UNIVERSITÉ DE LYON

HORIZON 2020

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MINES Saint-Étienne
Une école de l'IMT

Inverse problems in cardiovascular continuum mechanics and medical applications

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

Inserm
Institut national de la santé et de la recherche médicale

TU WIEN
TECHNISCHE UNIVERSITÄT WIEN
Vienna | Austria

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

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OUTLINE

- **PART I: Risk factors for aortic rupture**
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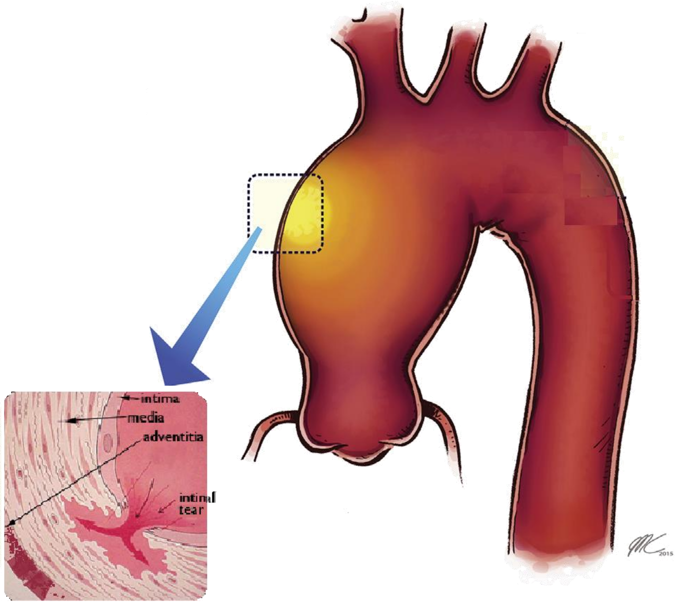
Aneurysms and Dissections of the ascending thoracic aorta



Goal: find factors of aortic rupture

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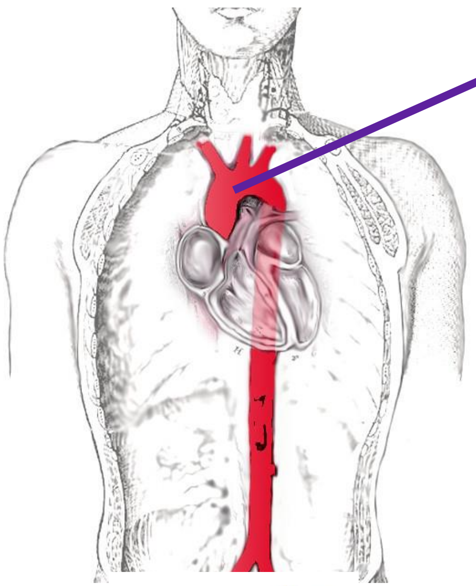
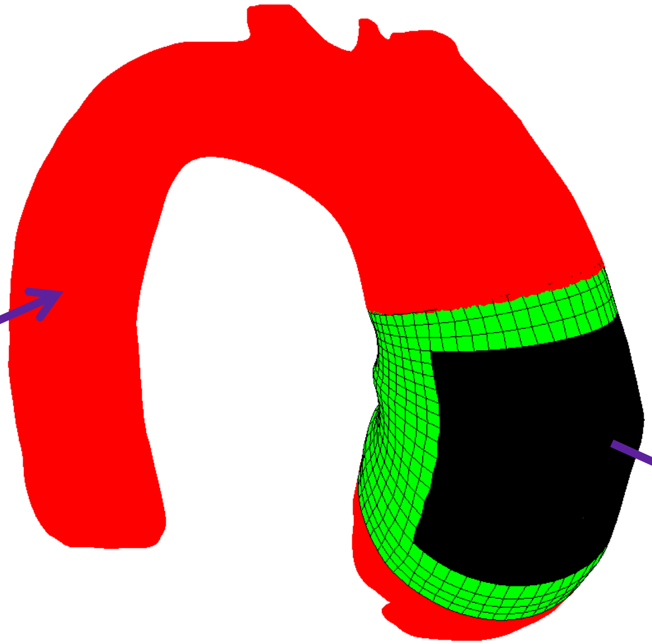
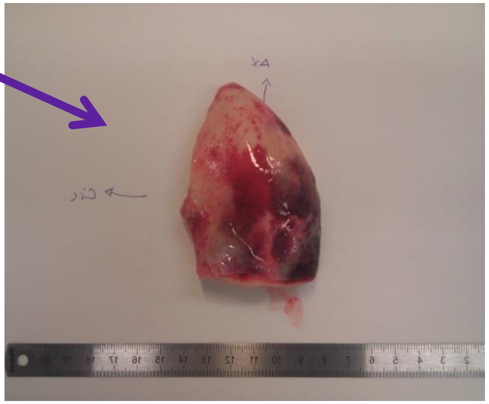
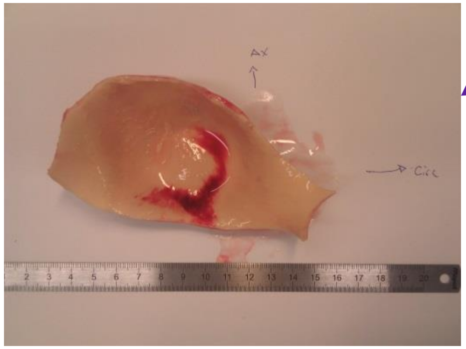
Collection of human samples









