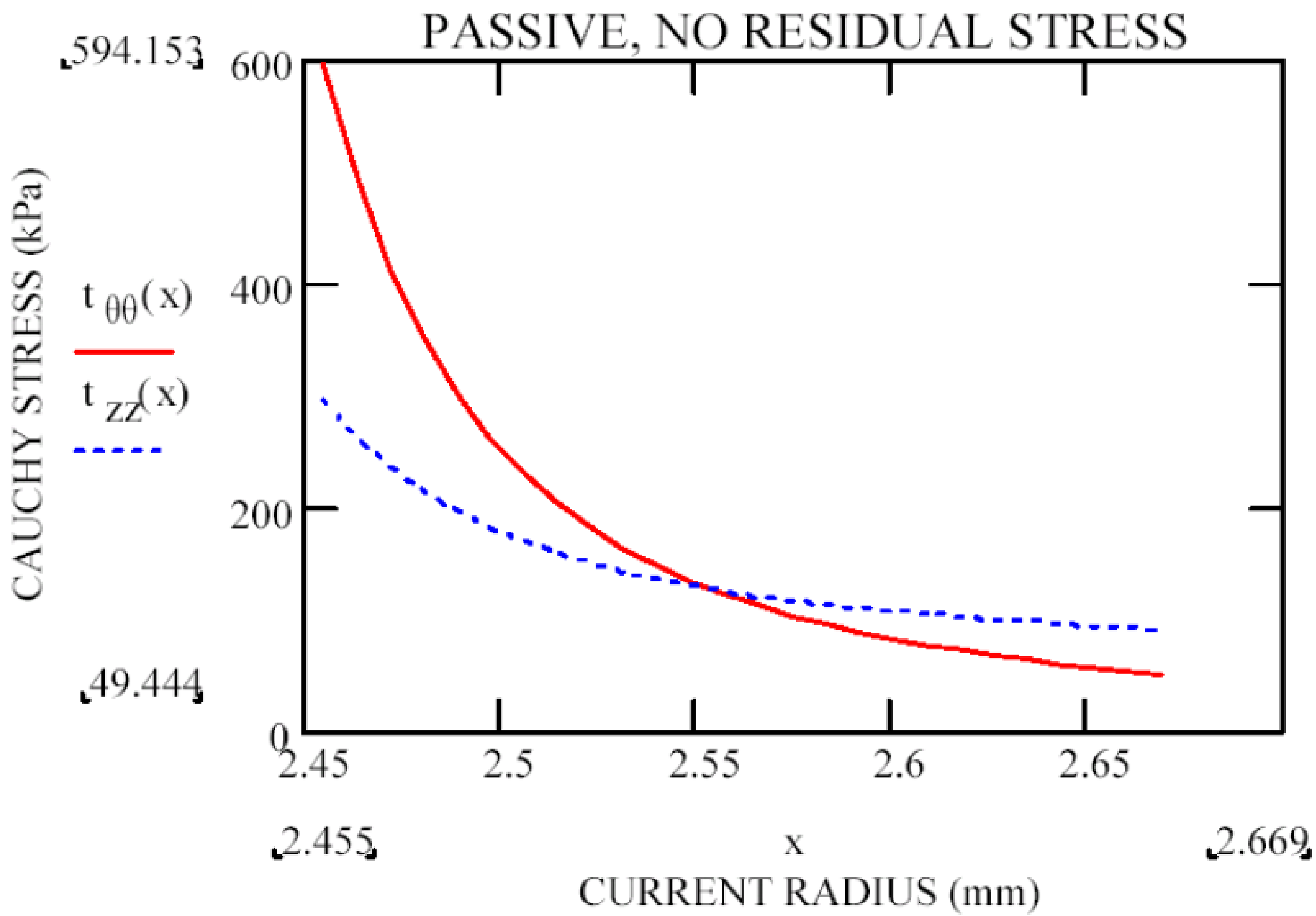
$$\mathbf{t} = -p\mathbf{I} + \tfrac{1}{2}ce^{Q}\mathbf{F}\cdot\frac{\partial Q}{\partial \mathbf{E}}\cdot\mathbf{F}^{T}$$

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



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

Early Stress Analyses (~1979)



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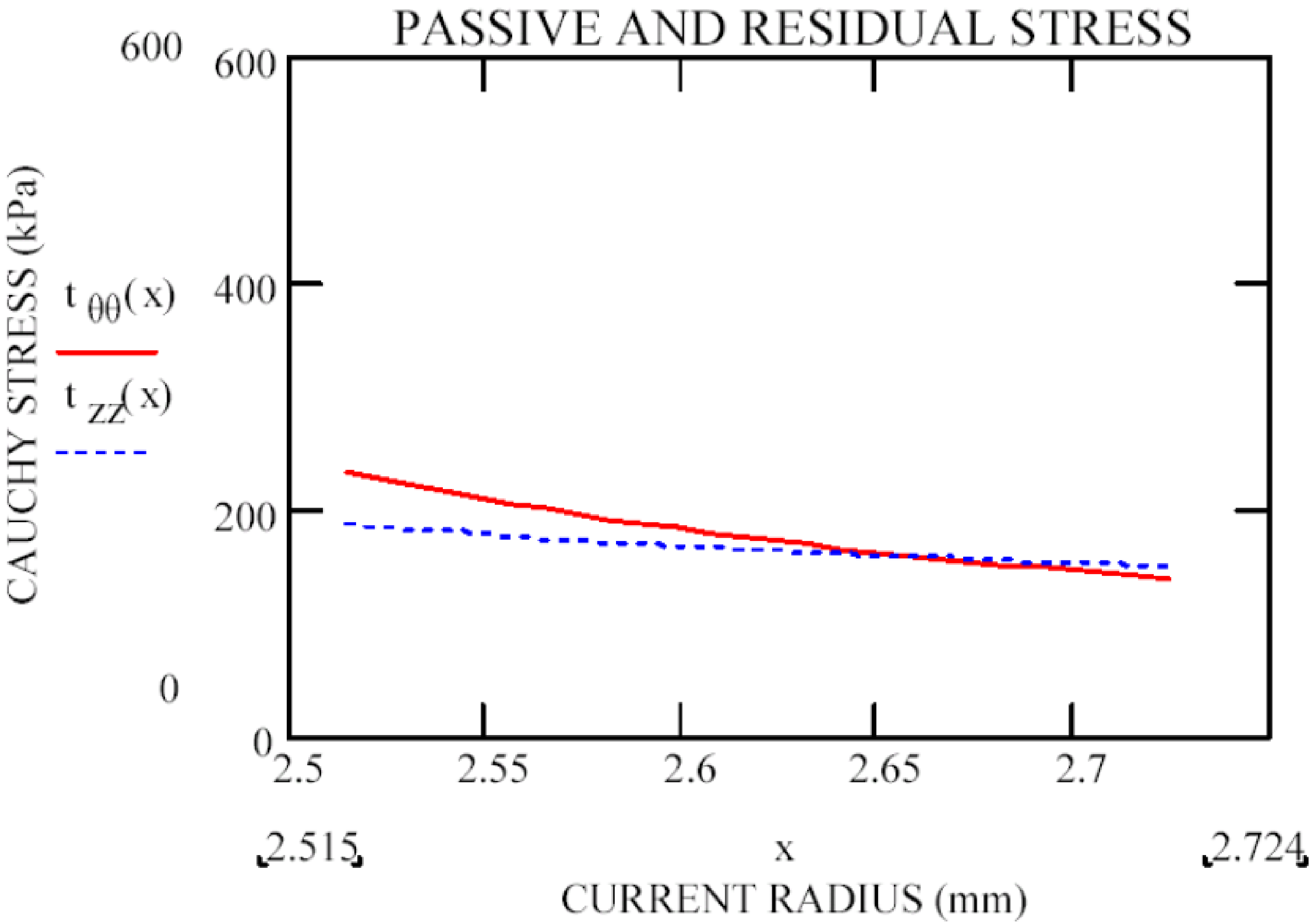
Importance of Residual Stress (~1986)

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

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

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

Importance of Residual Stress (~1986)



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Importance of Smooth Muscle (~1999)

