



UNIVERSITÉ  
DE LYON



**SAINBIOSE**  
Santé INgénierie  
BIOlogie Saint-Etienne

U1059 • INSERM • SAINT-ETIENNE



TECHNISCHE  
UNIVERSITÄT  
WIEN  
Vienna | Austria



European Research Council

Established by the European Commission  
© ERC

# From patient-specific finite-element modeling towards prediction of aneurysm progression

Prof Stéphane AVRIL



# OUTLINE

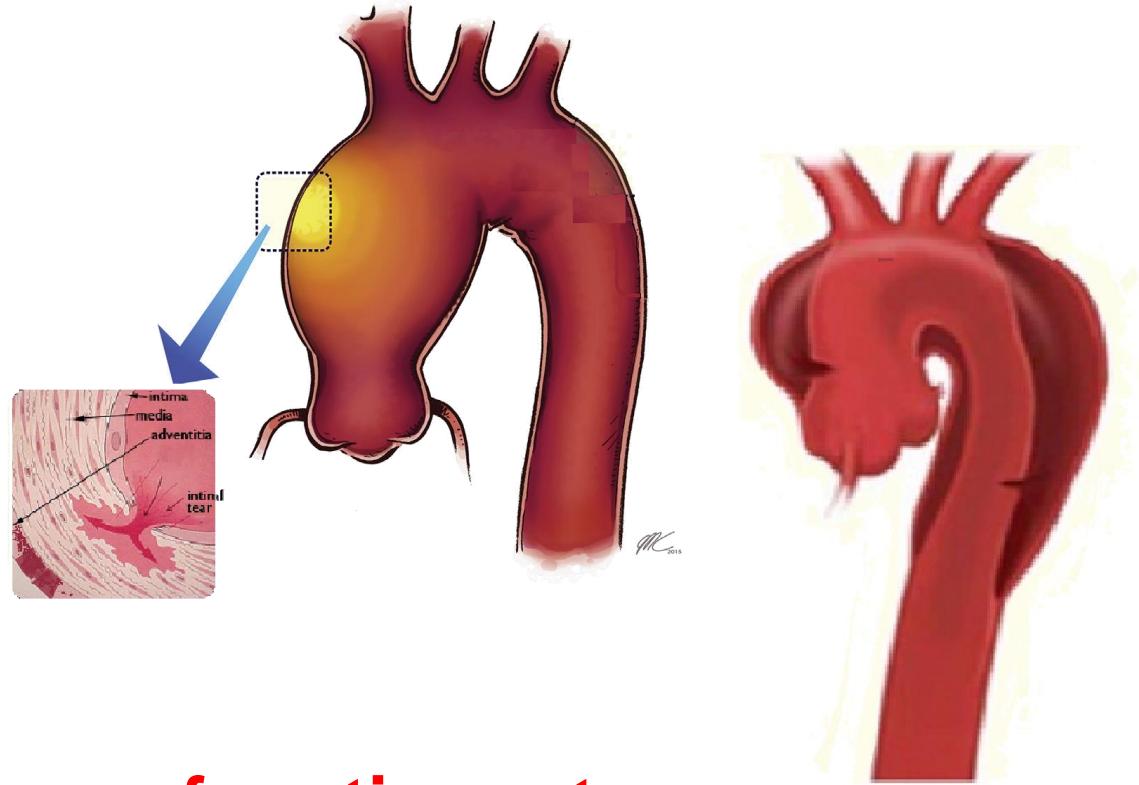
- PART I: Risk factors for aortic rupture
- PART II: Computational prediction of aortic weakening
- PART III: Role of SMCs in aortic weakening



# OUTLINE

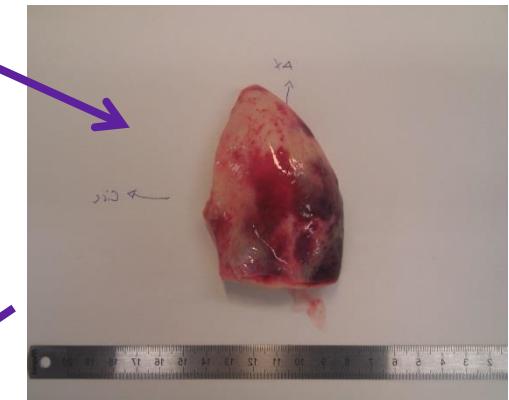
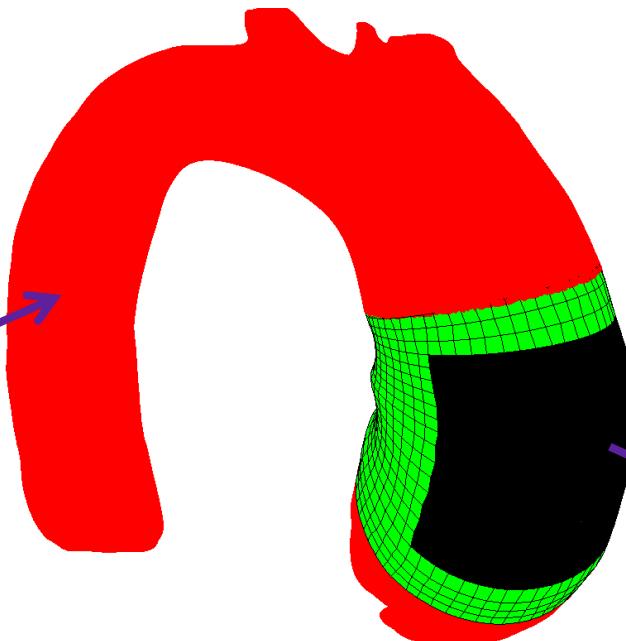
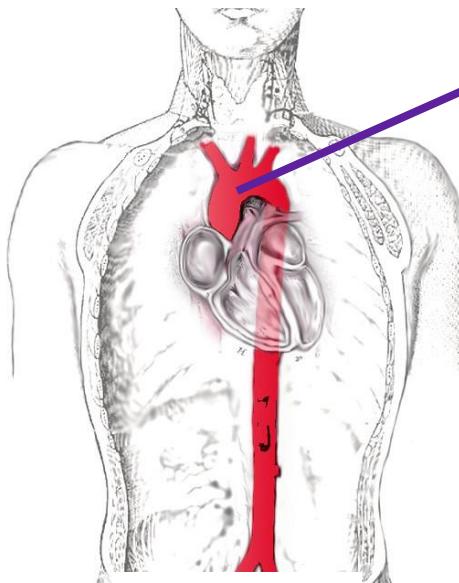
- PART I: Risk factors for aortic rupture
- PART II: Computational prediction of aortic weakening
- PART III: Role of SMCs in aortic weakening

# Aneurysms and Dissections of the ascending thoracic aorta



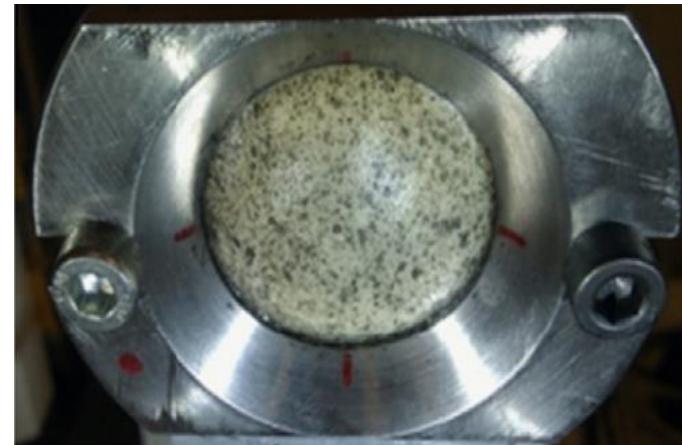
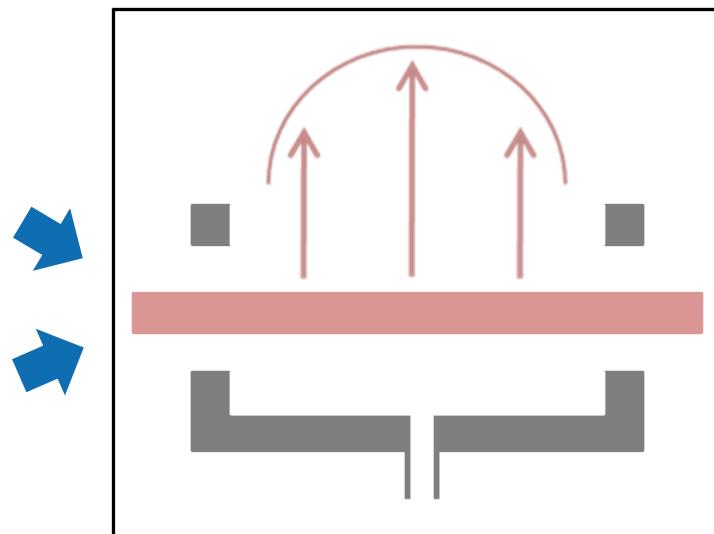
**Goal: find factors of aortic rupture**

# Collection of human samples

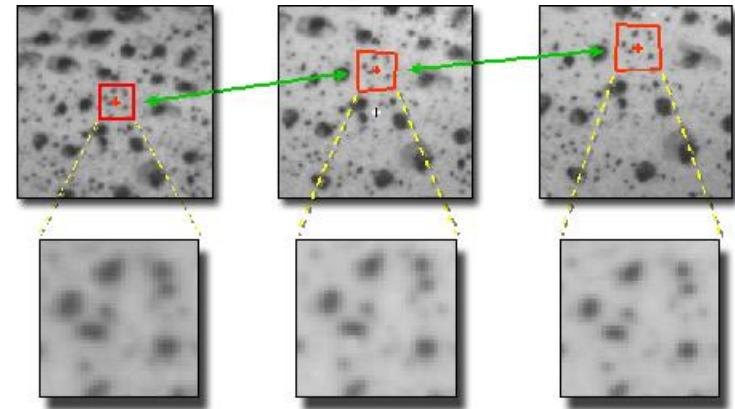


# Bulge inflation test

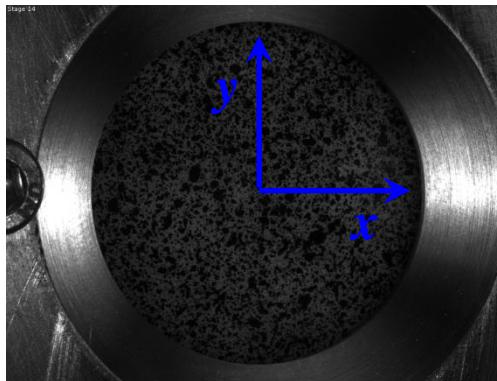
Romo et al. Journal of Biomechanics -2014.



# Full-field measurements using sDIC



Undeformed



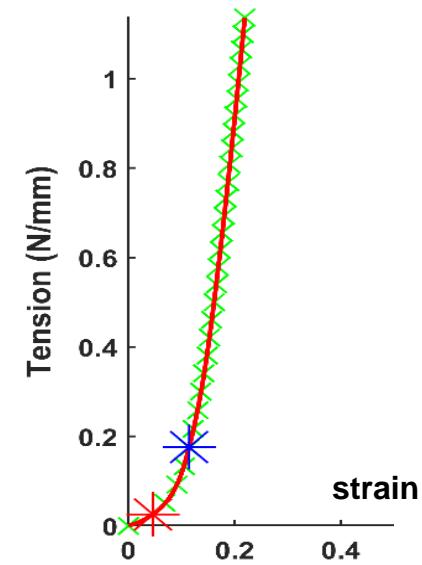
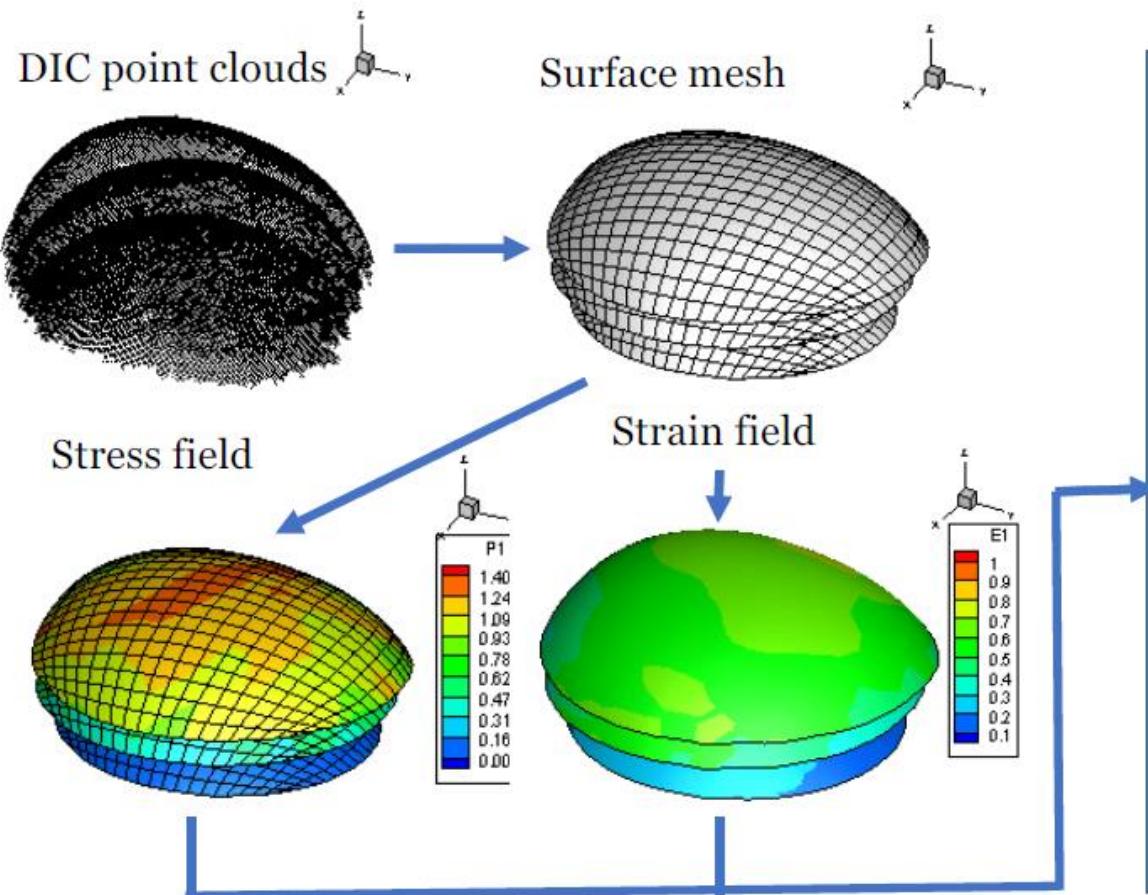
Deformed