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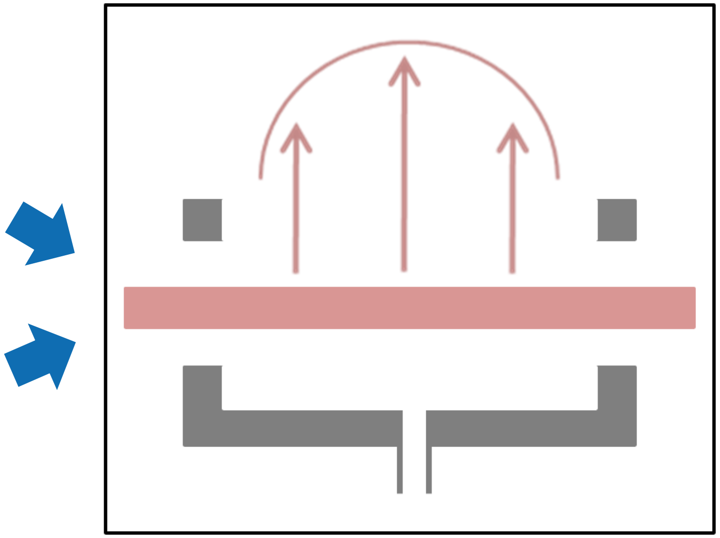
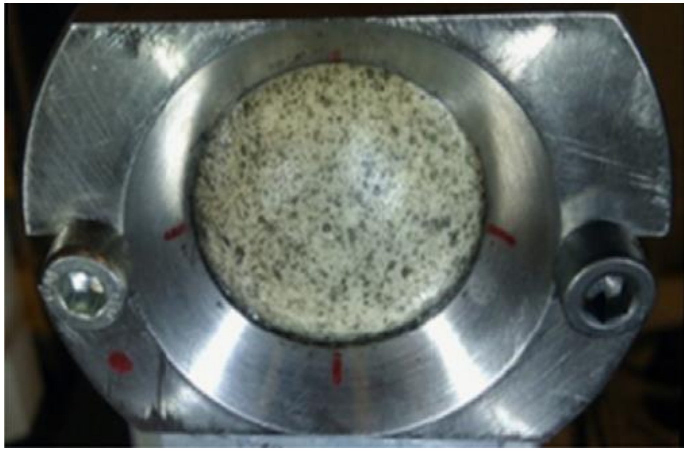
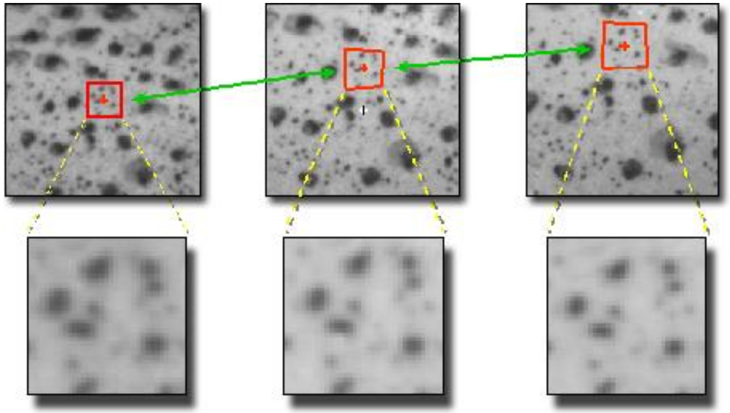
Bulge inflation test