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

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

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

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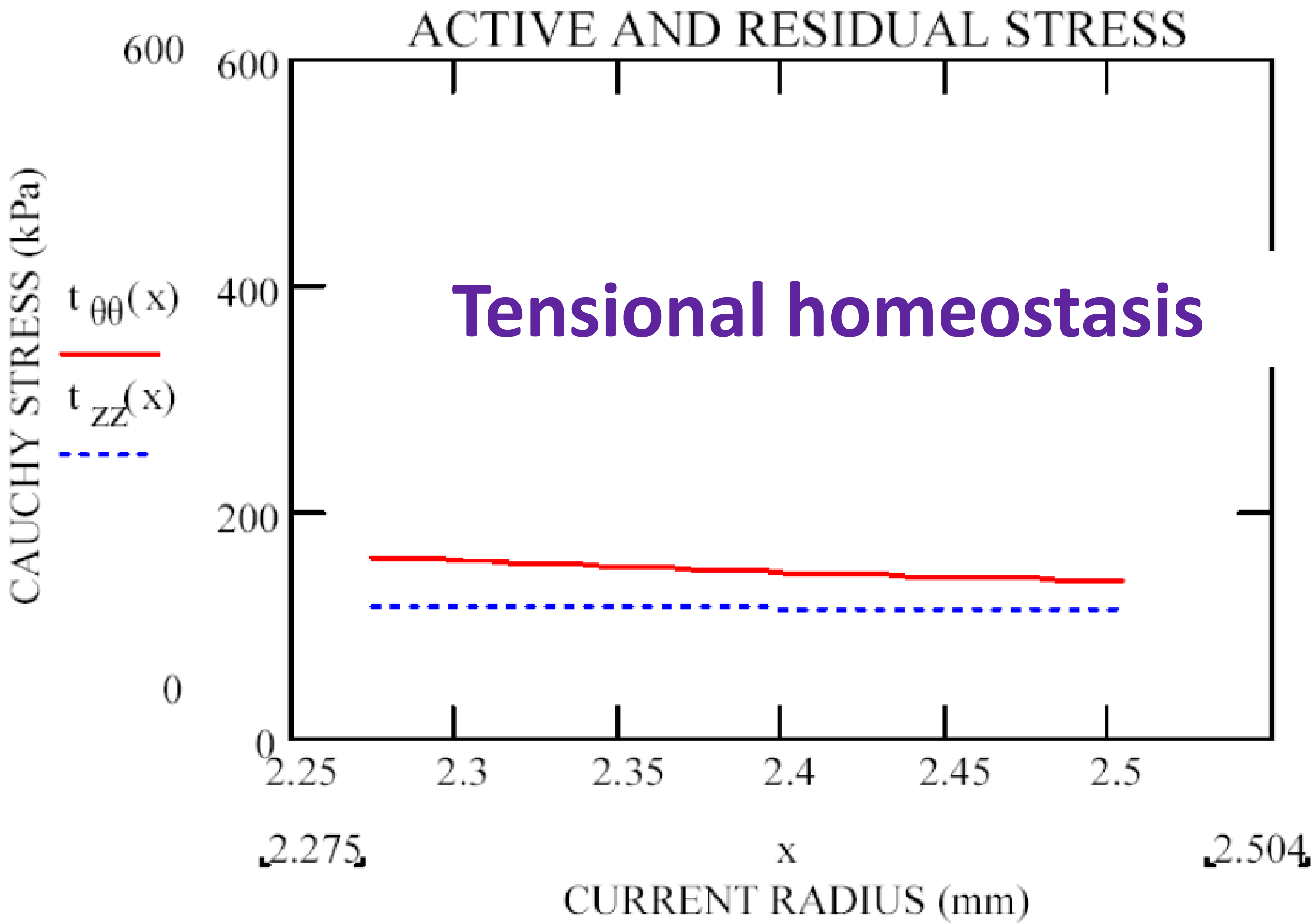
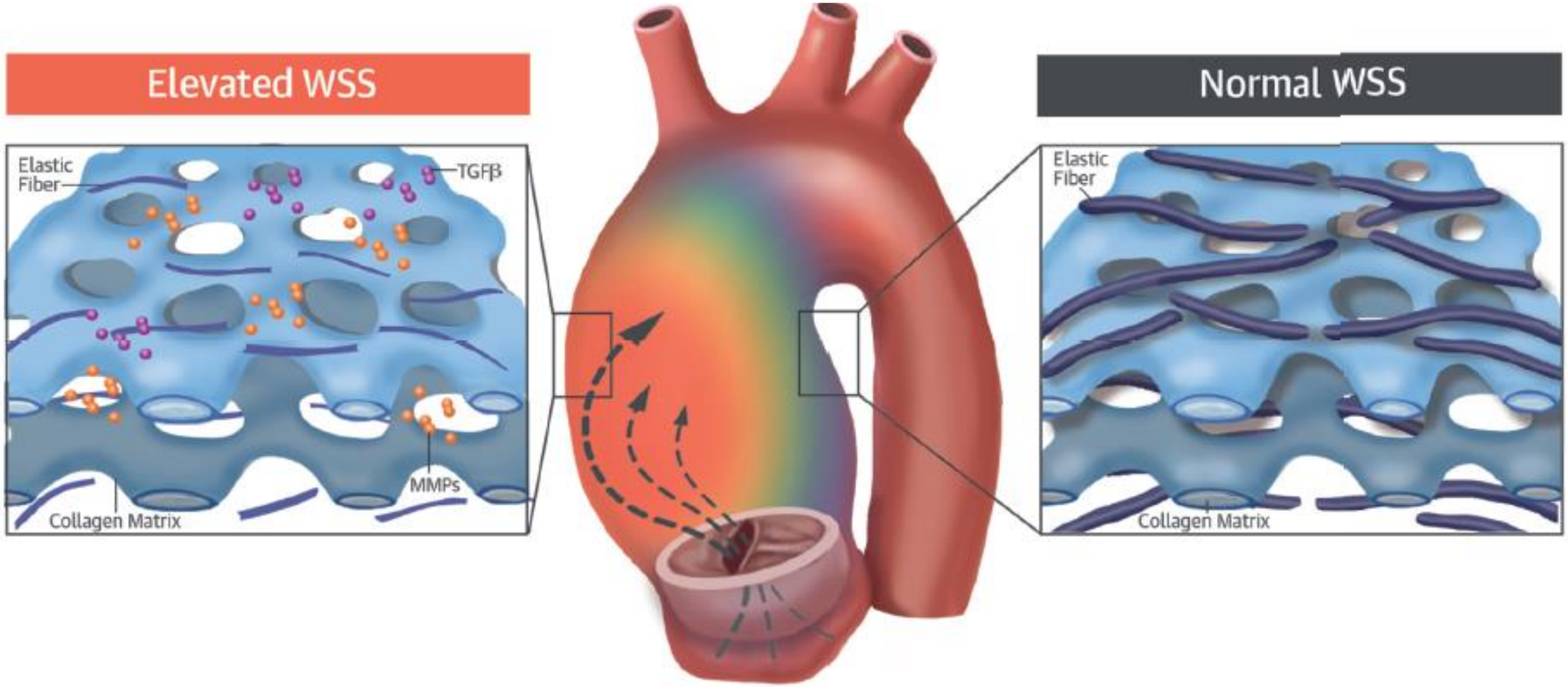
Importance of Smooth Muscle (~1999)



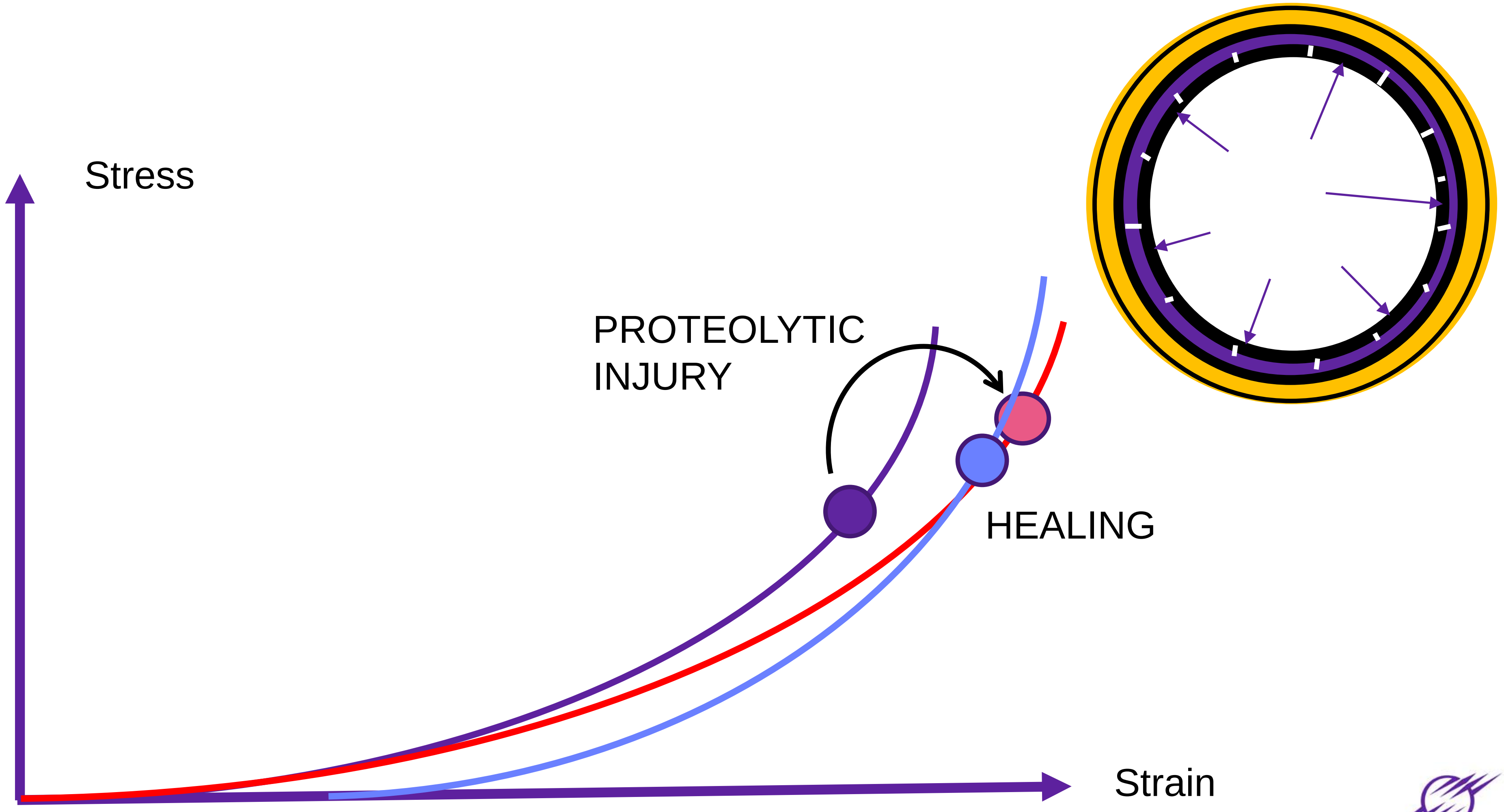
Tensional homeostasis in ATAA?