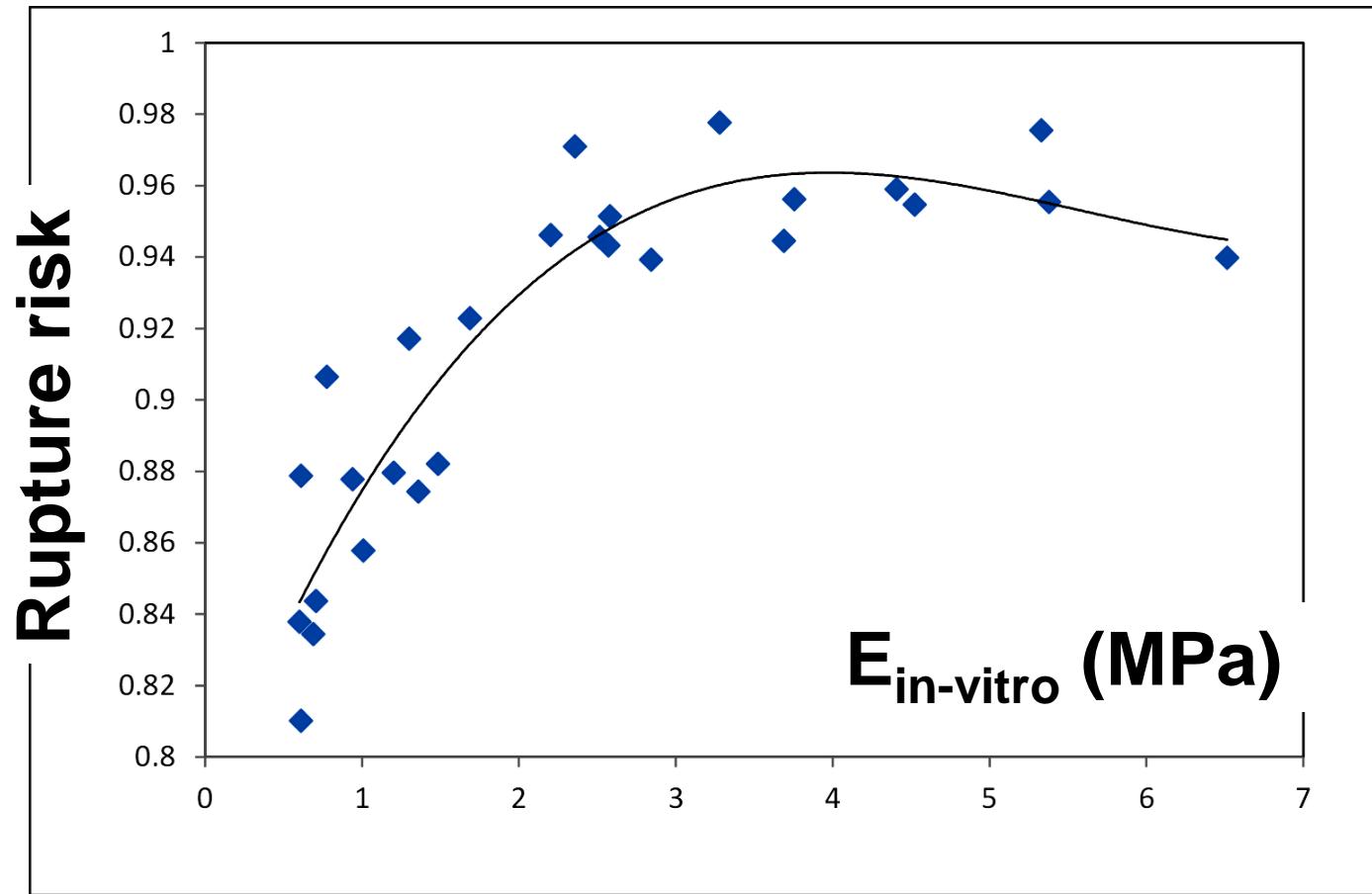
# Identification of local material properties

The WHITAKER Foundation



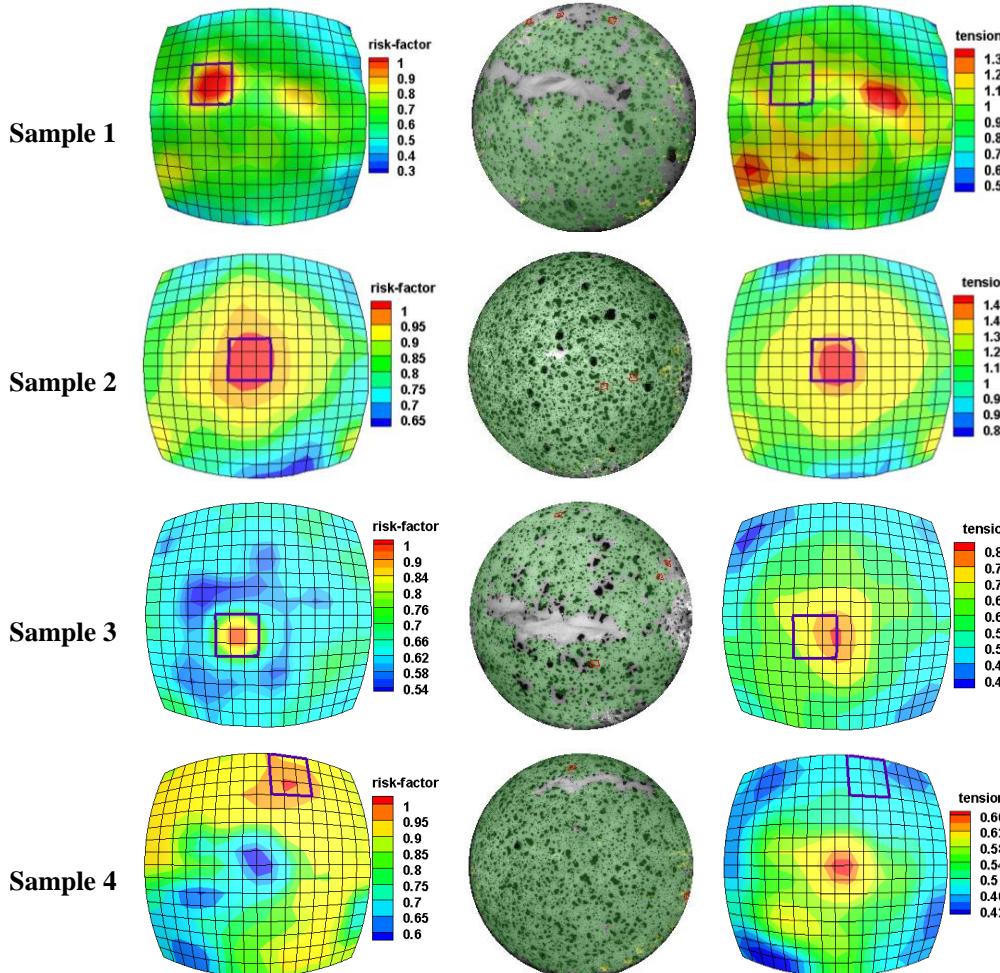
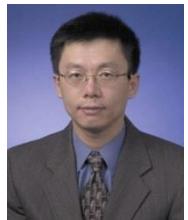
Davis et al. BMMB – 2015.  
Davis et al. JMBBM – 2016  
Zhao et al. Acta Biomaterialia - 2016

# Correlation between the stretch-based rupture risk and the tangent elastic modulus



Duprey A, et al. Biaxial rupture properties of ascending thoracic aortic aneurysms. *Acta Biomaterialia* 2016.

# Prediction of tissue rupture with the local tangent stiffness



# SUMMARY

- Local tangent stiffness is heterogeneous and a risk factor for aortic rupture

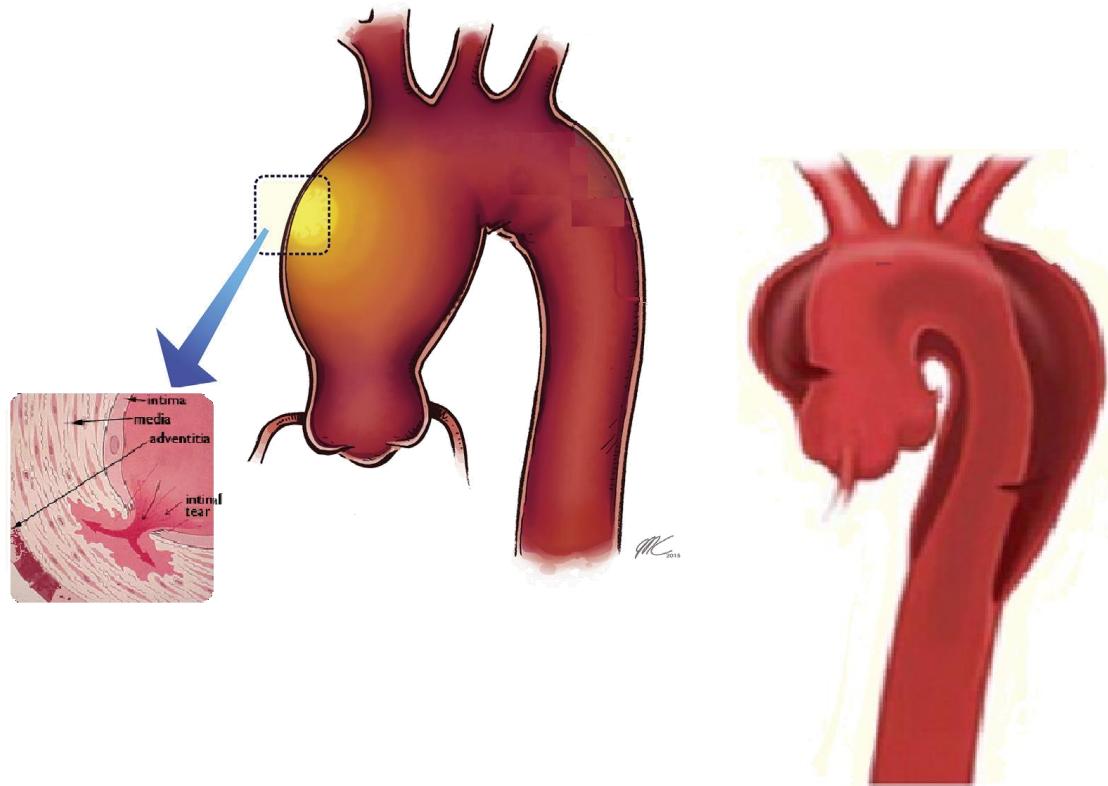
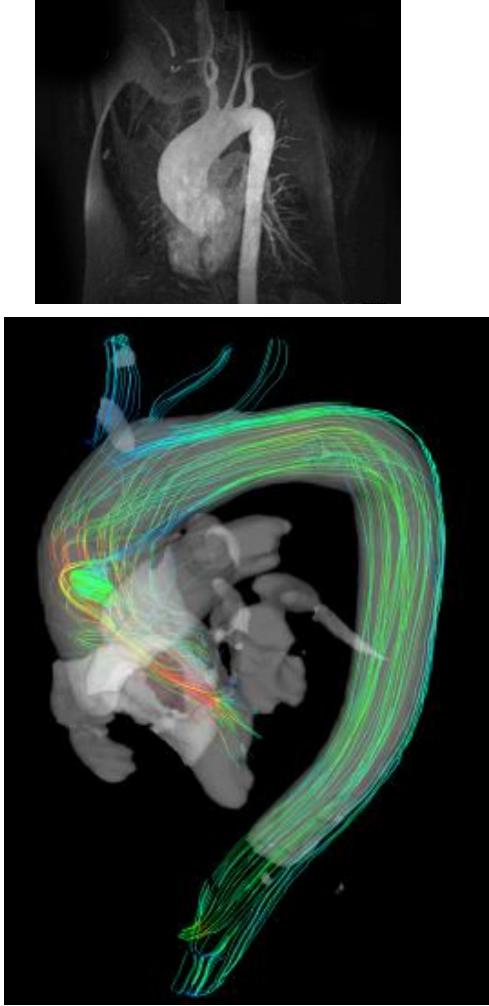




# OUTLINE

- PART I: Risk factors for aortic rupture
- PART II: Computational prediction of aortic weakening
- PART III: Role of SMCs in aortic weakening