Romo et al. Journal of Biomechanics -2014.

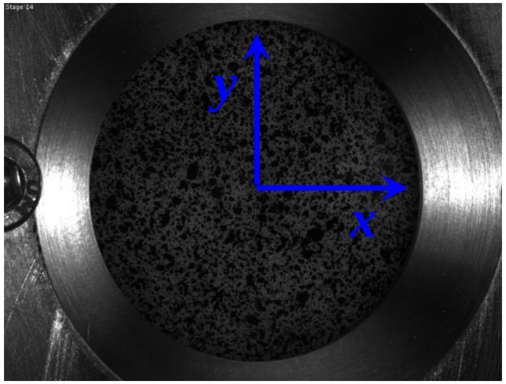




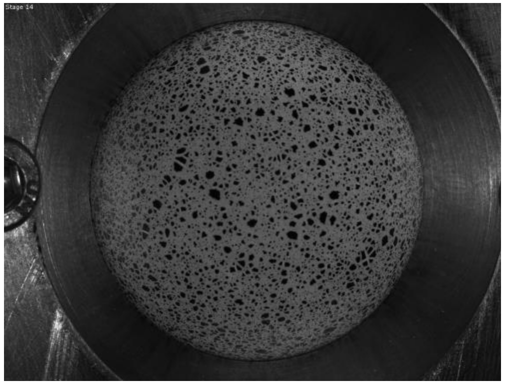
Full-field measurements using sDIC



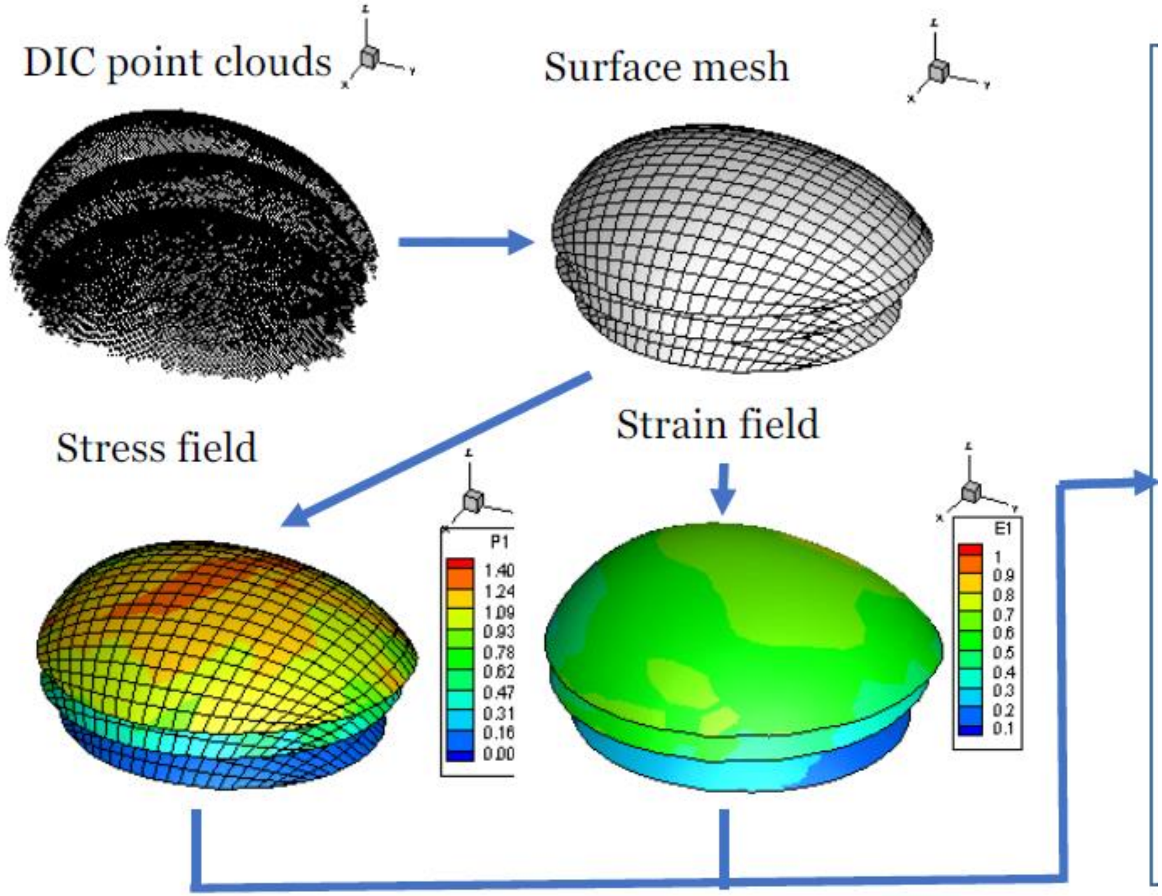
Undeformed

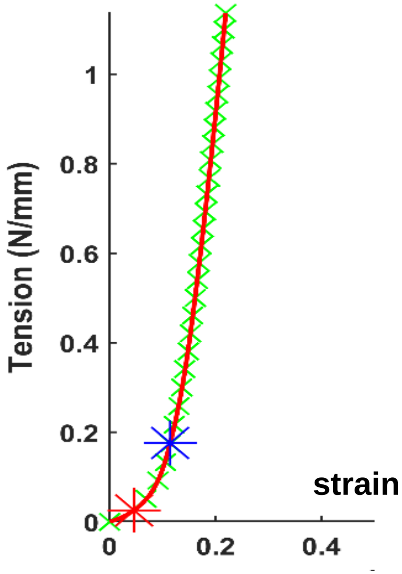