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

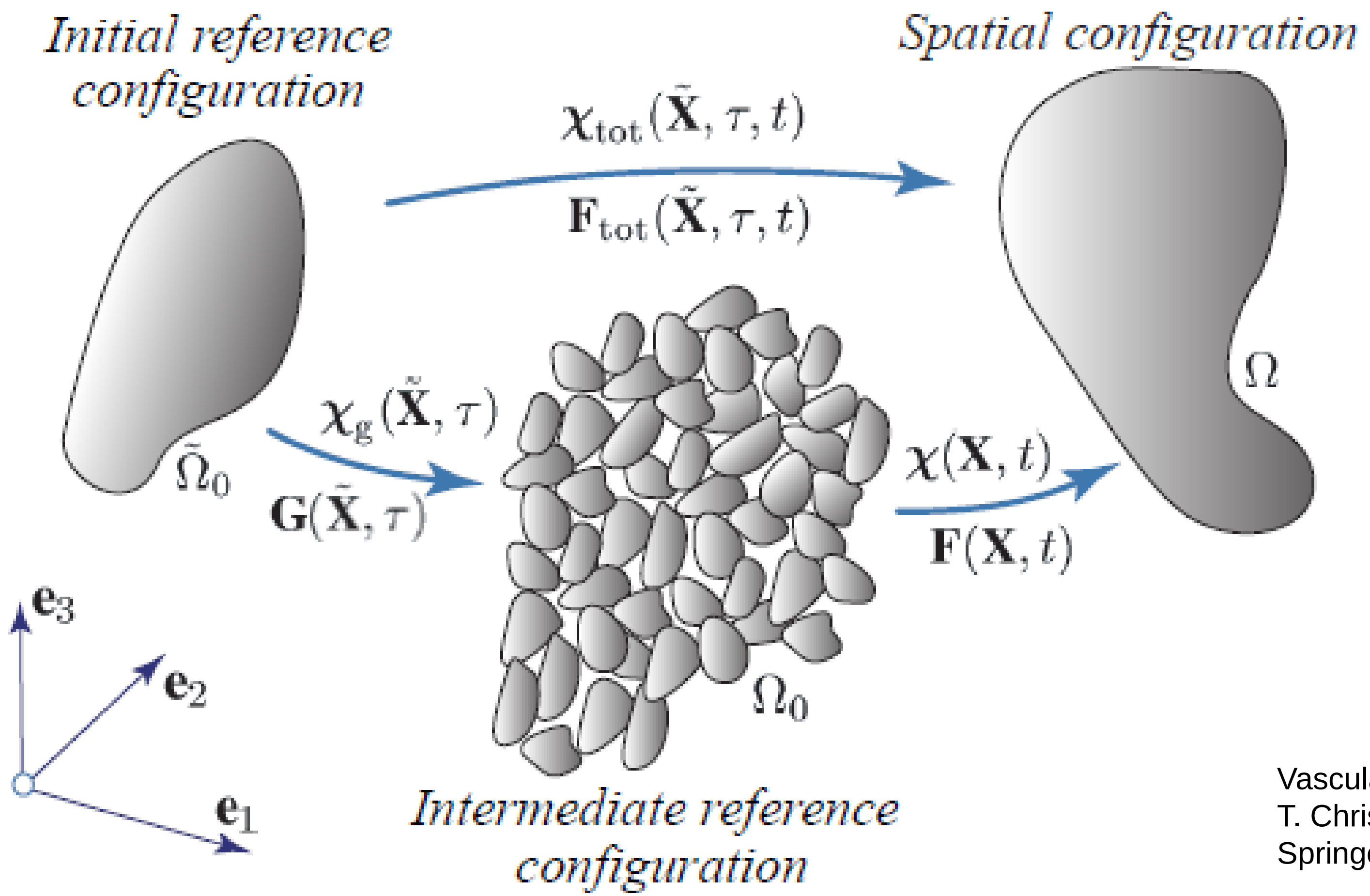


Guzzardi et al, JACC (2014), Condemi et al, IEEE TBME (2019)

Proteolytic injury and tissue adaptation

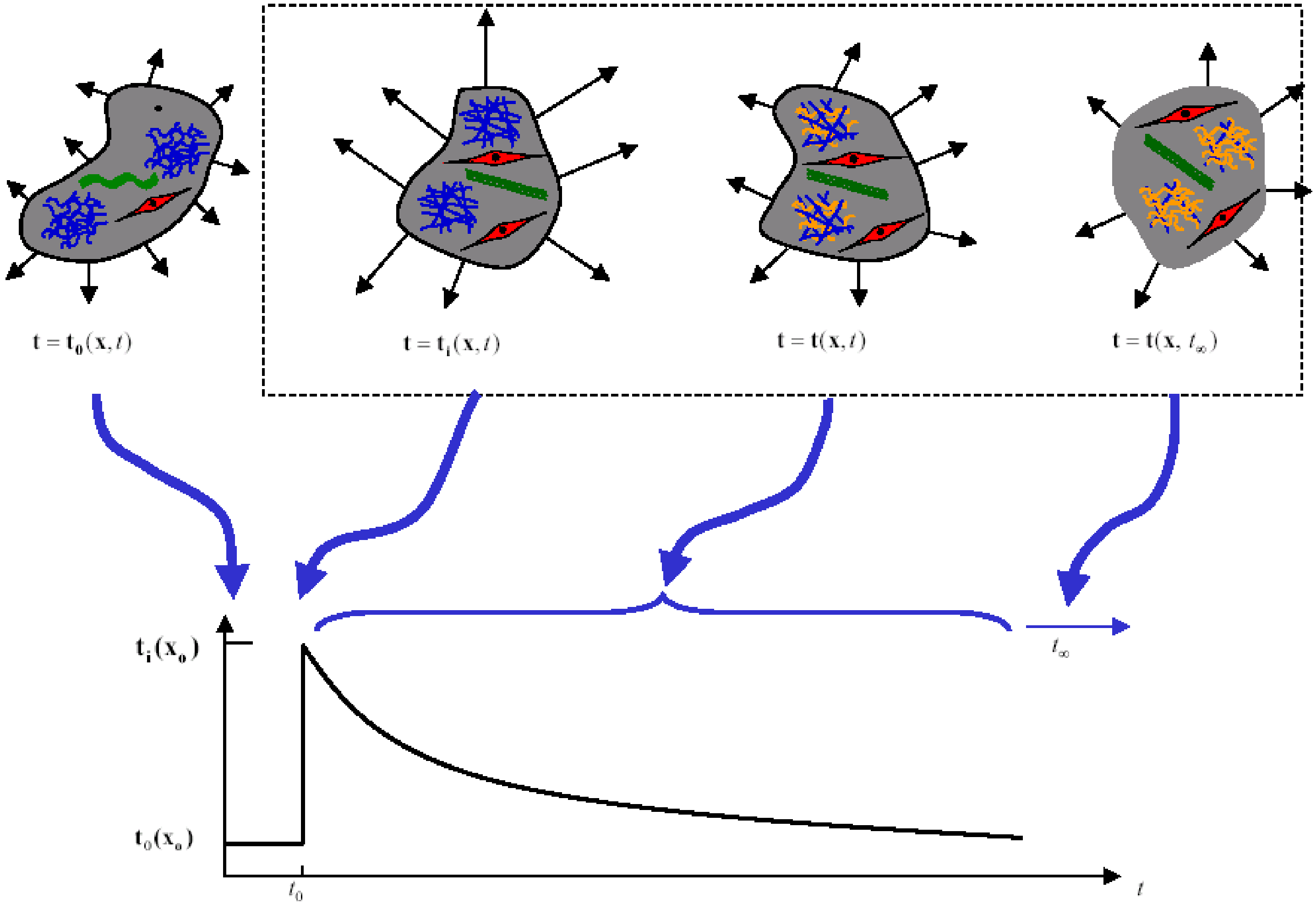


Kinematics-based growth description



Vascular Biomechanics
T. Christian Gasser
Springer

Constrained mixture models



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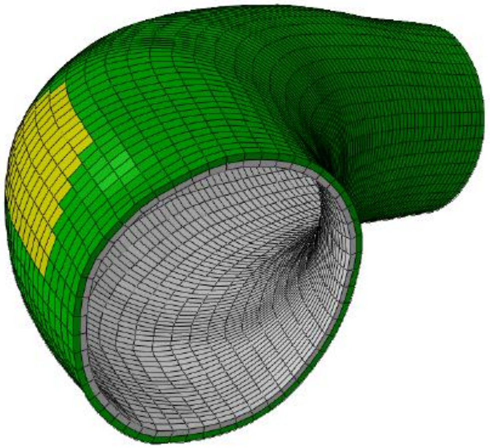
Finite-element simulations

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

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

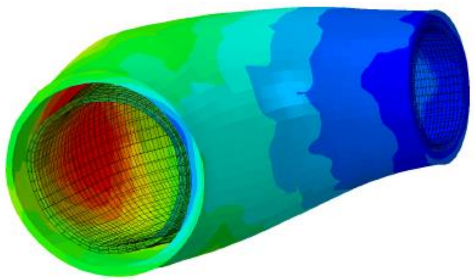
$$\dot{\varrho}^{\mathrm{e}} = -\frac{\varrho^{\mathrm{e}}(\mathbf{X},t)}{T^{\mathrm{e}}} - \frac{D_{\max}}{t_{\mathrm{dam}}}\varrho^{\mathrm{e}}(\mathbf{X},0)\,e^{-0.5\left(\frac{X_3}{L_{\mathrm{dam}}}\right)^2 - \frac{t}{t_{\mathrm{dam}}}}$$