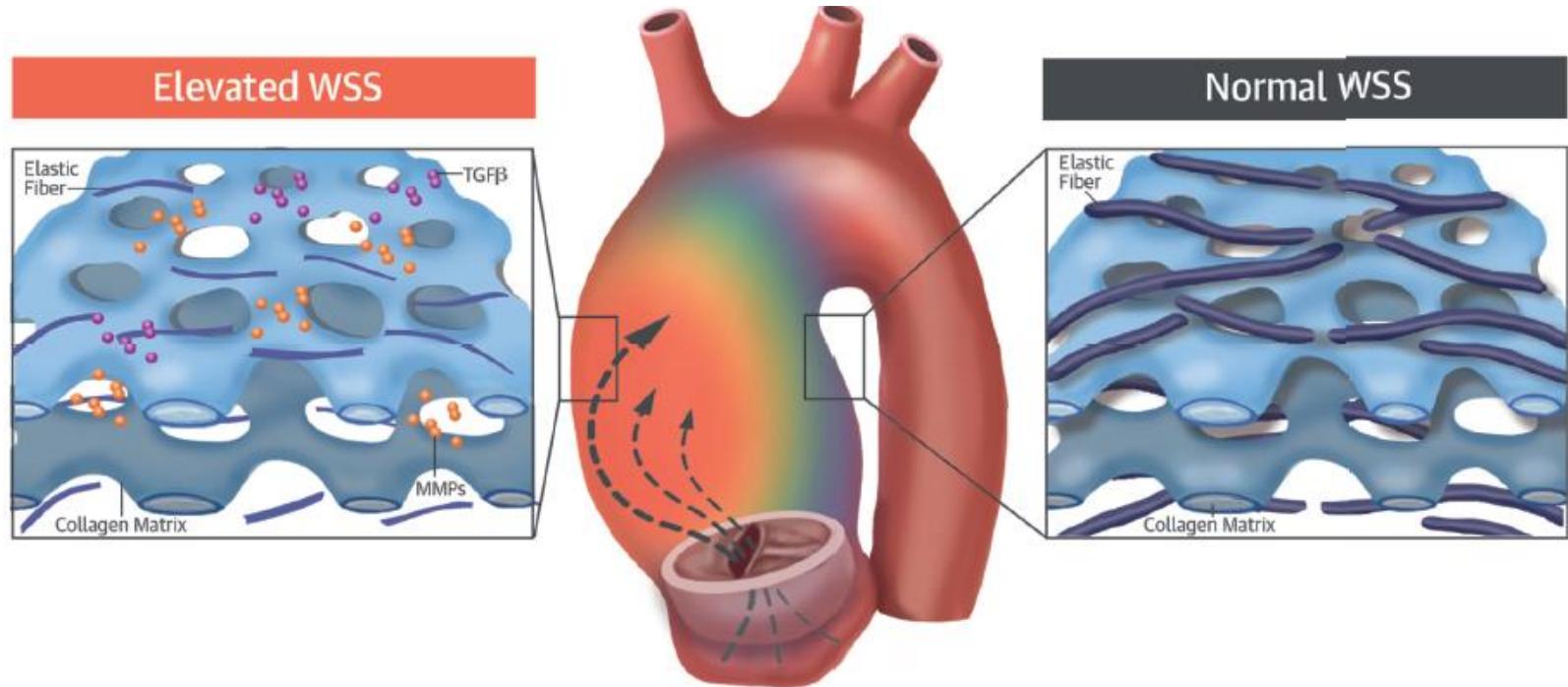
# Aneurysms and Dissections of the ascending thoracic aorta



**Goal: Predict weakening in the aortic wall**

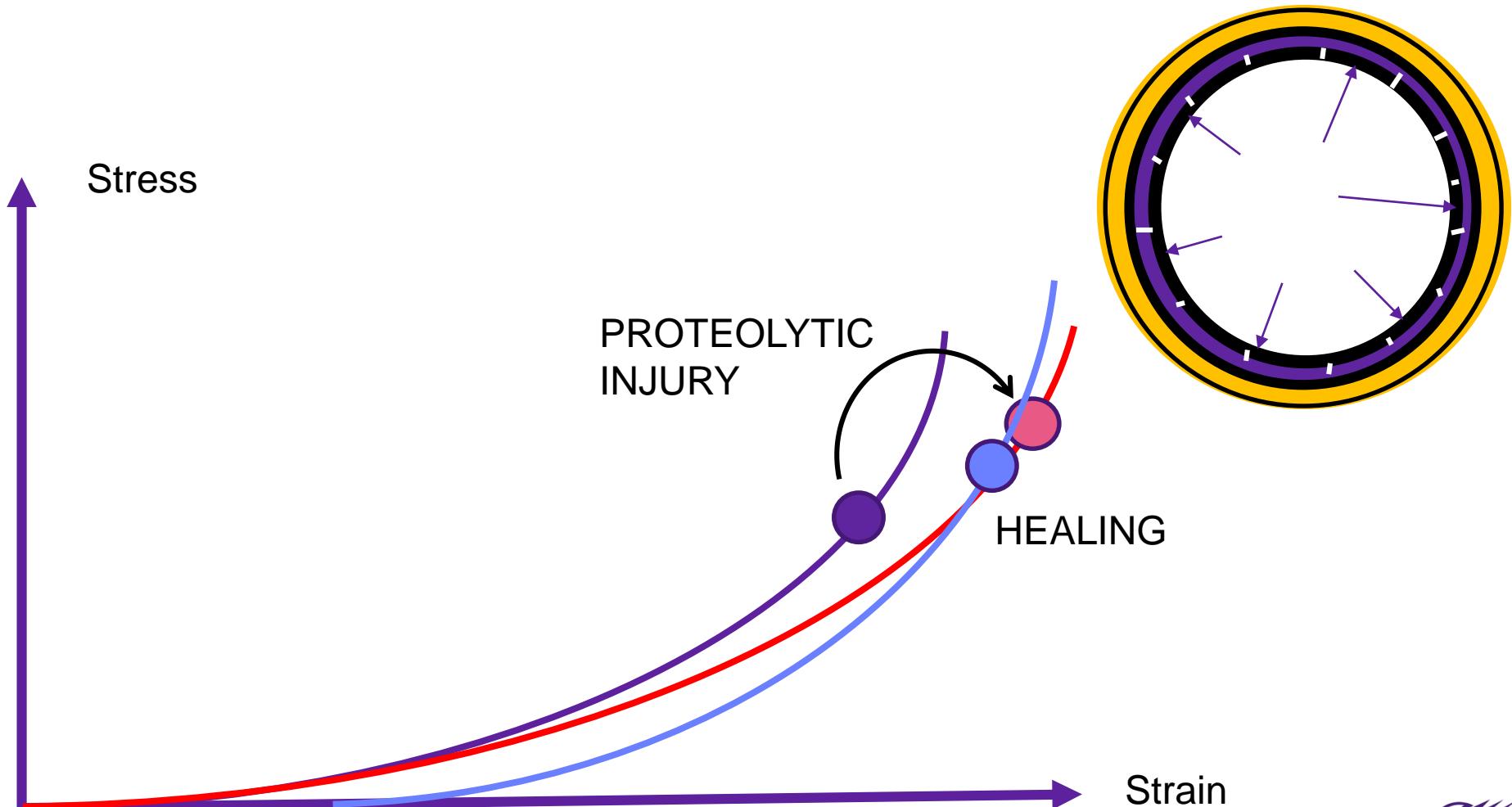
# Introduction - Assumption

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

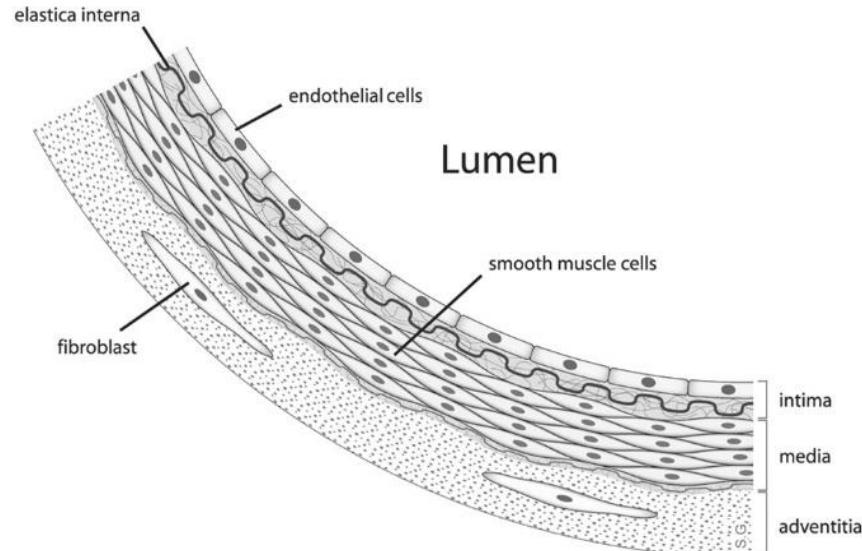
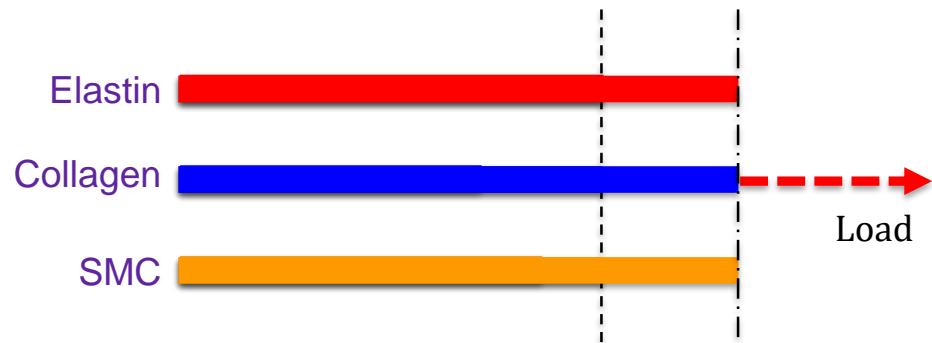


# Layer-specific constitutive model

Strain-energy function based on the constrained mixture theory

$$W = \varrho_t^e (\overline{W}^e(\bar{I}_1^e) + U(J_{\text{el}}^e)) + \sum_{j=1}^n \varrho_t^{c_j} W^{c_j}(I_4^{c_j}) + \varrho_t^m W^m(I_4^m)$$

Deposition stretch of each constituent:



Humphrey & Rajagopal, Math Models Methods Appl Sci. (2002) ; Bellini et al, ABME (2014), Mousavi & Avril, BMMB (2017)

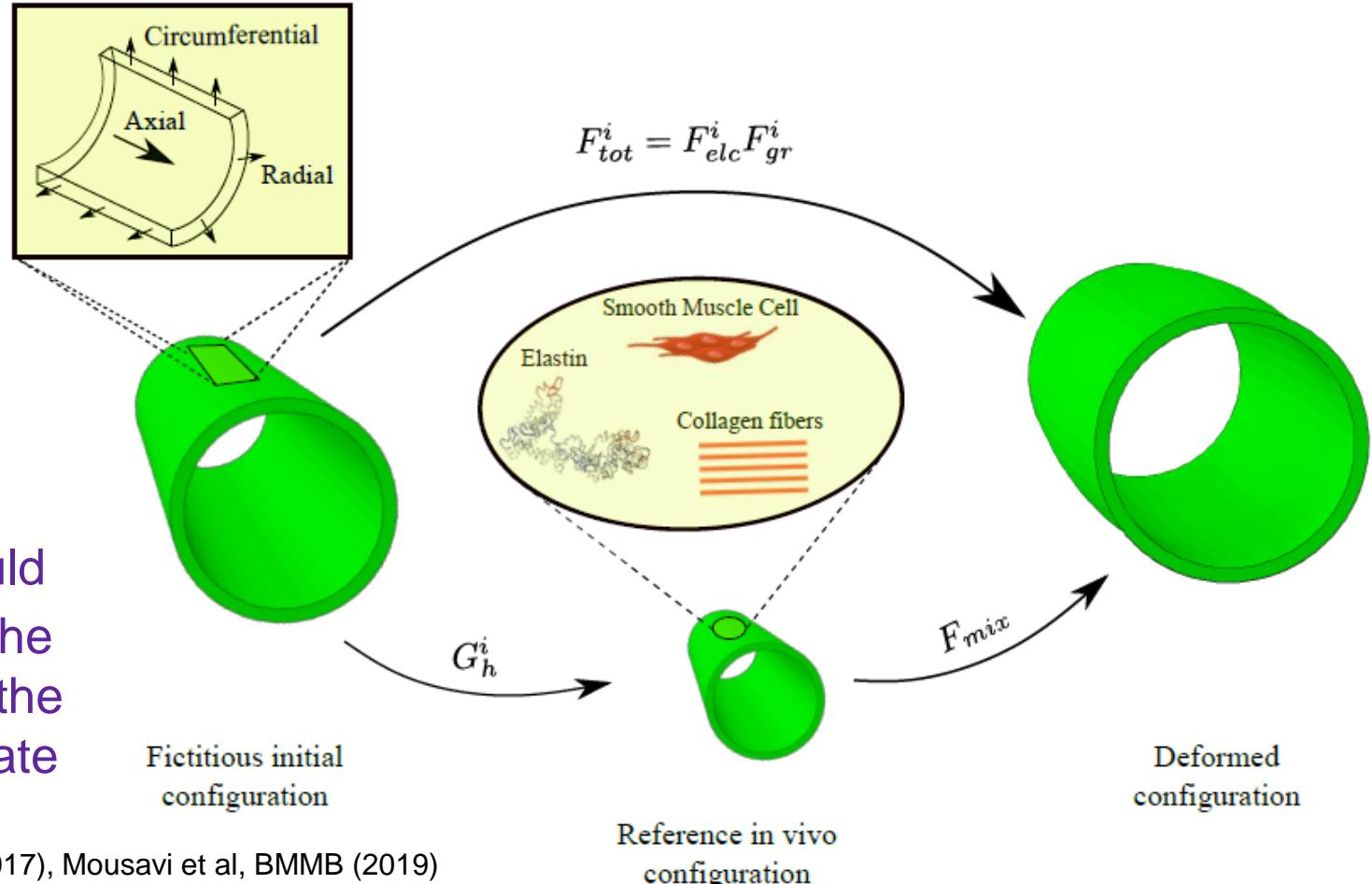
# Layer-specific constitutive model

Elastic and inelastic decomposition of deformation gradient

$$\mathbf{F}_{\text{tot}}^j = \mathbf{F}_{\text{elc}}^j \mathbf{F}_{\text{gr}}^j$$