Deformed



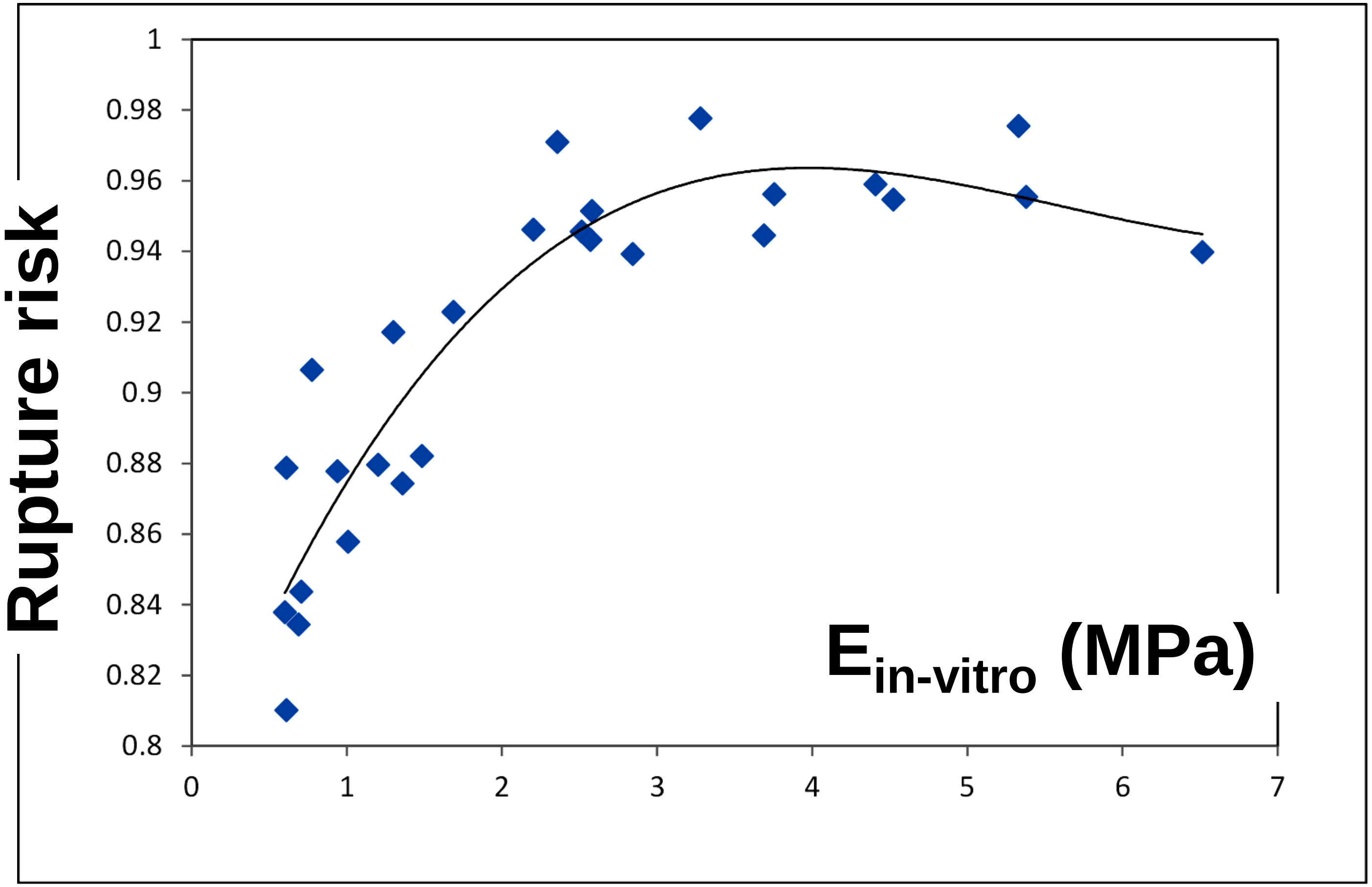
Identification of local material properties





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

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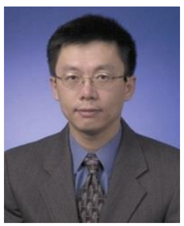