Localization function around the point of TAWSS max



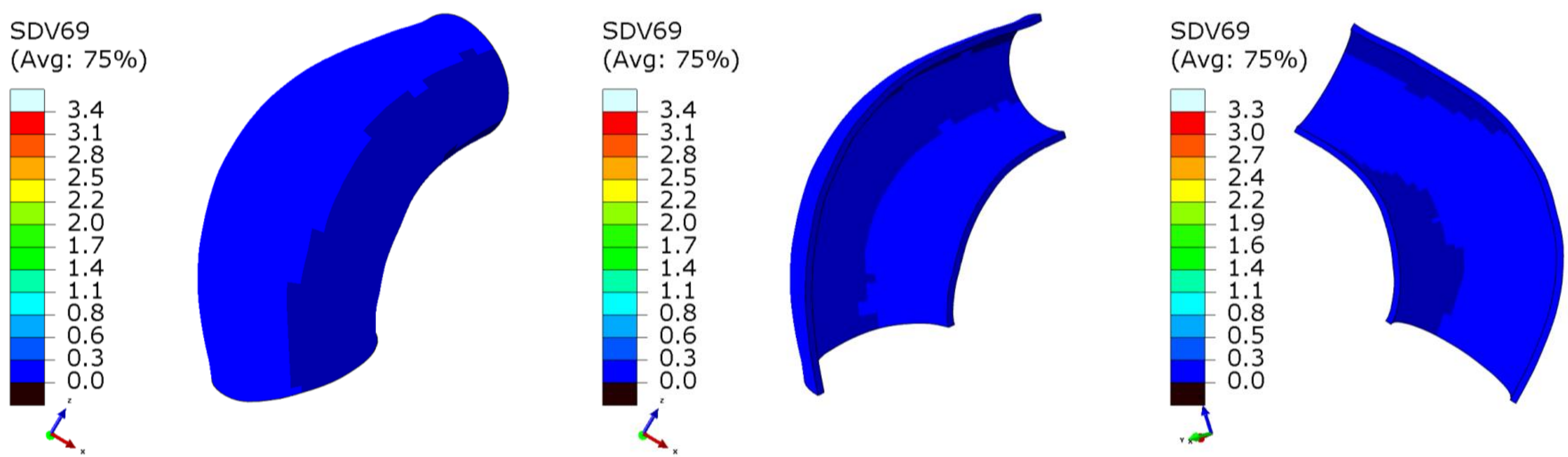
Mousavi et al, BMMB (2019)

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)

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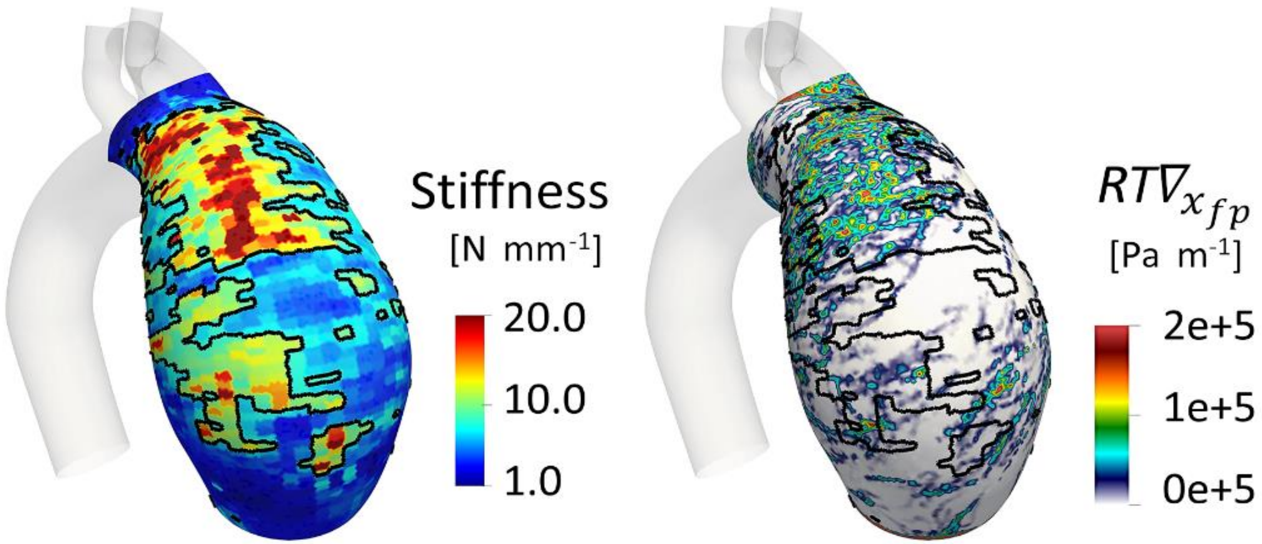
Some patients show local stiffness increase correlated with local hemodynamics



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

POLITECNICO DI TORINO

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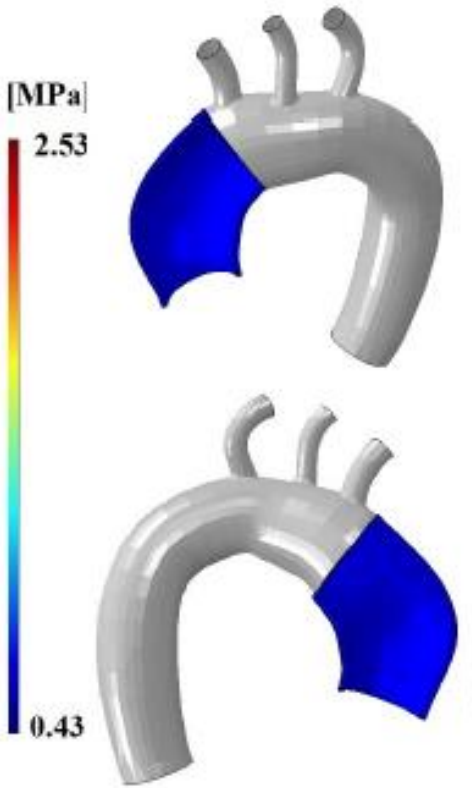
Patient-specific vascular adaptation

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

$$\chi = 1$$

Tangent stiffness after 10 years

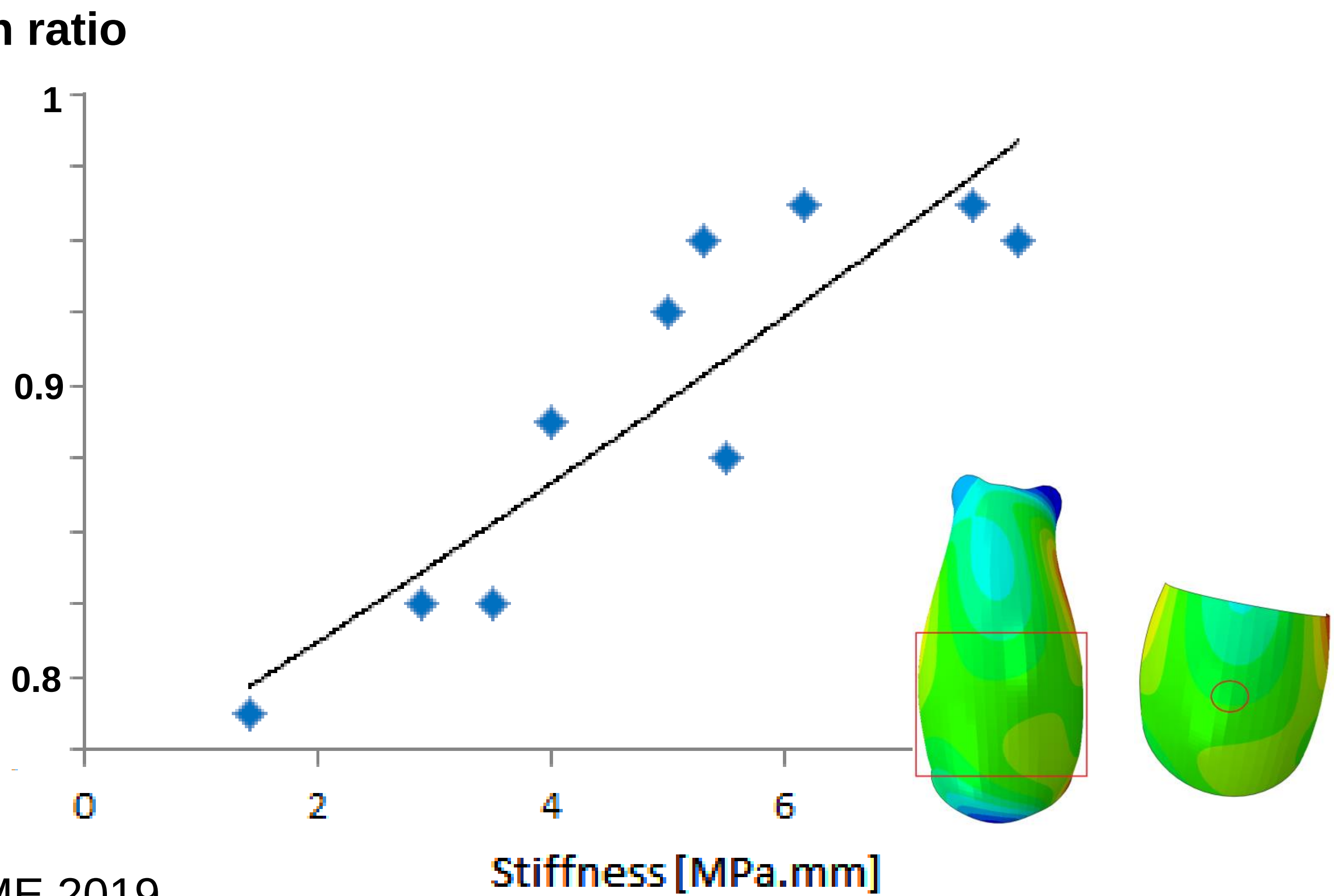


$$\dot{\varrho}^{j}(\mathrm{t}) = \varrho^{j}(\mathrm{t}) k_{\sigma}^{j} \frac{\sigma^{j}(t) - \chi * \sigma_{\mathrm{h}}^{j}}{\chi * \sigma_{\mathrm{h}}^{j}}$$

Mousavi et al, CMPB (2021)