$$\mathbf{F}_{\text{gr}}^j = \mathbf{F}_r^j \mathbf{F}_g^j$$

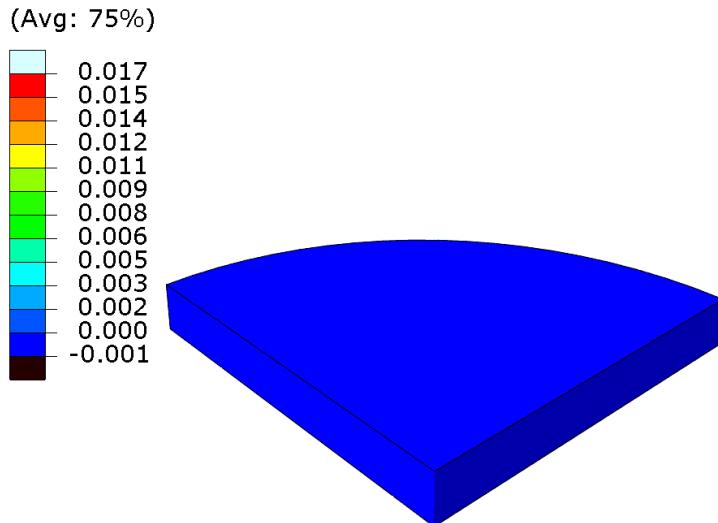
$\mathbf{F}_r^j$  and  $\mathbf{F}_g^j$  should be **updated** if the artery is not in the homeostatic state



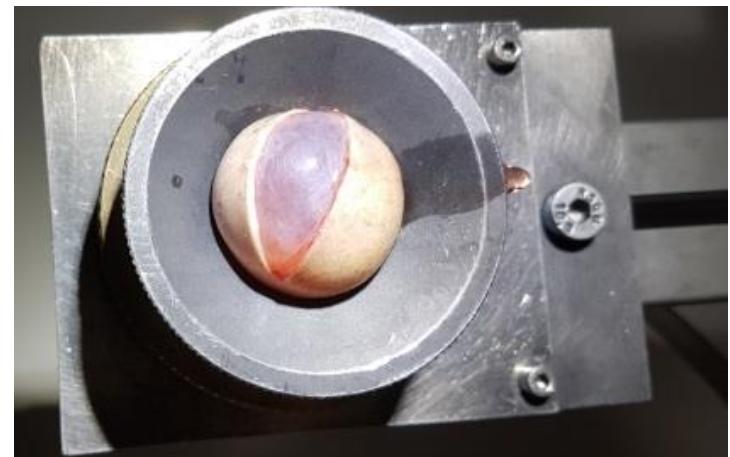
Mousavi & Avril, BMMB (2017), Mousavi et al, BMMB (2019)  
Ghavamian et al, Front Bioeng Biotech (2020)

# Abaqus finite-element implementation and verification

- ✓ FE software ABAQUS coupled with UMAT
- ✓ Hexahedral and tetrahedral elements
- ✓ Structural mesh ( $r, \theta, z$ )
- ✓ Two different layers (media and adventitia)



Mousavi et al, IJNMBE, 2018

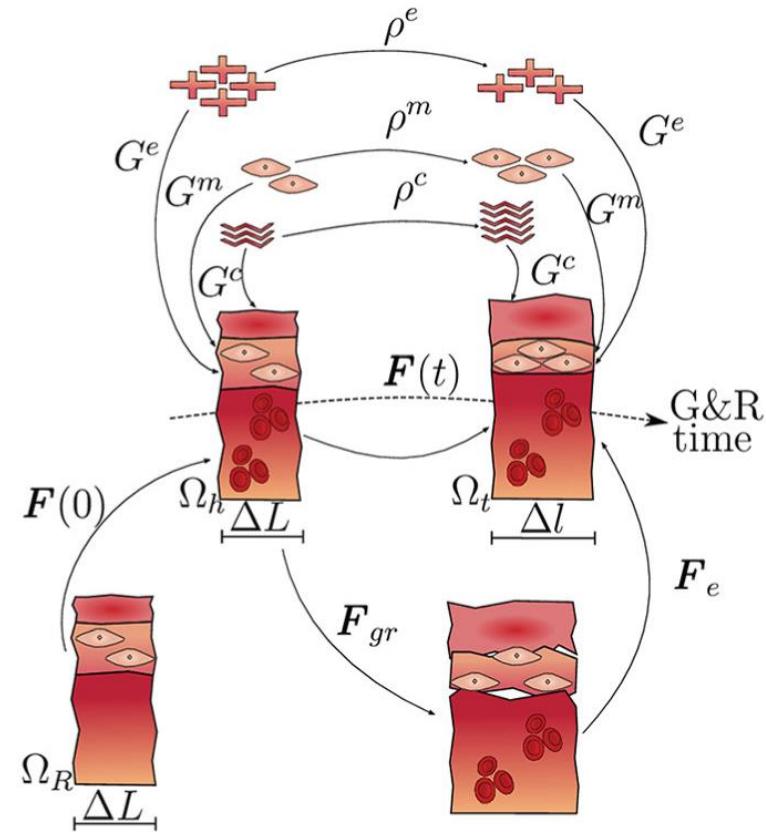
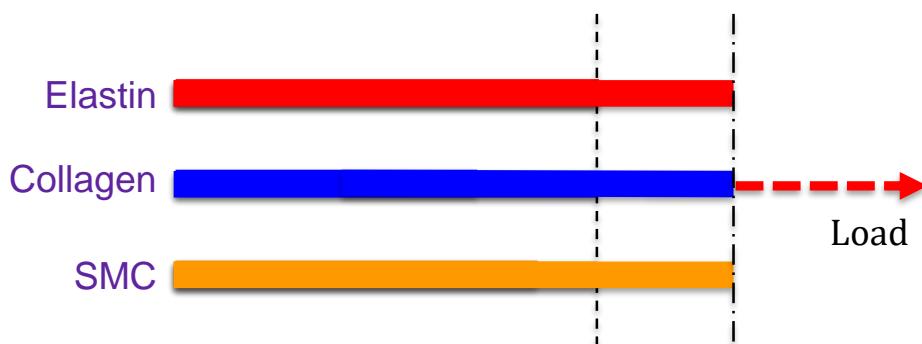


# Growth and Remodeling in homogenized constrained mixture

Collagen mass production

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

Inelastic deformation due to remodeling

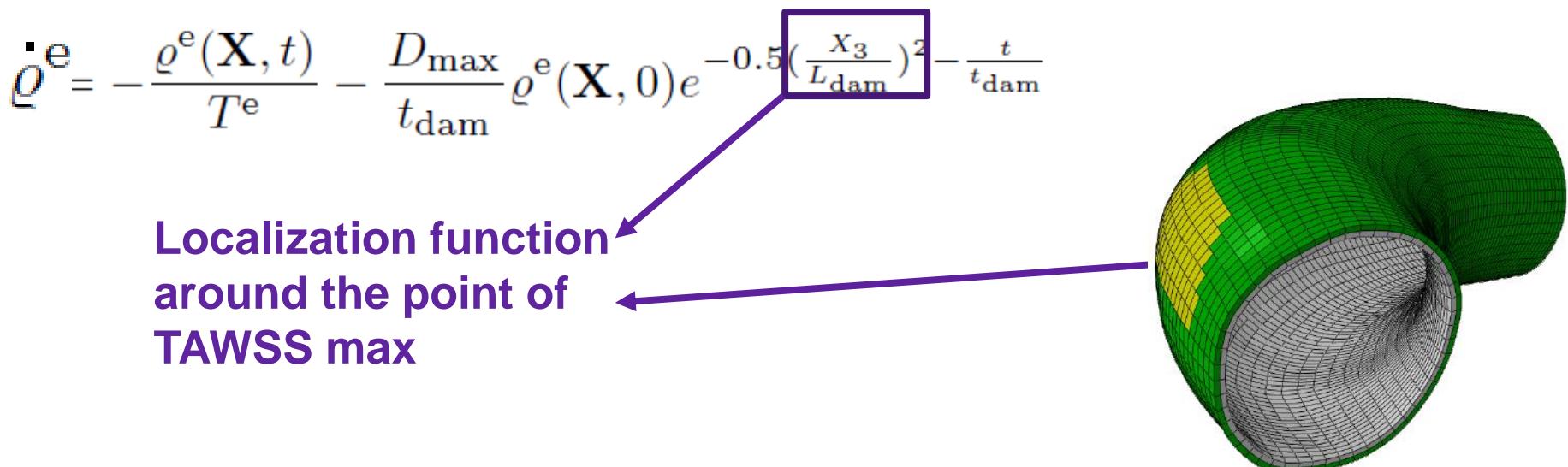


Cyron et al, BMBB (2016), Braeu et al, BMMB (2017), Laubrie et al, IJNMBE (2019)

# Patient-specific predictions

Growth and remodeling of a two-layer patient-specific human ATAAAs due to elastin loss

$$W = \varrho_t^e (\overline{W}^e(\bar{I}_1^e) + U(J_{el}^e)) + \sum_{j=1}^n \varrho_t^{c_j} W^{c_j}(I_4^{c_j}) + \varrho_t^m W^m(I_4^m)$$



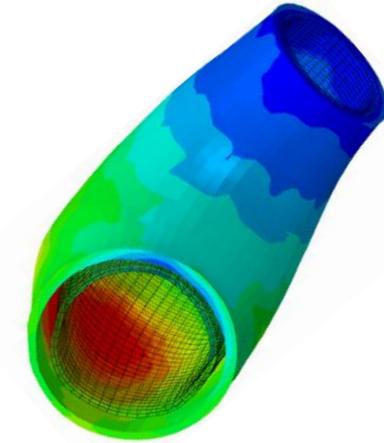
Mousavi et al, BMMB (2019)

avril@emse.fr

Stéphane Avril - 2020 Oct 30 - CBIO Santiago

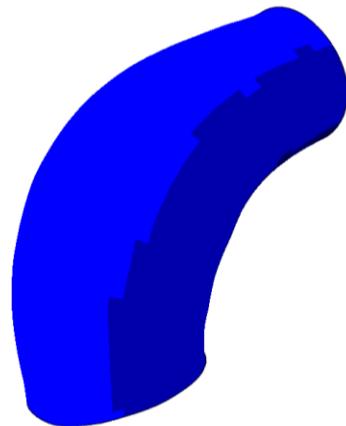
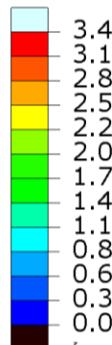
# Patient-specific predictions

Growth and remodeling of a two-layer patient-specific human ATAA due to elastin loss

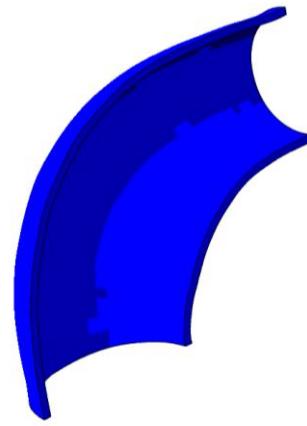
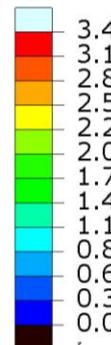


Small growth parameter

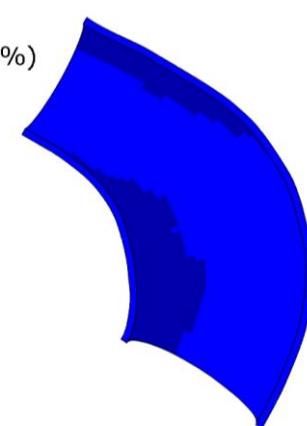
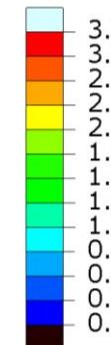
SDV69  
(Avg: 75%)



SDV69  
(Avg: 75%)



SDV69  
(Avg: 75%)