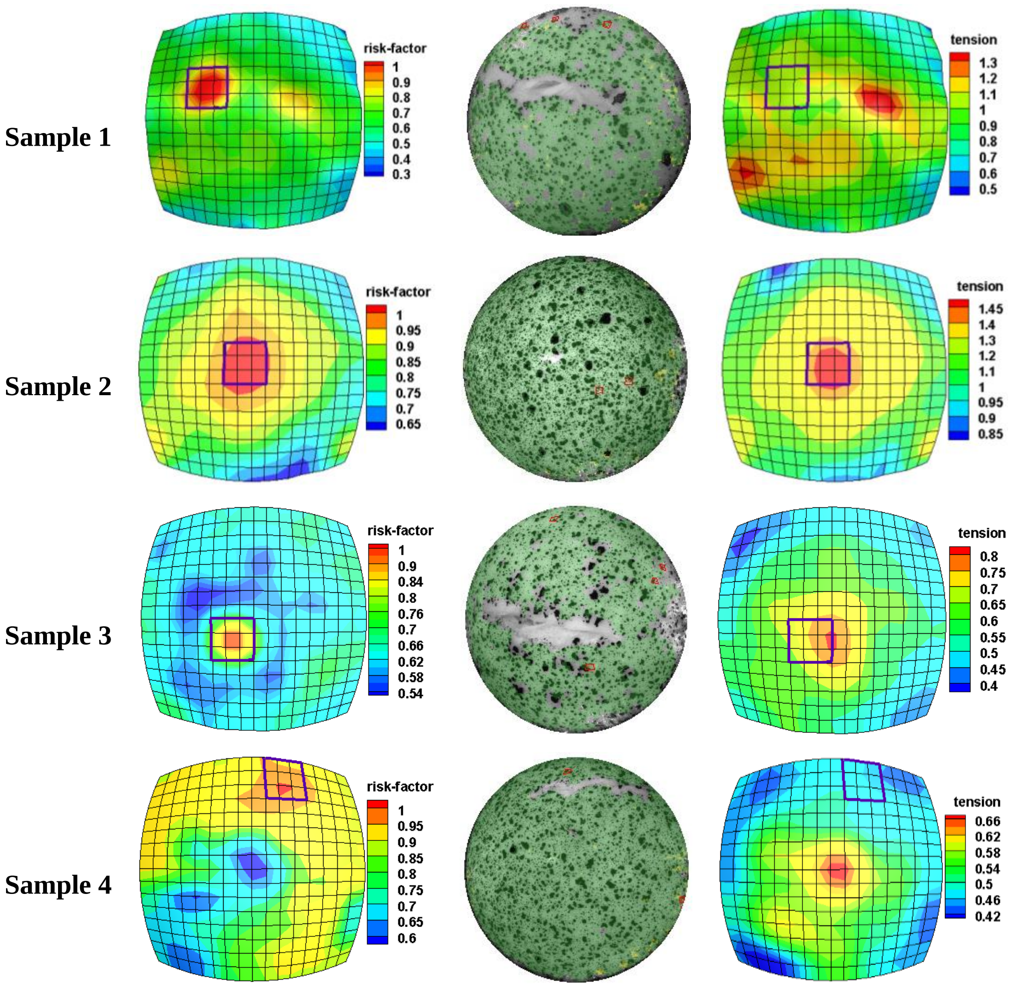

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SUMMARY

- ❑ Local **<u>tangent stiffness</u>** is heterogeneous and a risk factor for aortic rupture