TOWARDS IMPROVED PROGNOSIS: AUGMENTED MEDICAL IMAGING

The maintenance of tensional homeostasis in the tissue is critical



Farzaneh et al, ABME 2019

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**

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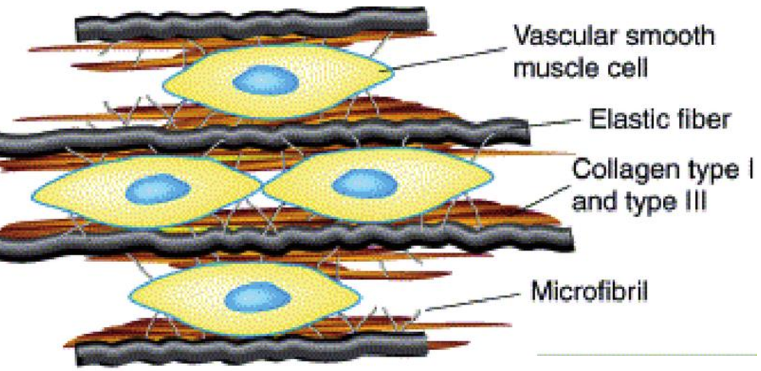
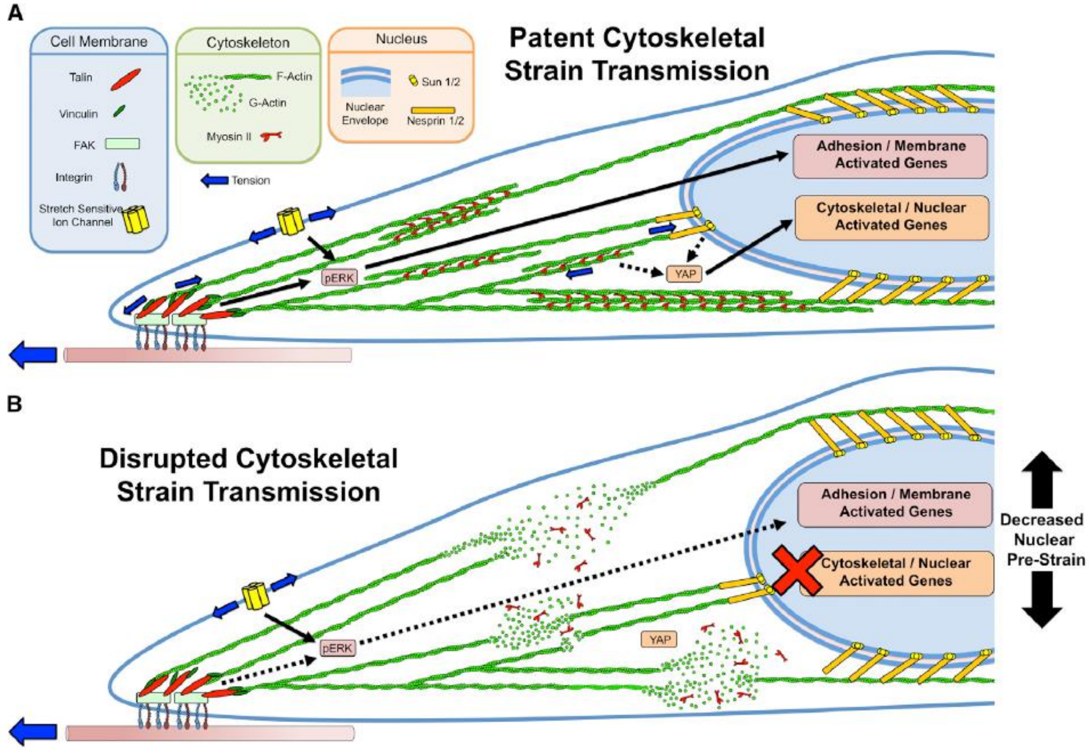
Introduction to arterial and cell mechanobiology



Driscoll et al, Biophysical Journal, 2015



Major role of smooth muscle cells in mechanoregulation

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Primary SMC cultures

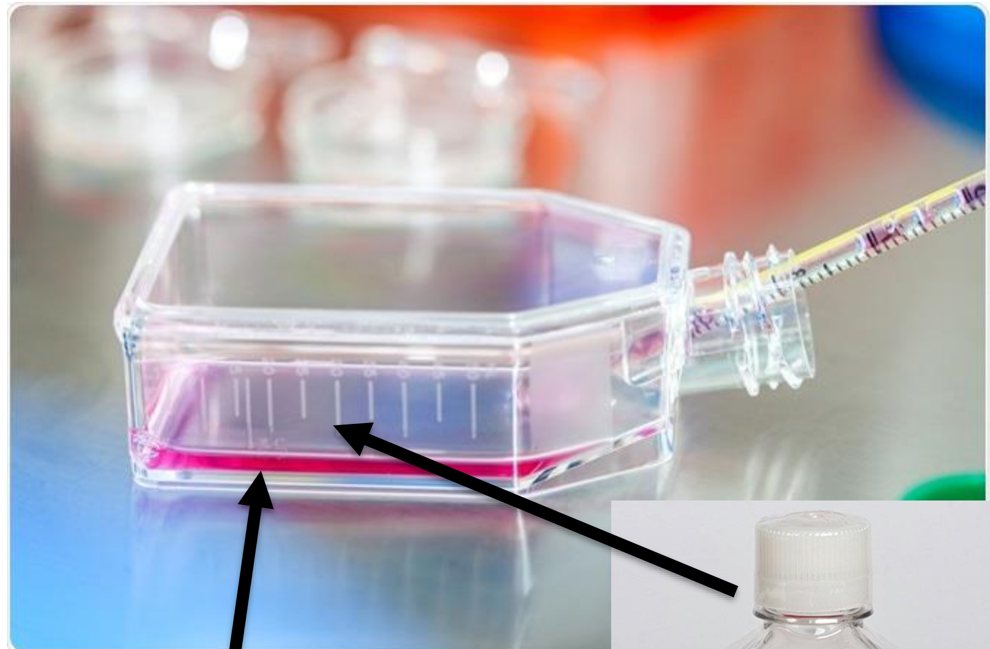
AoSMC lineage

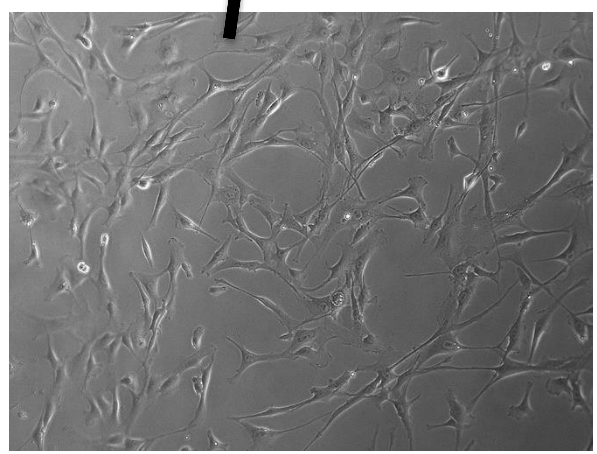
Thawing

Growing (SmGM-2)

Differenciation (SmBM)