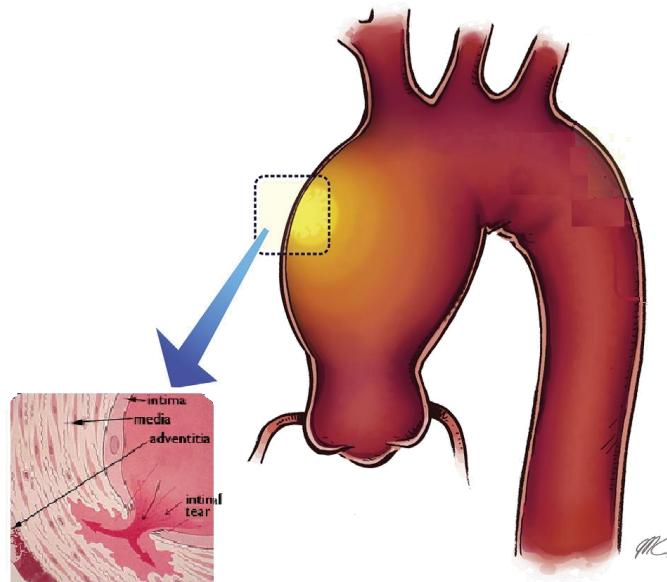
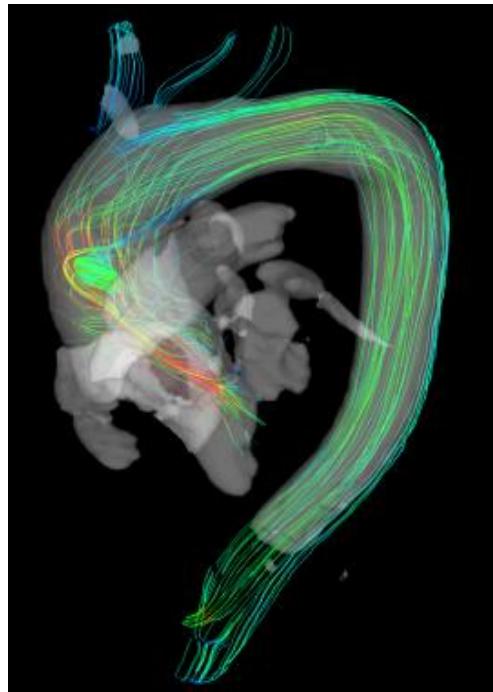
Normalized Thickness

Mousavi et al, BMMB (2019)

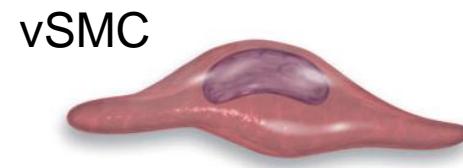
avril@emse.fr

Stéphane Avril - 2020 Oct 30 - CBIO Santiago

# Background: Aneurysms and Dissections of the ascending thoracic aorta



dissection

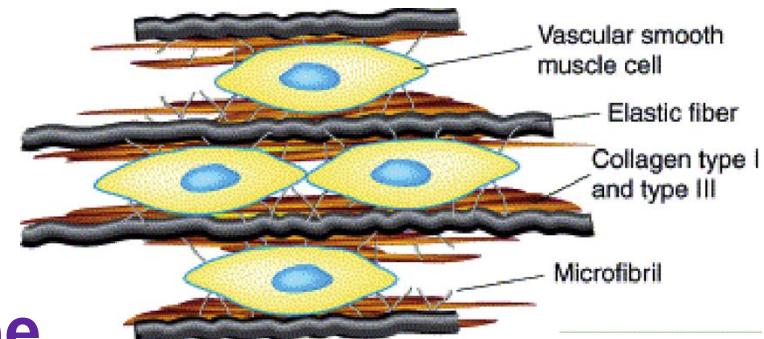
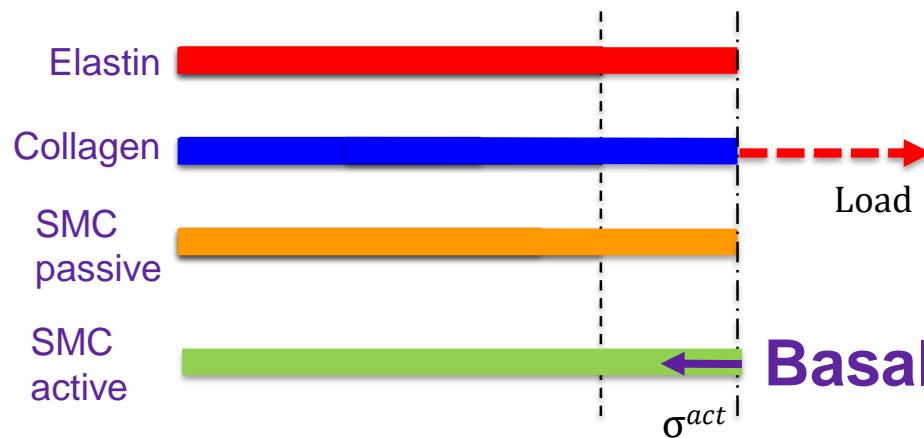


Humphrey et al, Science, 2014

# Effects of active SMC contraction

$$W = \varrho_t^e (\overline{W}^e(\bar{I}_1^e) + U(J_{\text{el}}^e)) + \sum_{j=1}^n \varrho_t^{c_j} W^{c_j}(I_4^{c_j}) + \varrho_t^m W^m(I_4^m)$$

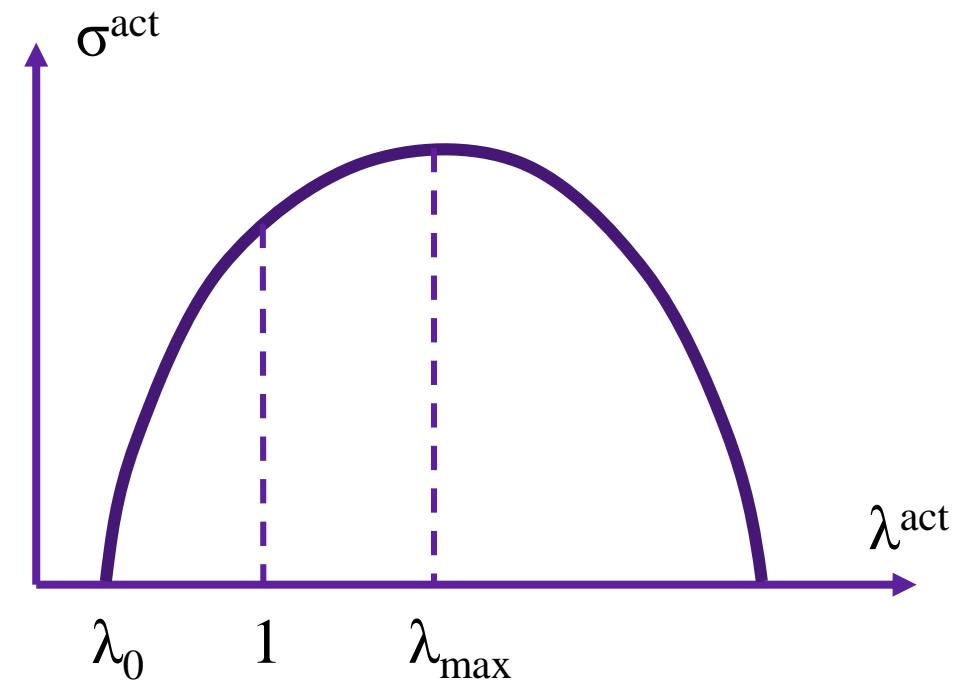
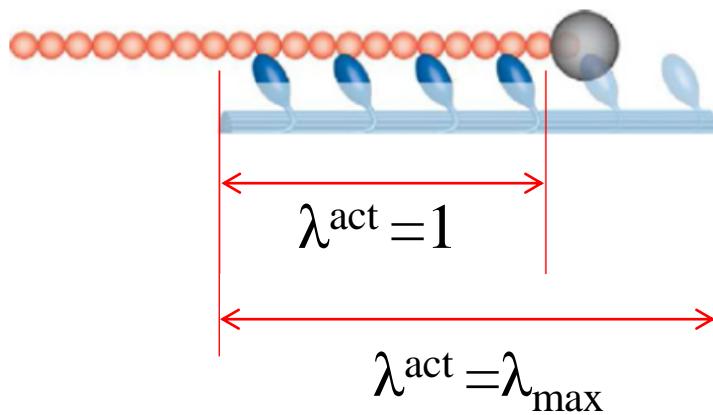
$$W^m(I_4^m, \lambda_{\text{act}}^m) = \underbrace{\frac{k_1^m}{2k_2^m} \left[ \exp^{k_2^m(I_4^m - 1)^2} - 1 \right]}_{W_{\text{pass}}^m} + \underbrace{\frac{\sigma_{\text{actmax}}}{\varrho_0} \left( \lambda_{\text{act}}^m + \frac{1}{3} \frac{(\lambda_{\text{max}}^m - \lambda_{\text{act}}^m)^3}{(\lambda_{\text{max}}^m - \lambda_0^m)^2} \right)}_{W_{\text{act}}^m}$$



# Length-tension relationship of SMCS

$$\sigma^{\text{act}} = \frac{\sigma_{\text{actmax}}}{\varrho_0(0) [C^m : (a_0^m \otimes a_0^m)]} \left( 1 - \frac{(\lambda_{\max}^m - \lambda_{\text{act}})^2}{(\lambda_{\max}^m - \lambda_0^m)^2} \right)$$

Basal tone ~50kPa

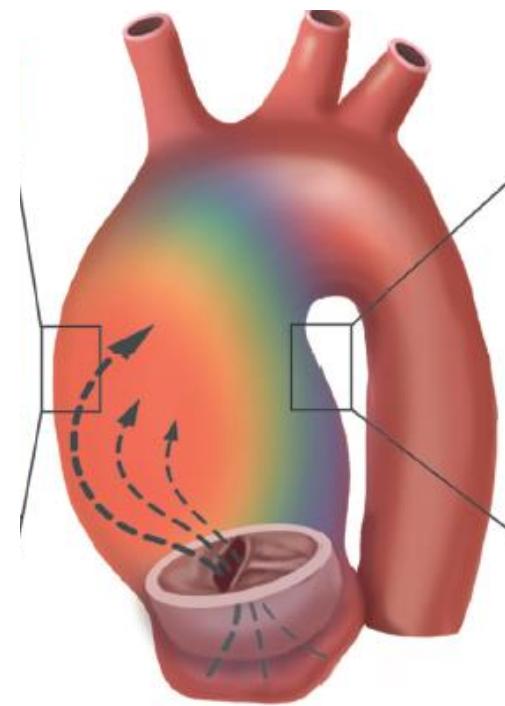


Murtada et al, J Theor Biol 2012, Ghavamian et al, Front Bioeng Biotech (2020)

# Future work: test other assumptions

Combination of local decrease of SMC active stress and proteolytic injury

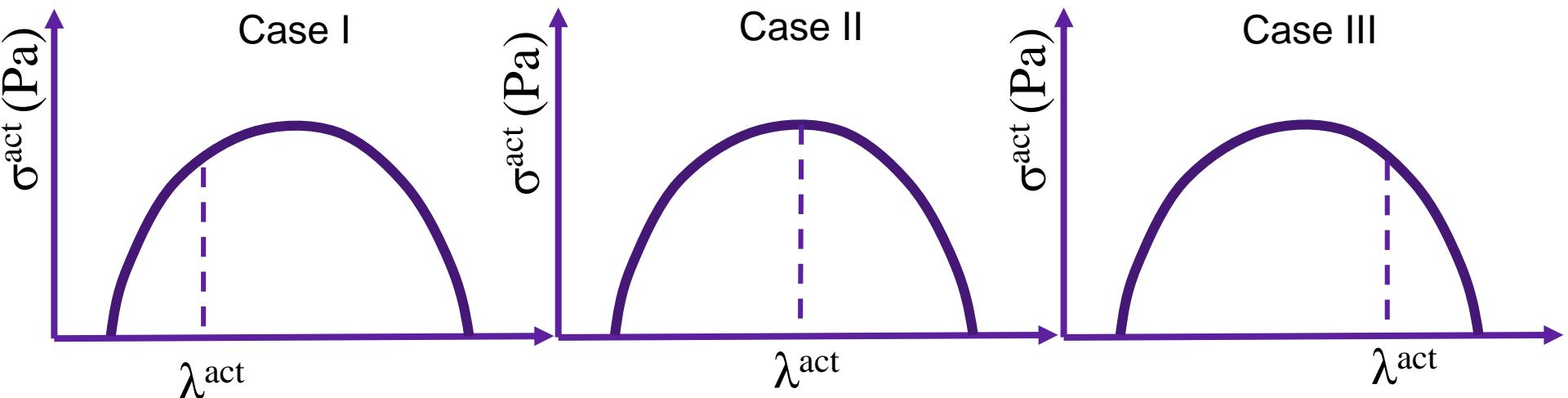
Large WSS  
resulting in reduced  
SMC contractility



Large RRT  
resulting in possibly  
increased  
proteolytic effects

# Sensitivity analysis

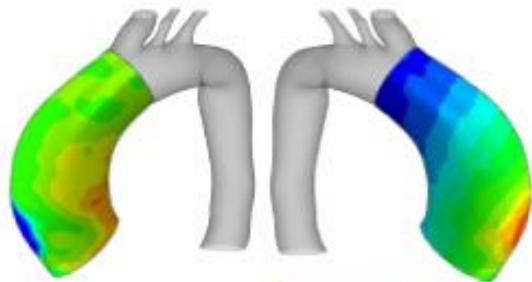
- The time of which the artery is maximally damaged ( $t_{\text{dam}}$ ),
- The rate of collagen deposition ( $k_{\sigma}^{c_j} / T^{c_j}$ ),
- The maximum contractility of SMCs ( $\lambda_{\max}^m$ ).