OUTLINE

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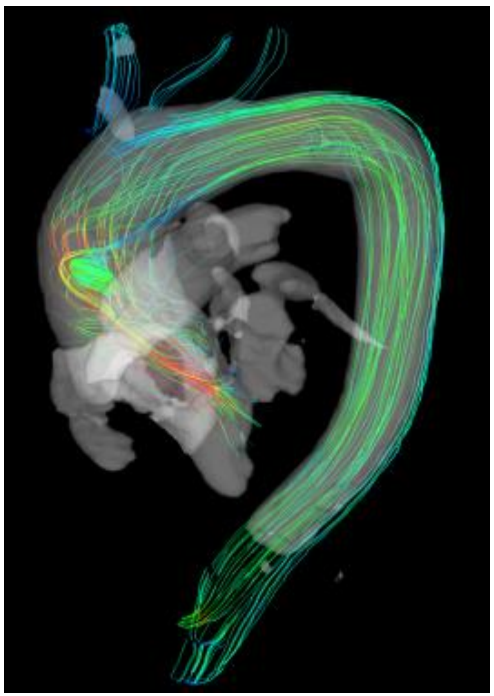
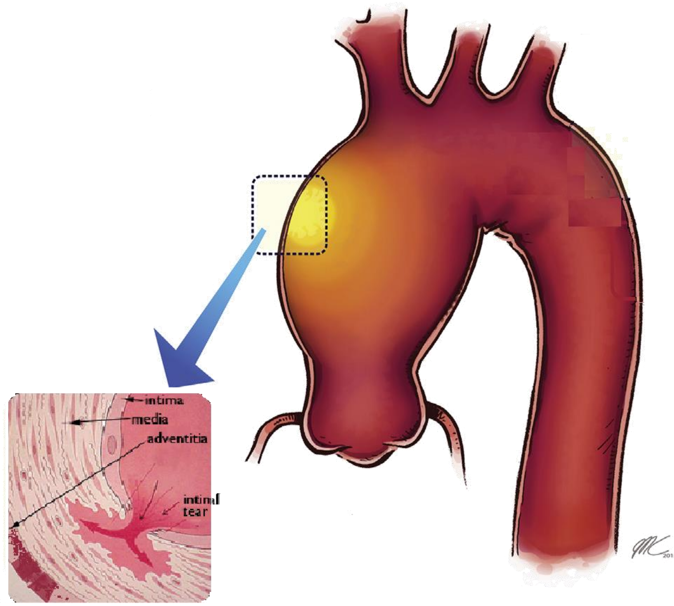
Aneurysms and Dissections of the ascending thoracic aorta