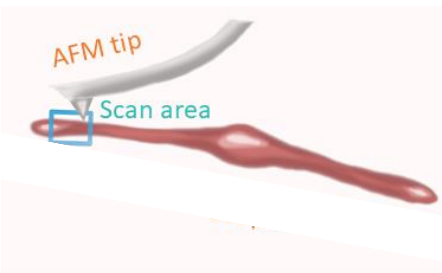
Sample preparation

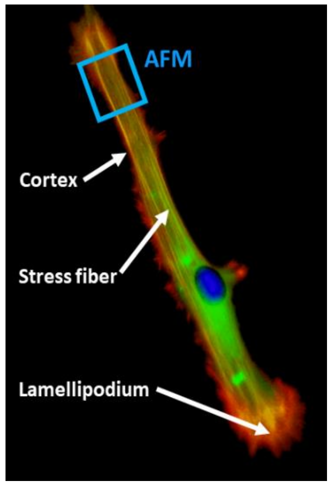


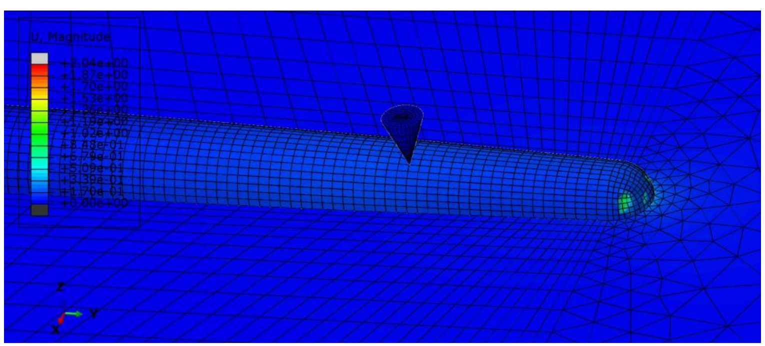


AFM nanoindentation of the cytoskeleton

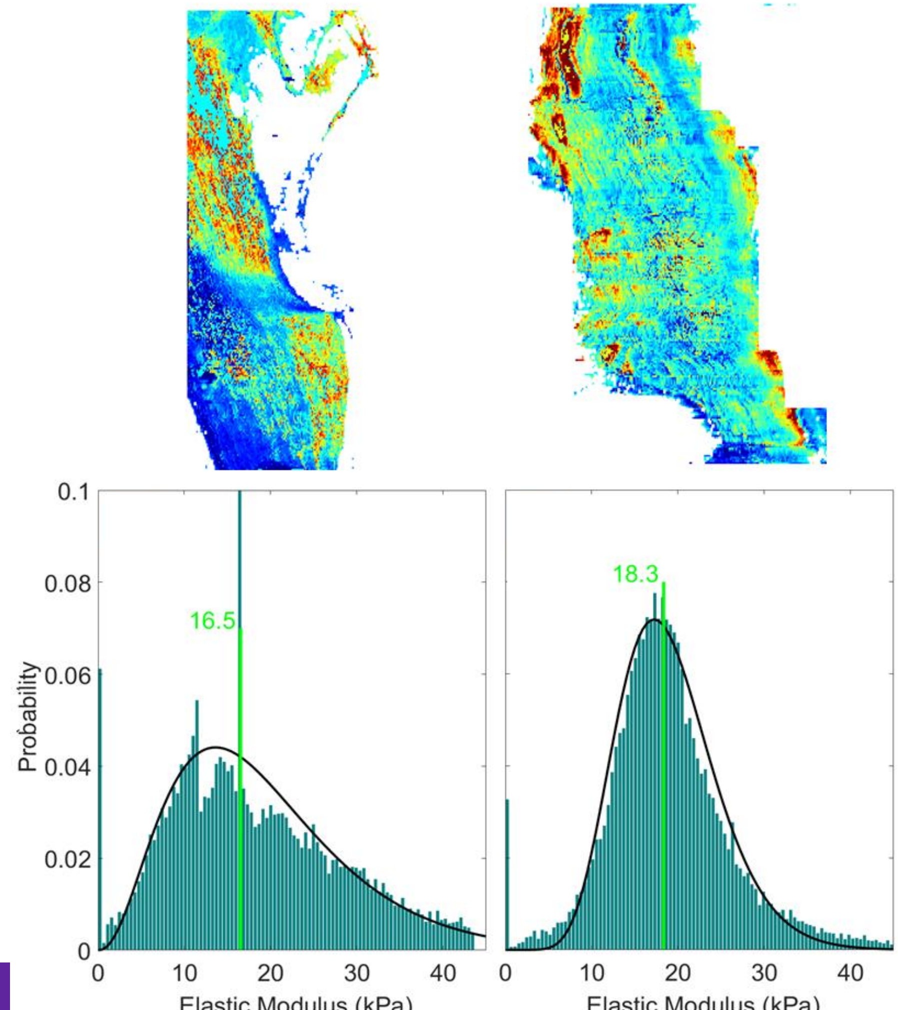
Petit et al, JBME, 2022







HEALTHY ANEURYSM



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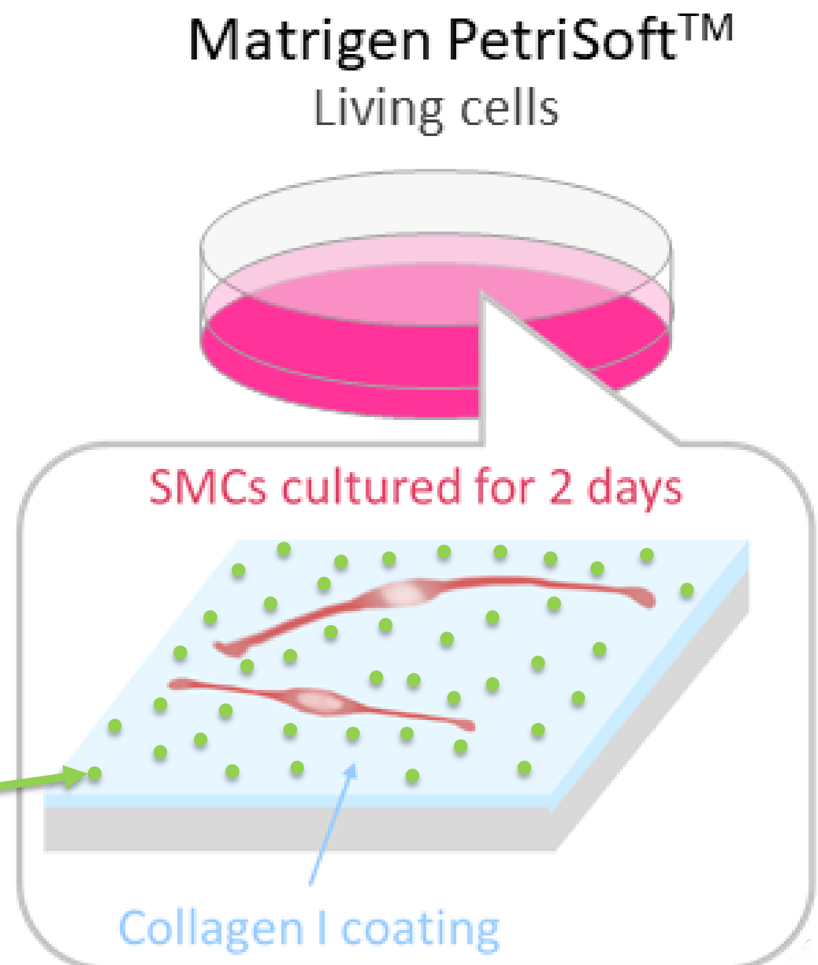
Traction force microscopy