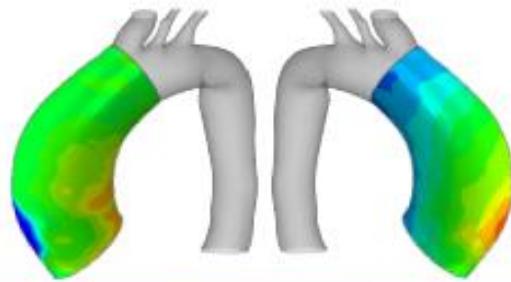
Ghavamian et al, Front Bioeng Biotech (2020)

# Evolution of the active stress of SMCs

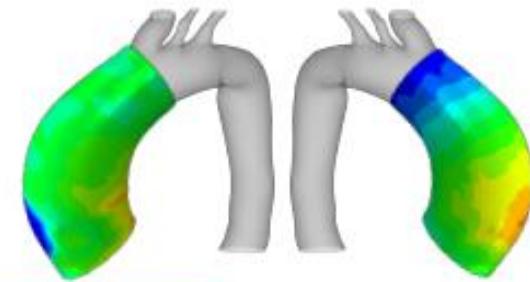
Case I



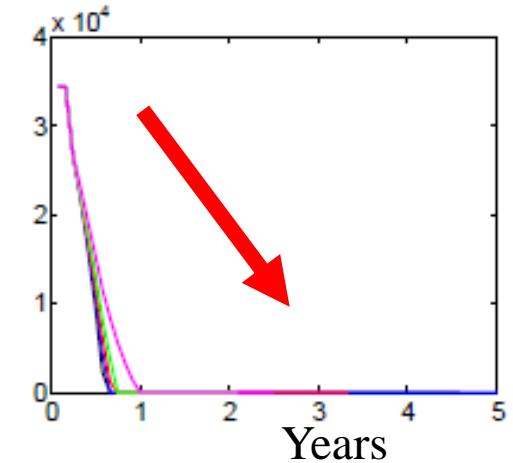
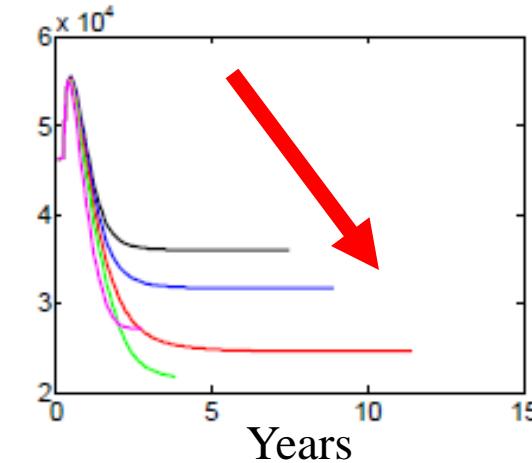
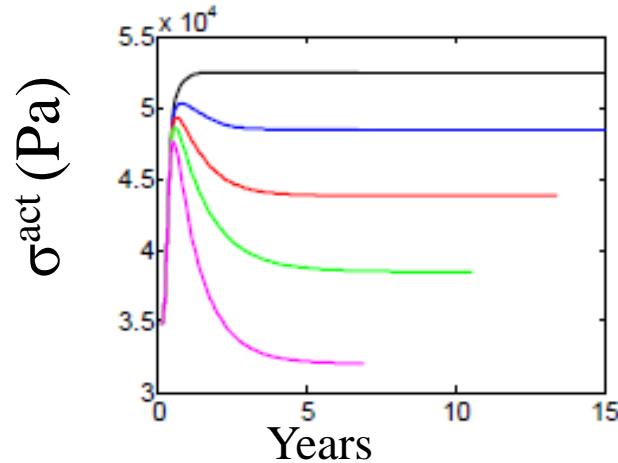
Case II



Case III



Relative displacement and thickness





# SUMMARY

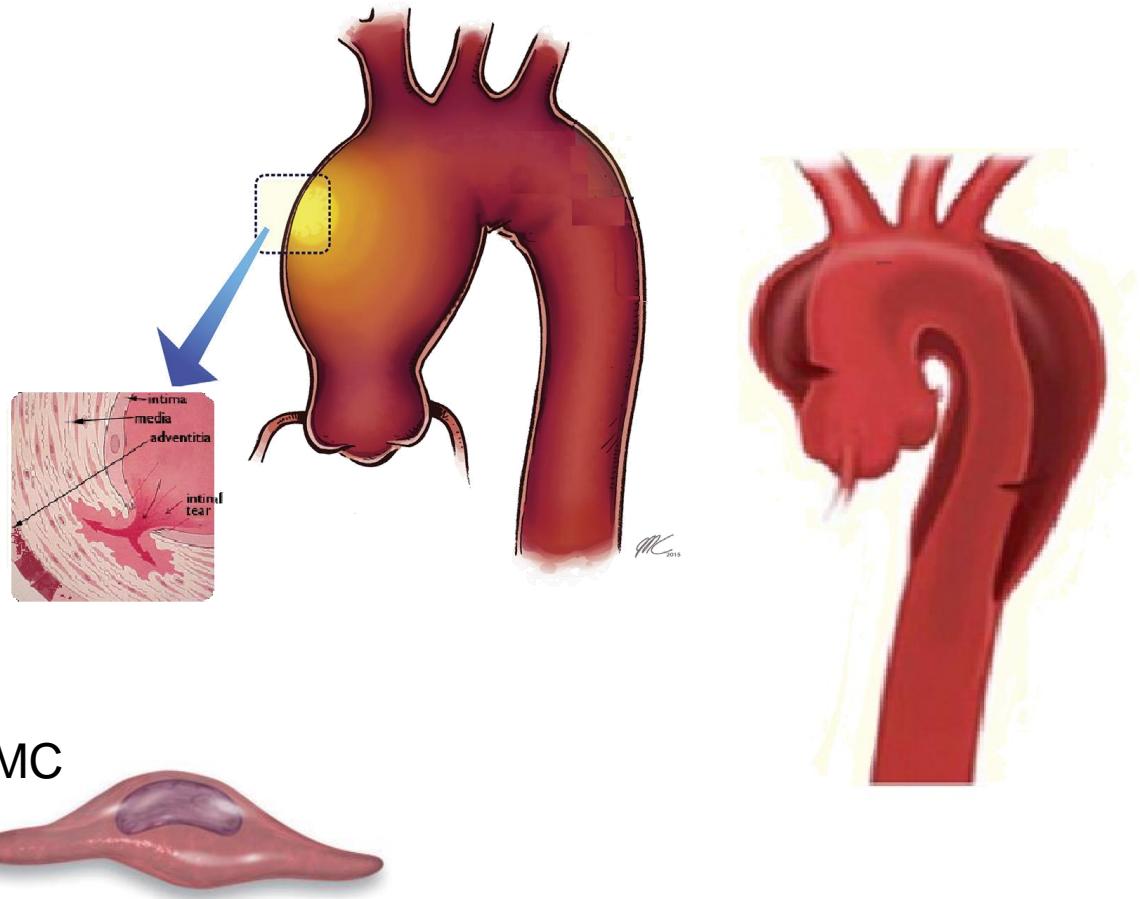
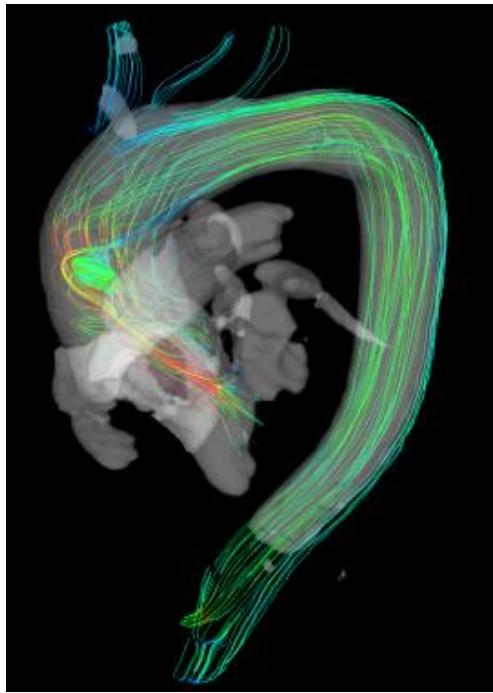
- Patient-specific numerical model based on the constrained mixture theory including damage and G&R – coupling with CFD analyses, + active role of SMCs
- Marginal contribution of the active stress of SMCs but a critical state can be reached when the active stress reaches zero due to large stretching
- One of the major role of SMCs is mechanoregulation.



# OUTLINE

- PART I: Risk factors for aortic rupture
- PART II: Computational prediction of aortic weakening
- **PART III: Role of SMCs in aortic weakening**

# The major role of SMCs in Aneurysms and Dissections of the ascending thoracic aorta

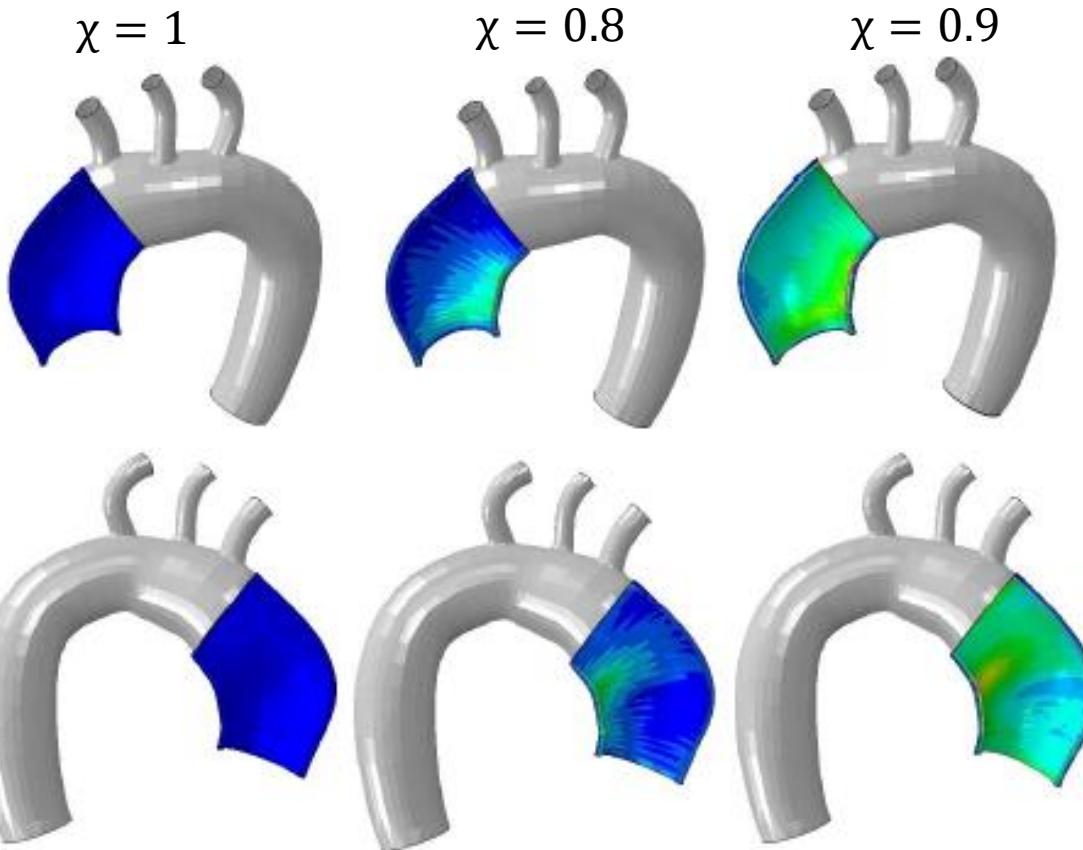


Humphrey et al, Science, 2014

# Future work: mechanosensitivity impairment

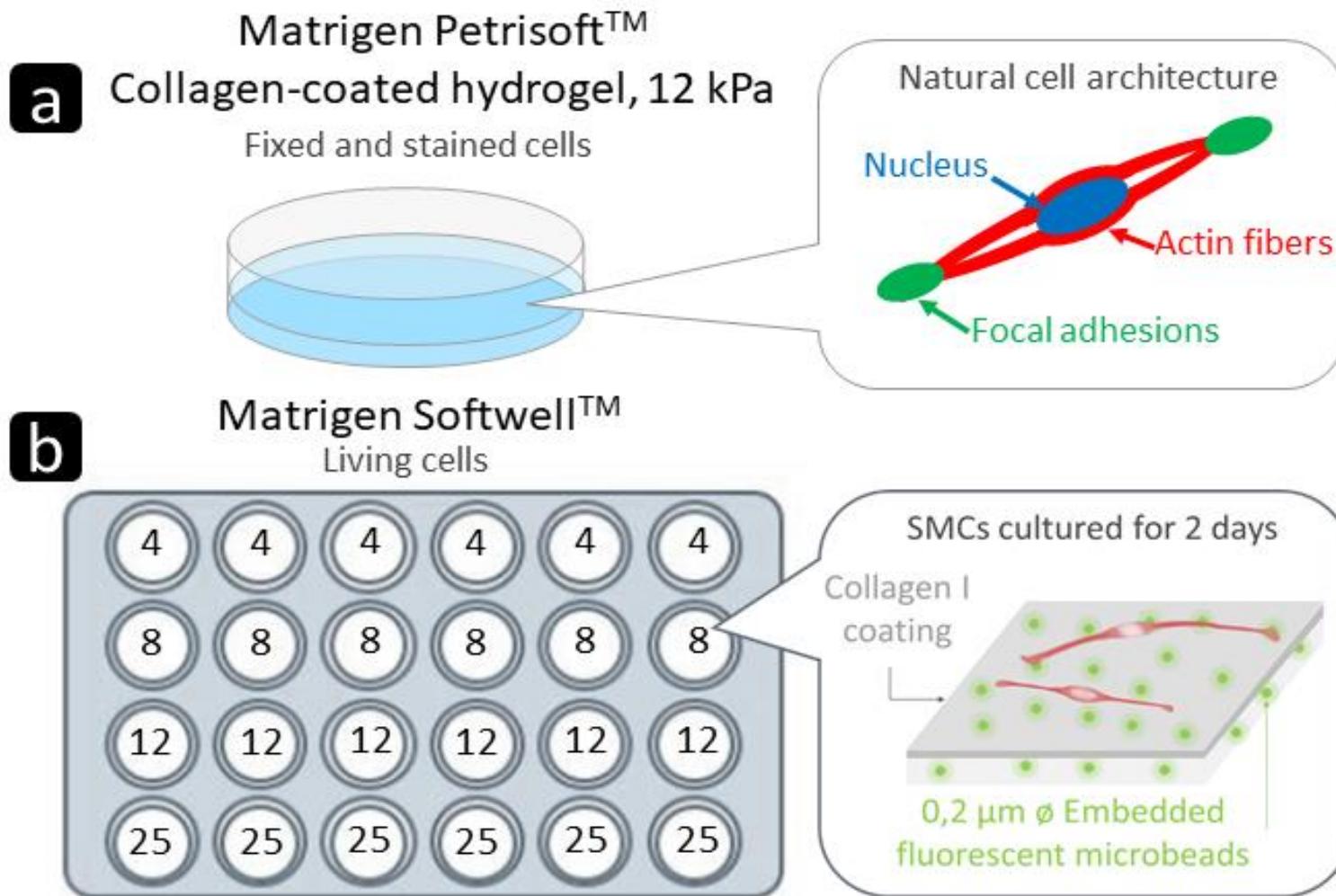
$$\dot{\varrho}^j(t) = \varrho^j(t) k_\sigma^j \frac{\chi * \sigma^j(t) - \sigma_h^j}{\sigma_h^j} + \dot{\xi}^j(t) \quad 0 \leq \chi \leq 1: \text{impairment coefficient}$$