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

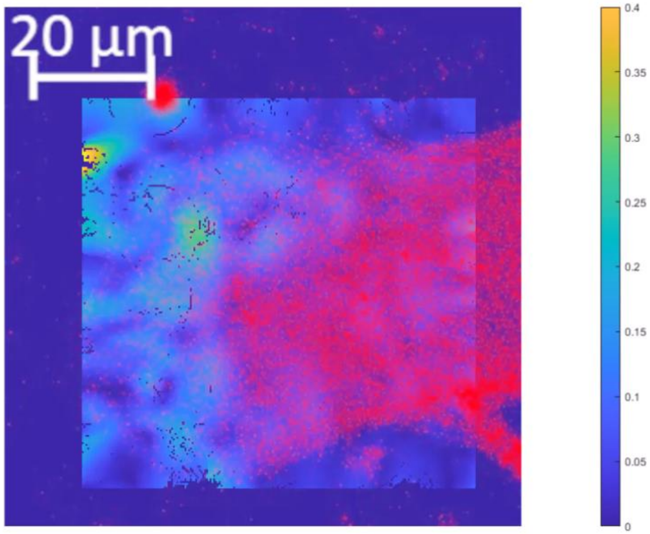
Age

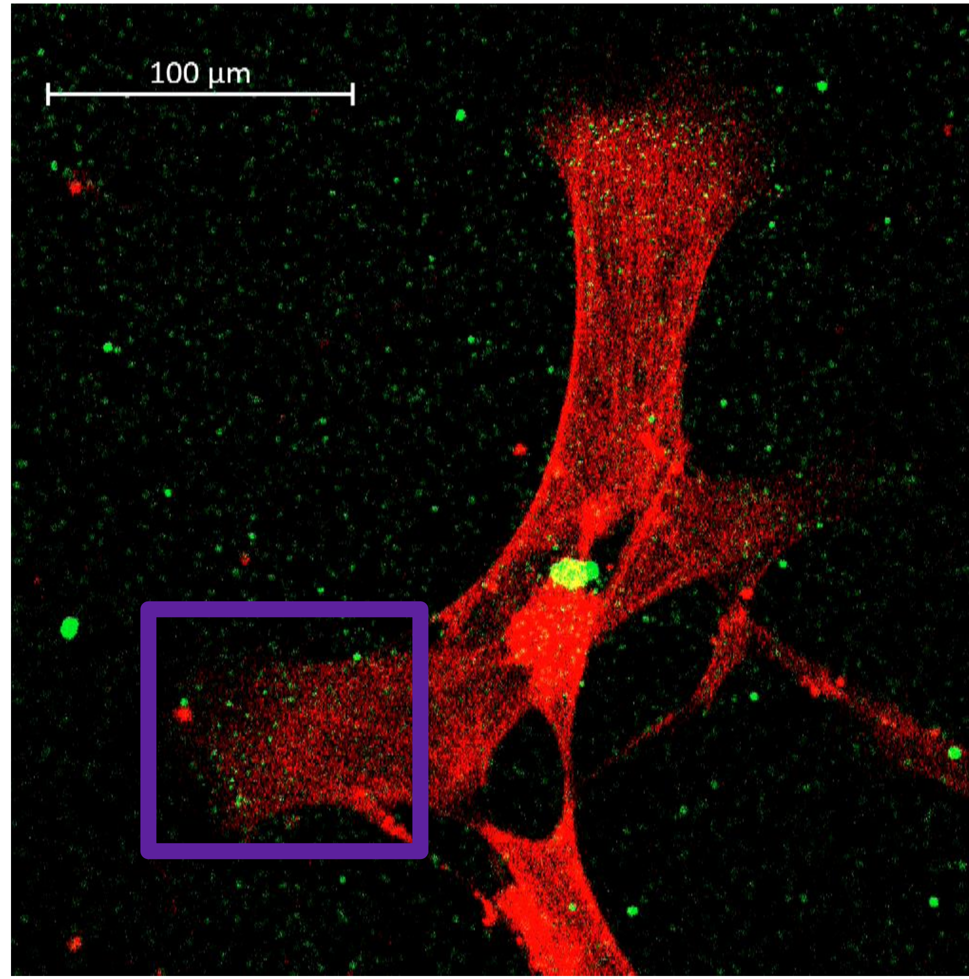
Pathology



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

Monitoring mechanobiology of live SMCs





Confocal microscopy + DIC combined with Siractin staining on living cells

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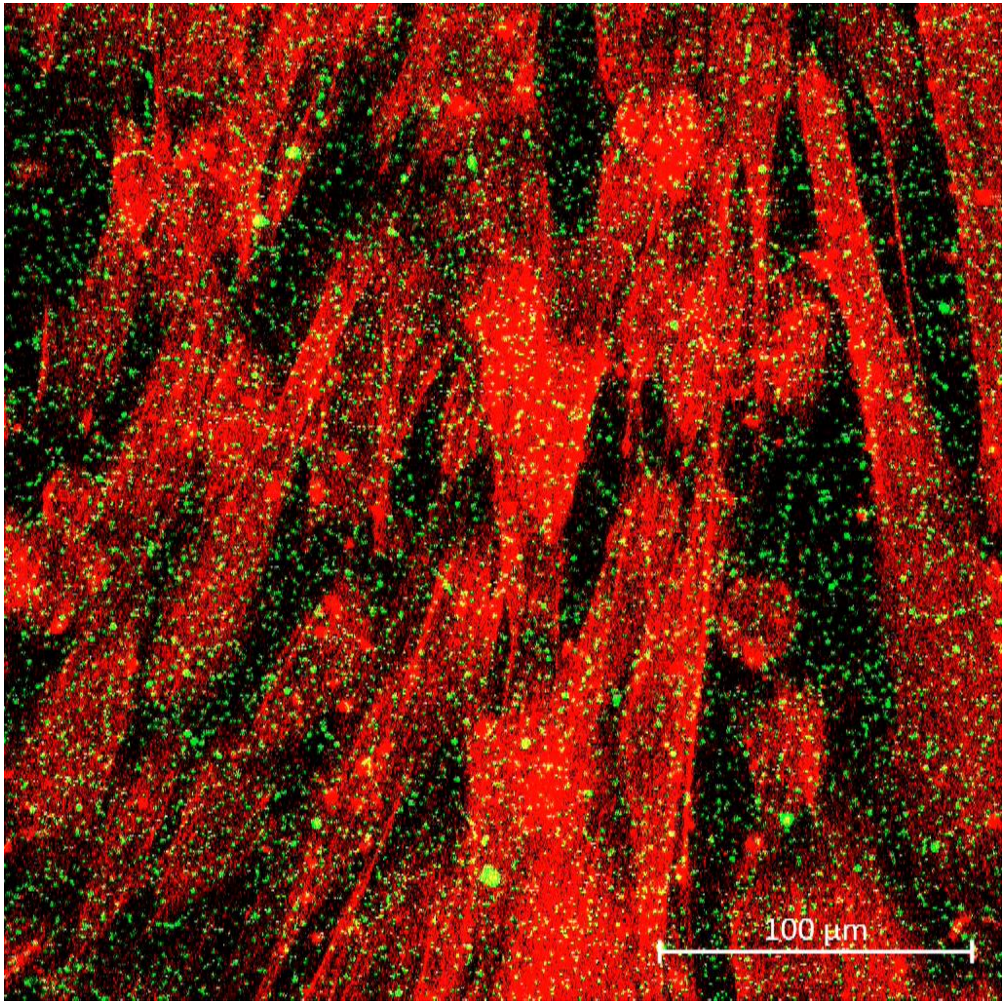
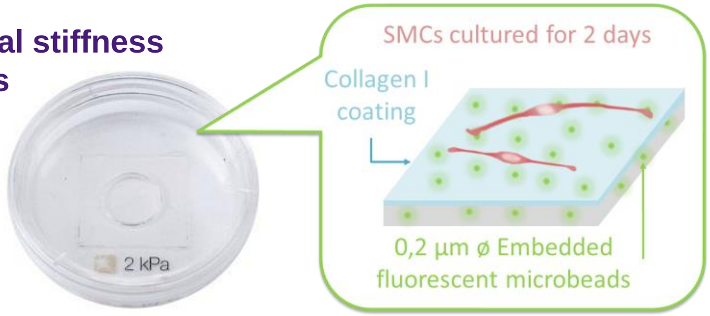
Isolated SMCs versus confluent SMCs

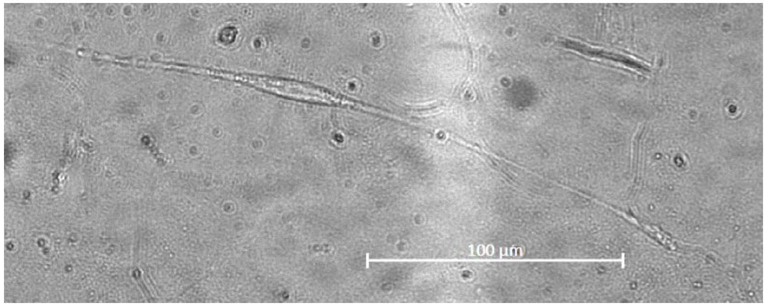


Monitoring mechanobiology *in vivo*

Several stiffness values

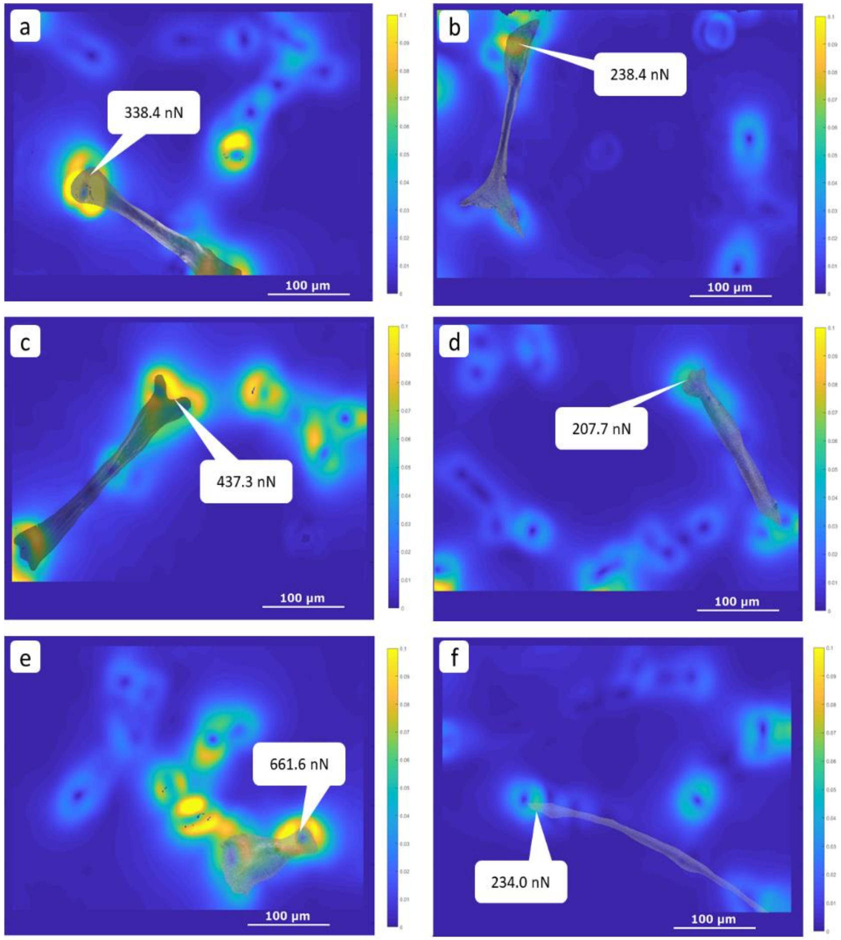


Aortic SMCs from human primary culture (AoSMC, Lonza), passages 5-7, cultured in a **differenciating medium** (SmBM, Lonza)



Fluorescent microscopy + DIC : track the displacement of fluorescent microbeads

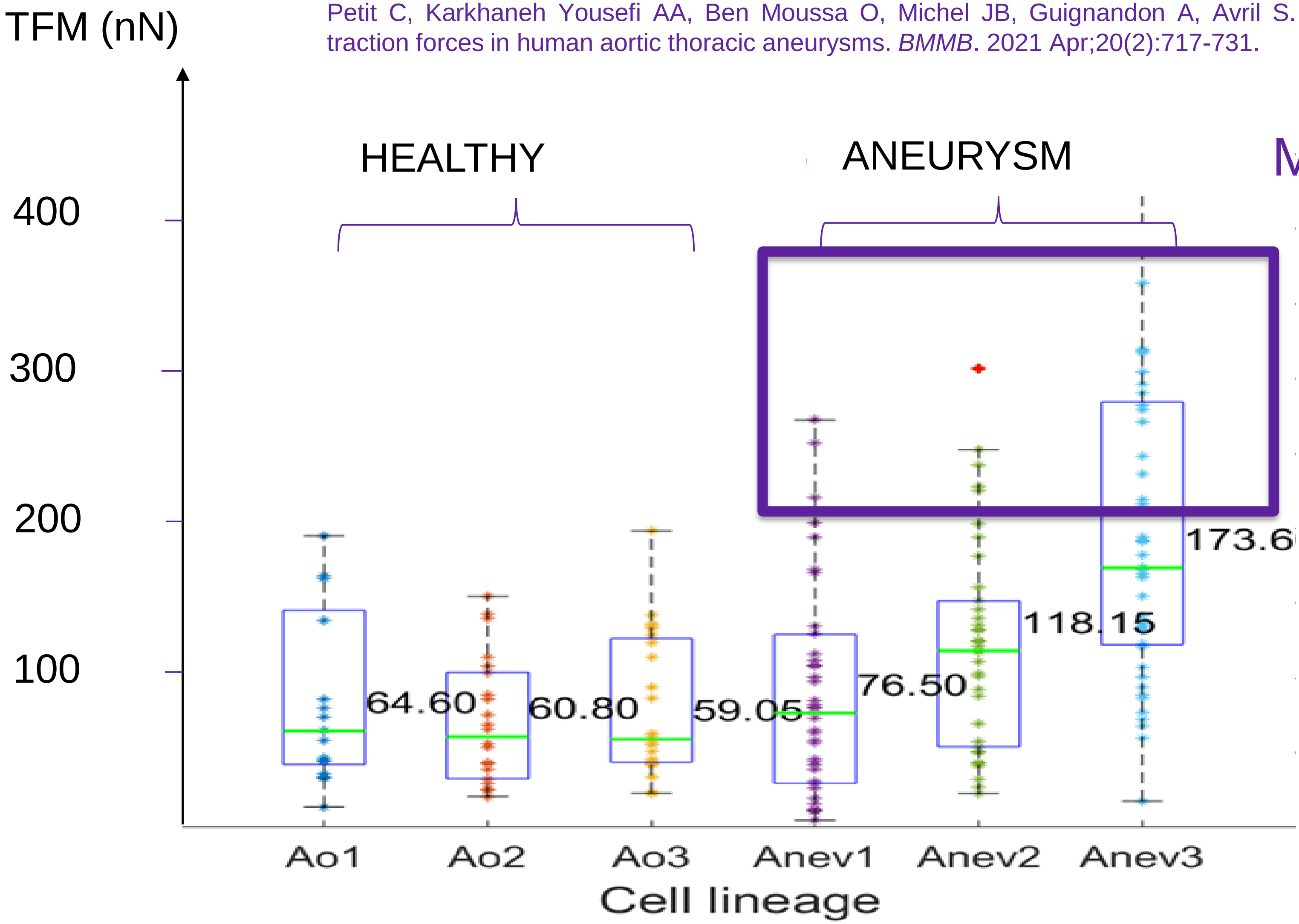
Cell unbinding method (with trypsin) : assess the homeostatic state of single SMCs



Petit et al, BMMB, 2021

Aneurysmal SMCs express stronger phenotypes

Petit C, Karkhaneh Yousefi AA, Ben Moussa O, Michel JB, Guignandon A, Avril S. Regulation of SMC traction forces in human aortic thoracic aneurysms. *BMMB*. 2021 Apr;20(2):717-731.