Tangent stiffness after 10 years



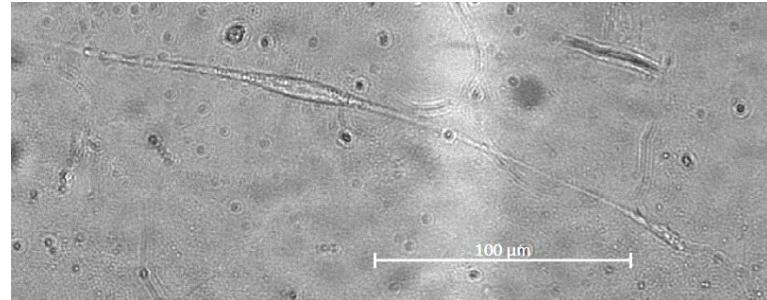
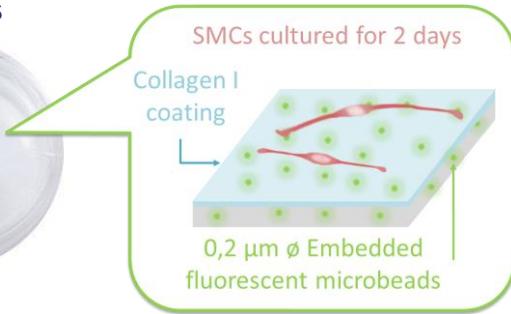
Mousavi et al, ABME (2020, submitted)

# Traction force microscopy on aortic smooth muscle cells

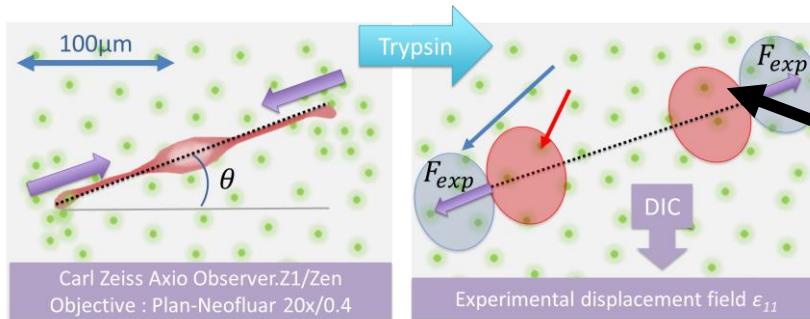


# Traction force microscopy on aortic smooth muscle cells

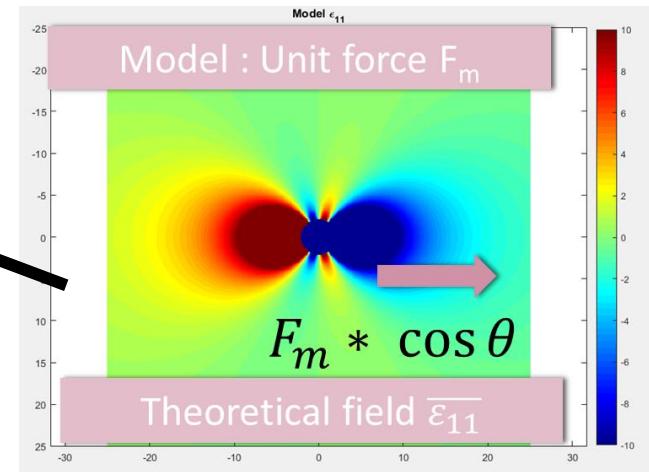
Several stiffness values



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

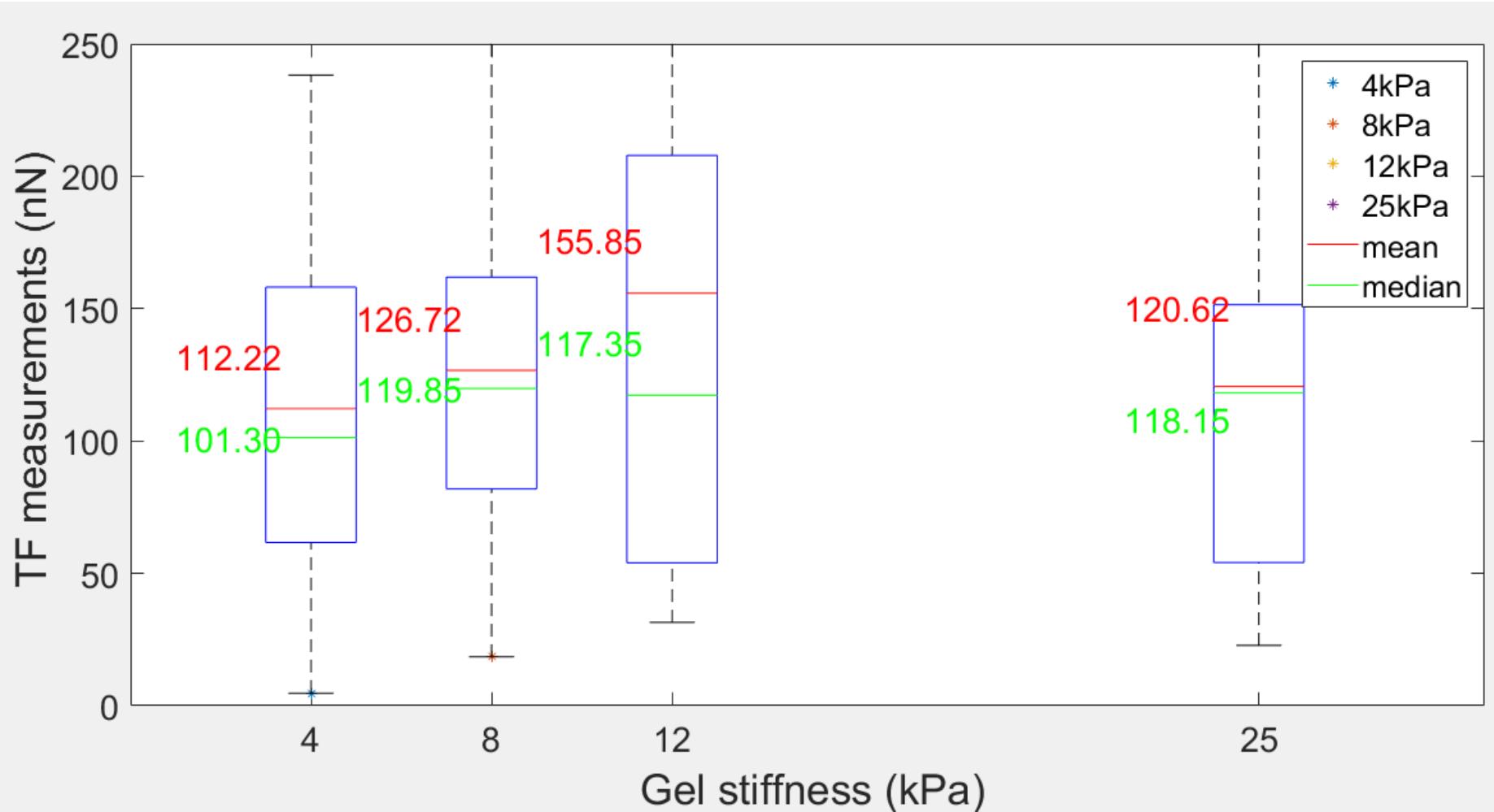


- **Fluorescent microscopy + DIC** : track the displacement of fluorescent microbeads
- **Cell unbinding method (with trypsin)** : assess the homeostatic state of single SMCs

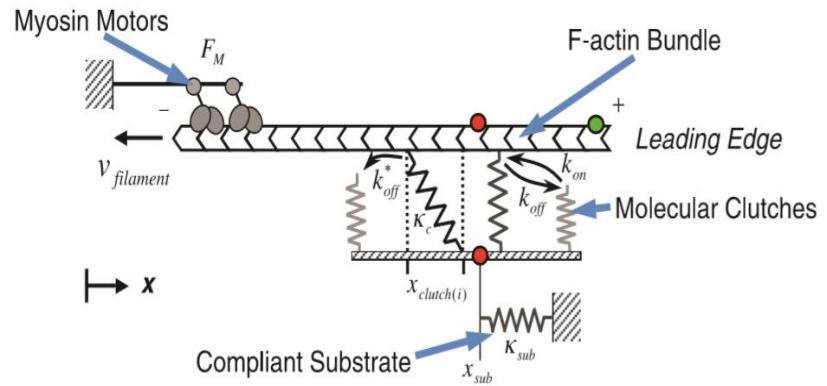
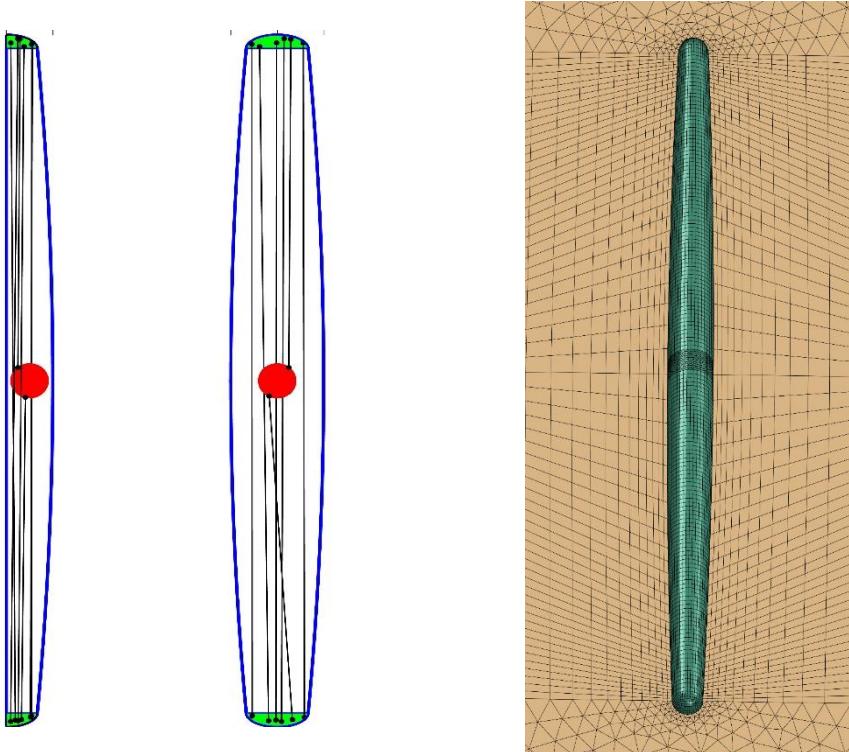


$K = 2$

# Traction force of aortic smooth muscle cells depend on the surrounding stiffness

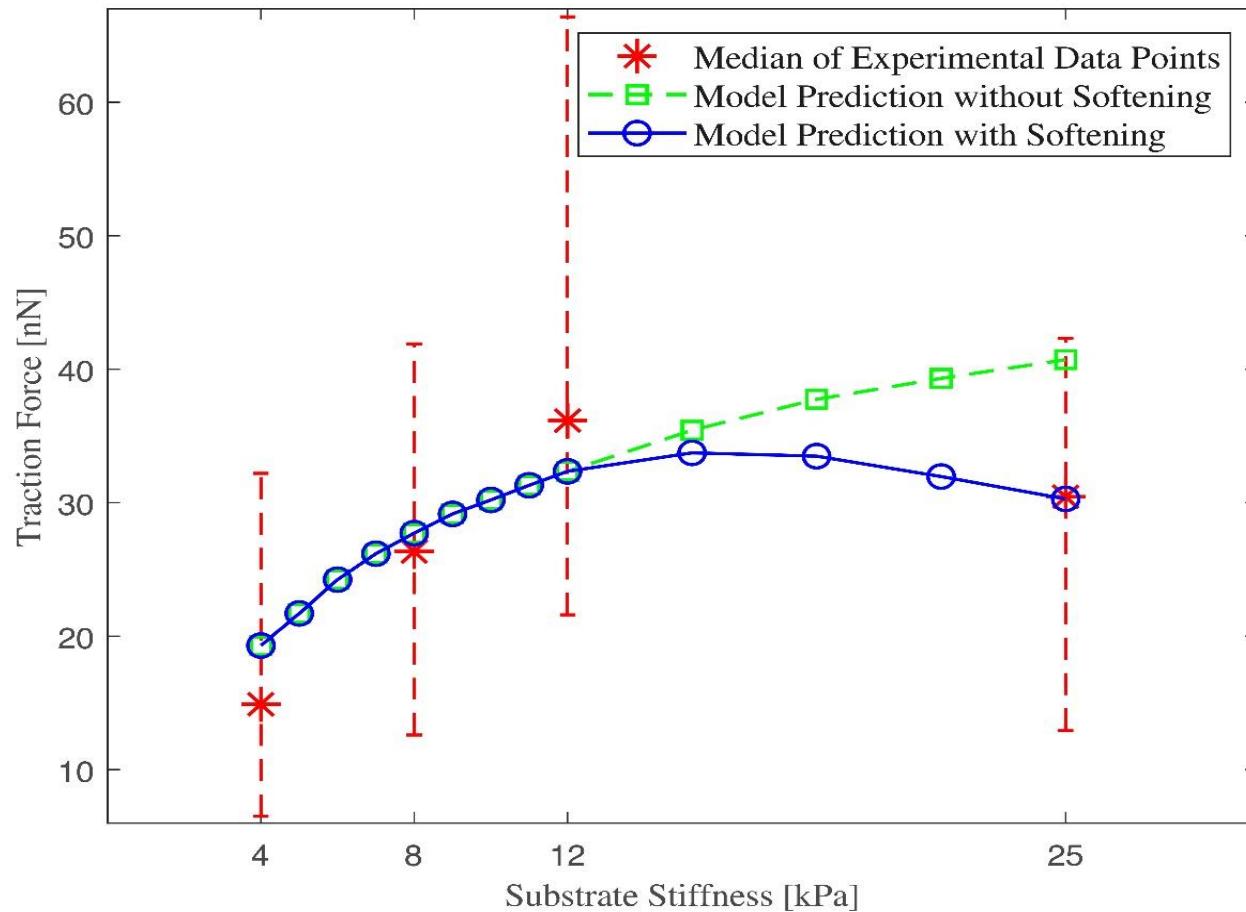


# Modelling of SMCs cytoskeletal mechanics

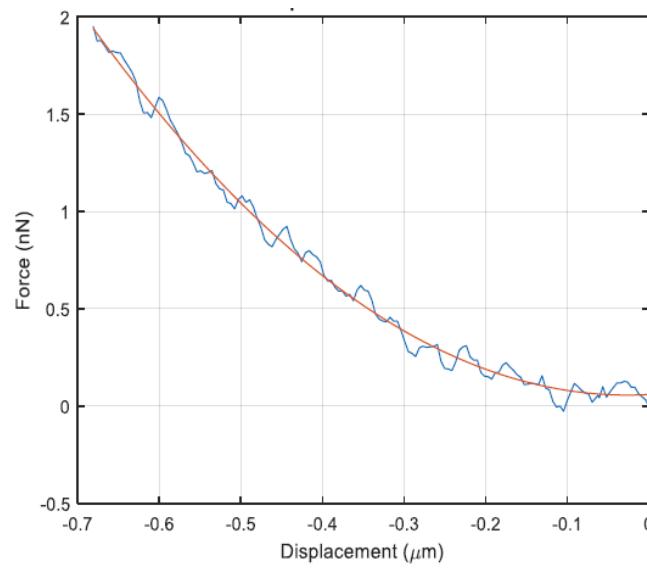
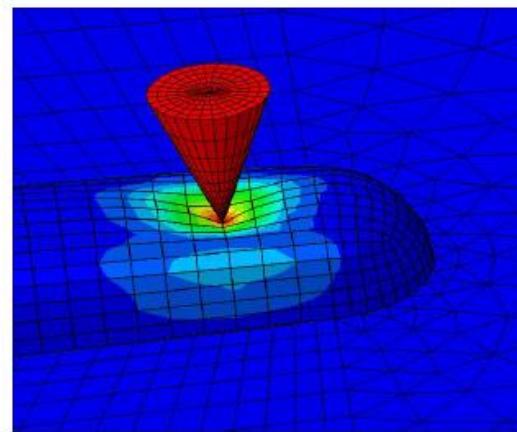
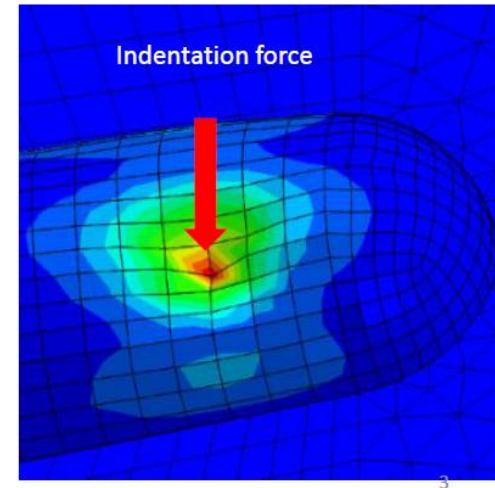
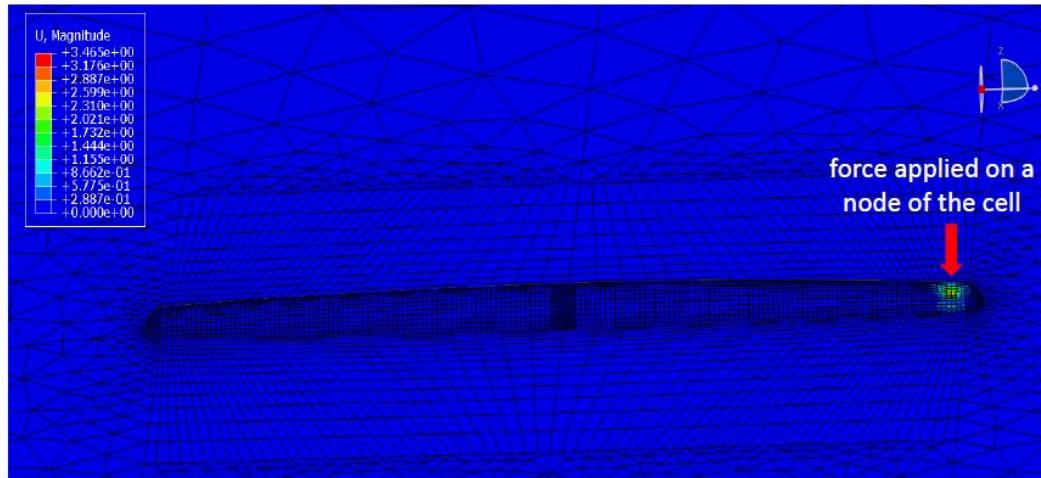


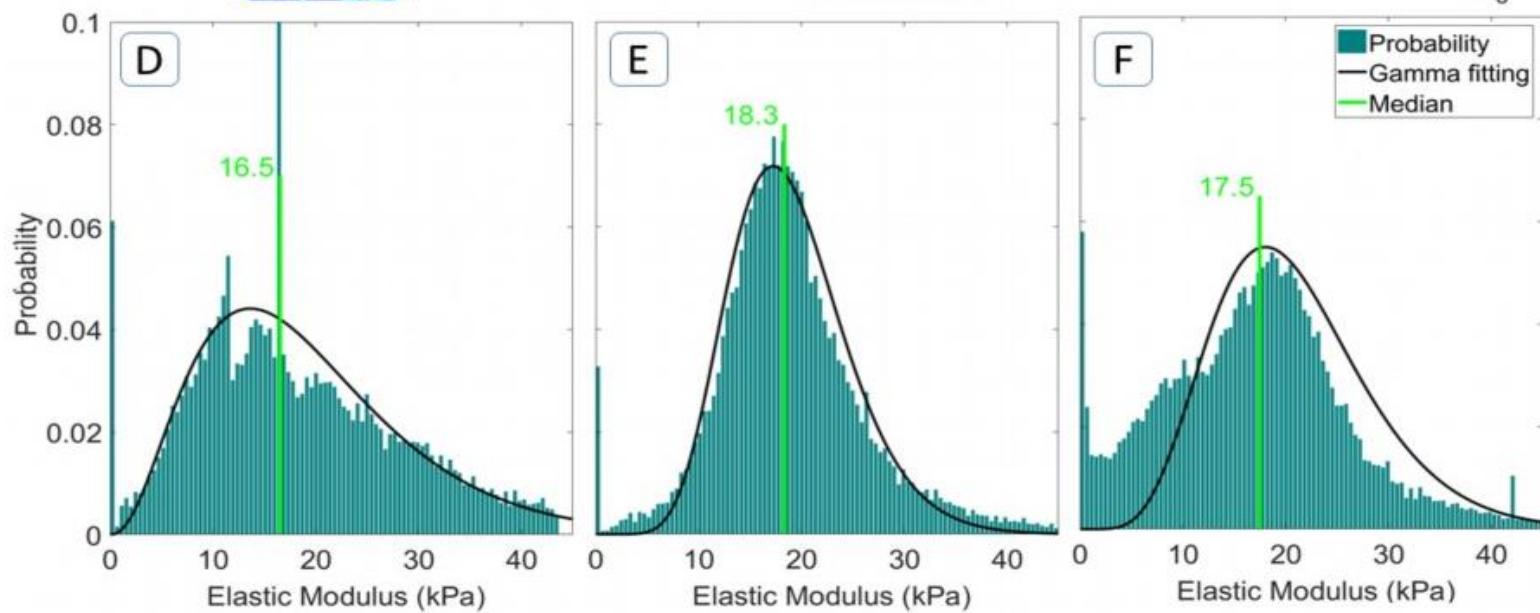
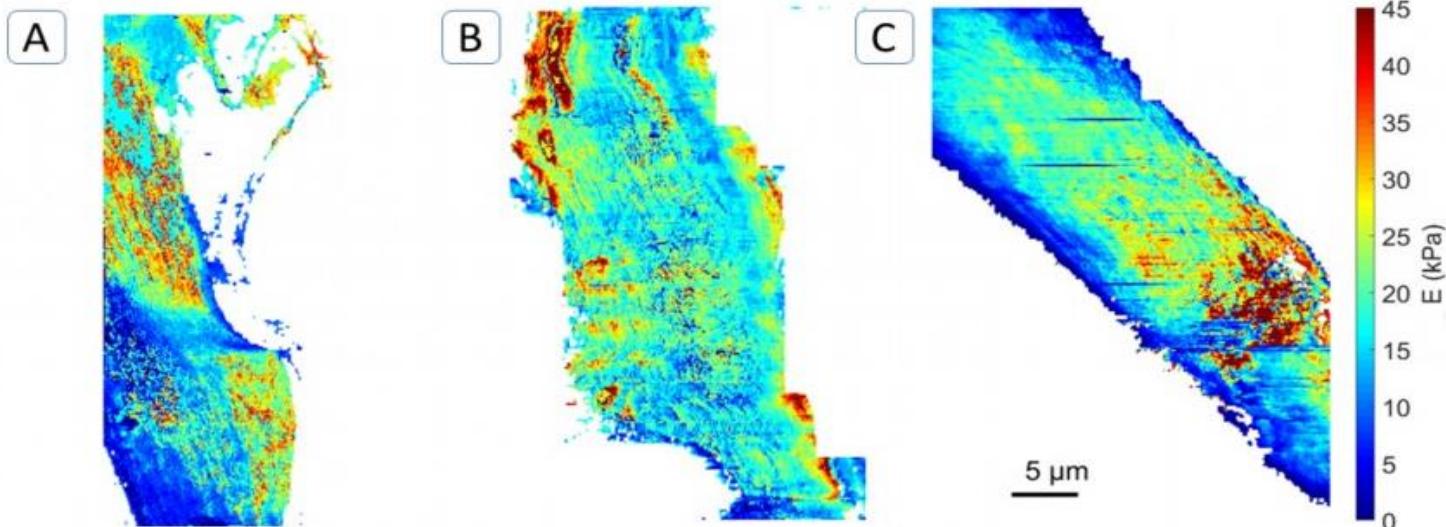
Chan & Odde, Science 2008.  
Kharkaneh et al, Acta Biomaterialia 2020.

# Modelling of SMCs cytoskeletal mechanics



# Stiffness characterization of aortic smooth muscle cells using AFM indentation





# SUMMARY AND FUTURE WORK

- Decipher the link between cytoskeletal SMC mechanics and mechanosensitivity in aortic aneurysms
- Include SMC models into the G&R models of aortic aneurysms
- Clinical translation



# Computational mechanics in the OR for vascular surgery?

[www.predisurge.com](http://www.predisurge.com)



Chimneys simulation / Cook SG  
D. Perrin, Predisurge / 24/01/2018



# Acknowledgements

- Olfa Trabelsi
  - Aaron Romo
  - Jin Kim
  - Pierre Badel
  - Frances Davis
  - Victor Acosta
  - Jamal Mousavi
  - Solmaz Farzeneh
  - Francesca Condemi
  - Cristina Cavinato
  - Jérôme Molimard
  - Baptiste Pierrat
  - Joan Laubrie
  - Claudie Petit
  - Ali Kharkaneh
  - Ataollah Ghavamian
- 
- Ambroise Duprey
  - Jean-Pierre Favre
  - Jean-Noël Albertini
  - Salvatore Campisi
  - Magalie Viallon
  - Pierre Croisille
- 
- Chiara Bellini
  - Matthew Bersi
  - Jay Humphrey
  - Katia Genovese



Funding:  
ERC-2014-CoG BIOLOCHANICS



European Research Council  
Established by the European Commission  
©ERC