Myofibroblast phenotype

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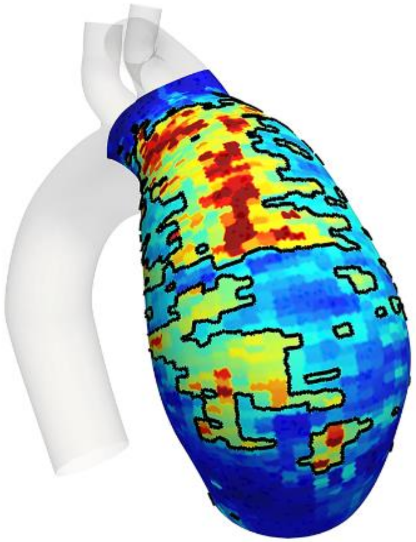
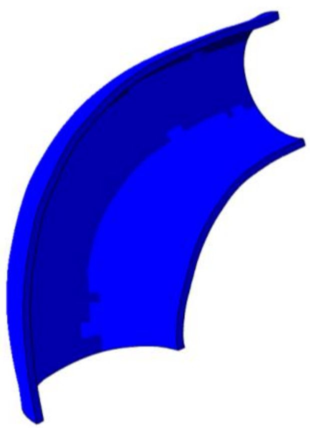
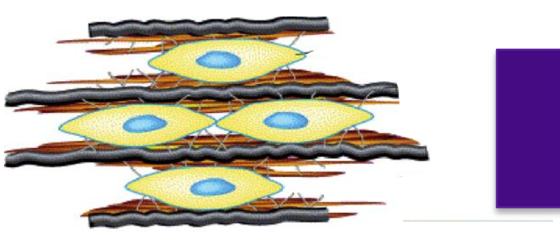
HOW TO HELP BIOLOGISTS: TOWARDS DIGITAL TWINS



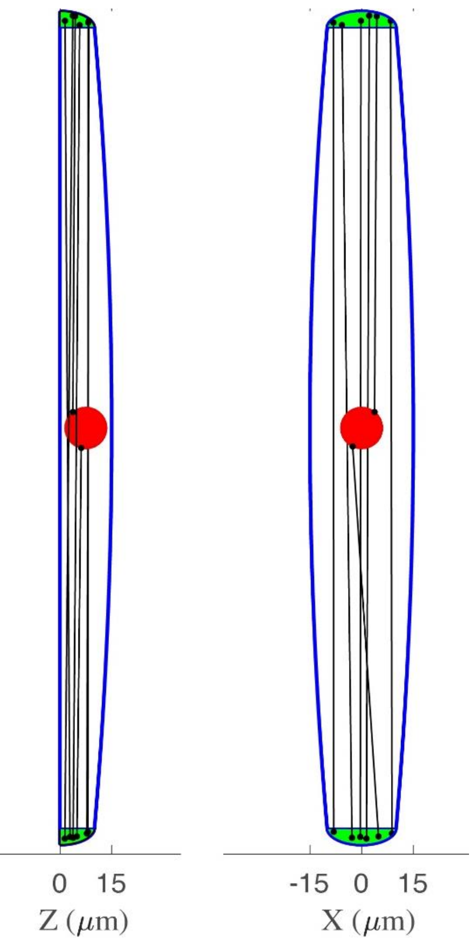
Monitoring gene expressions, tissue stiffness and hemodynamics

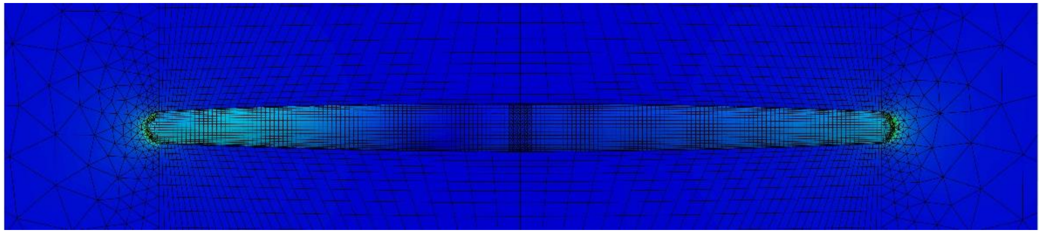


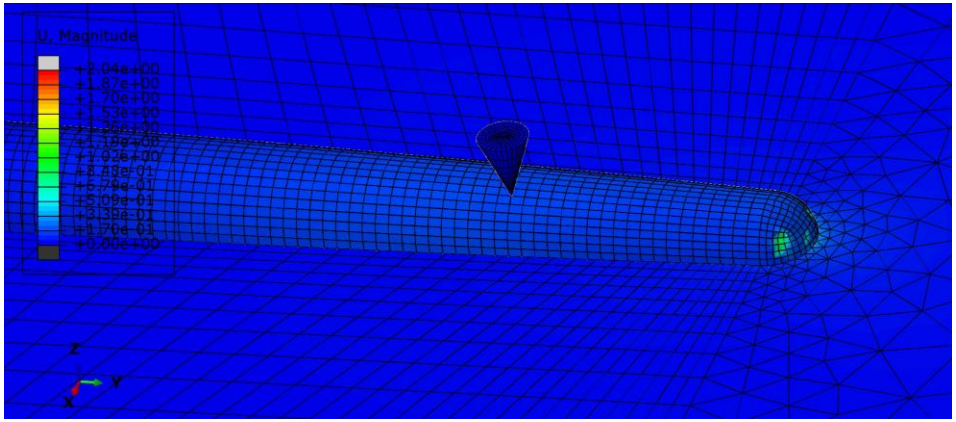


Predicting mechanical regulation, tissue deformations, stresses and stiffness

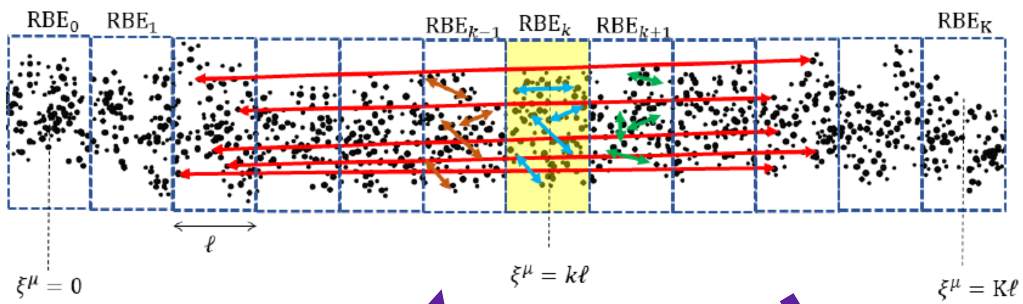
Finite Element model of SMCs

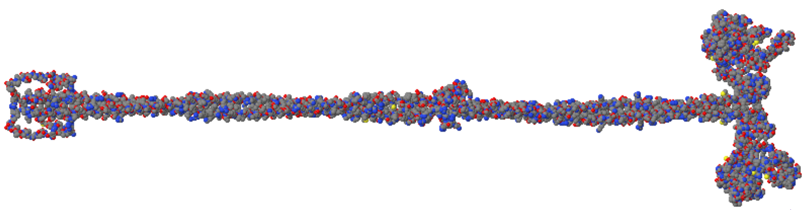


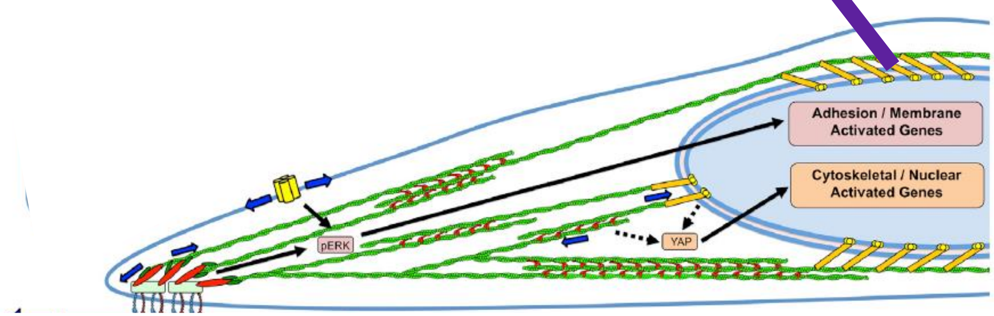




HOMOGENIZATION OF PROTEINS INTO BEAMS







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