Goal: Predict weakening in the aortic wall

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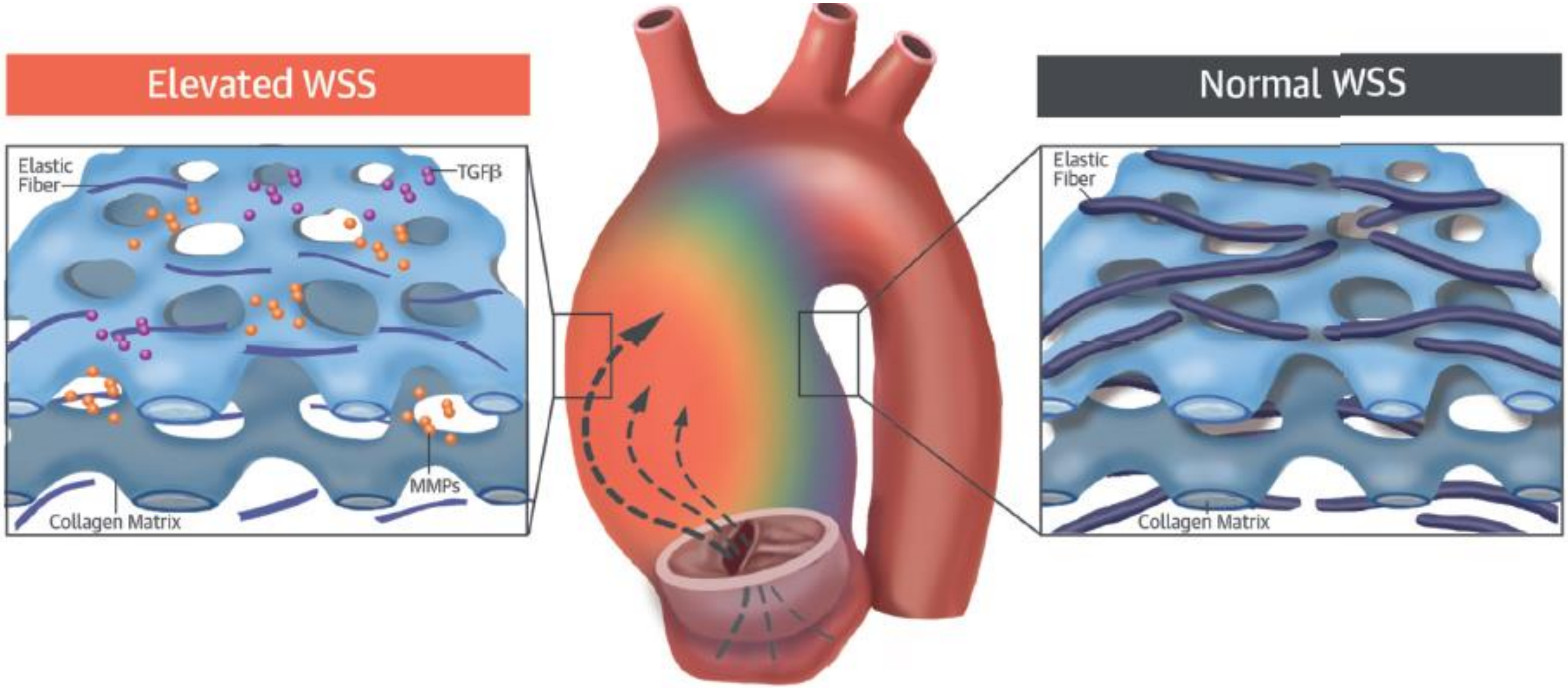
Introduction - Assumption

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)

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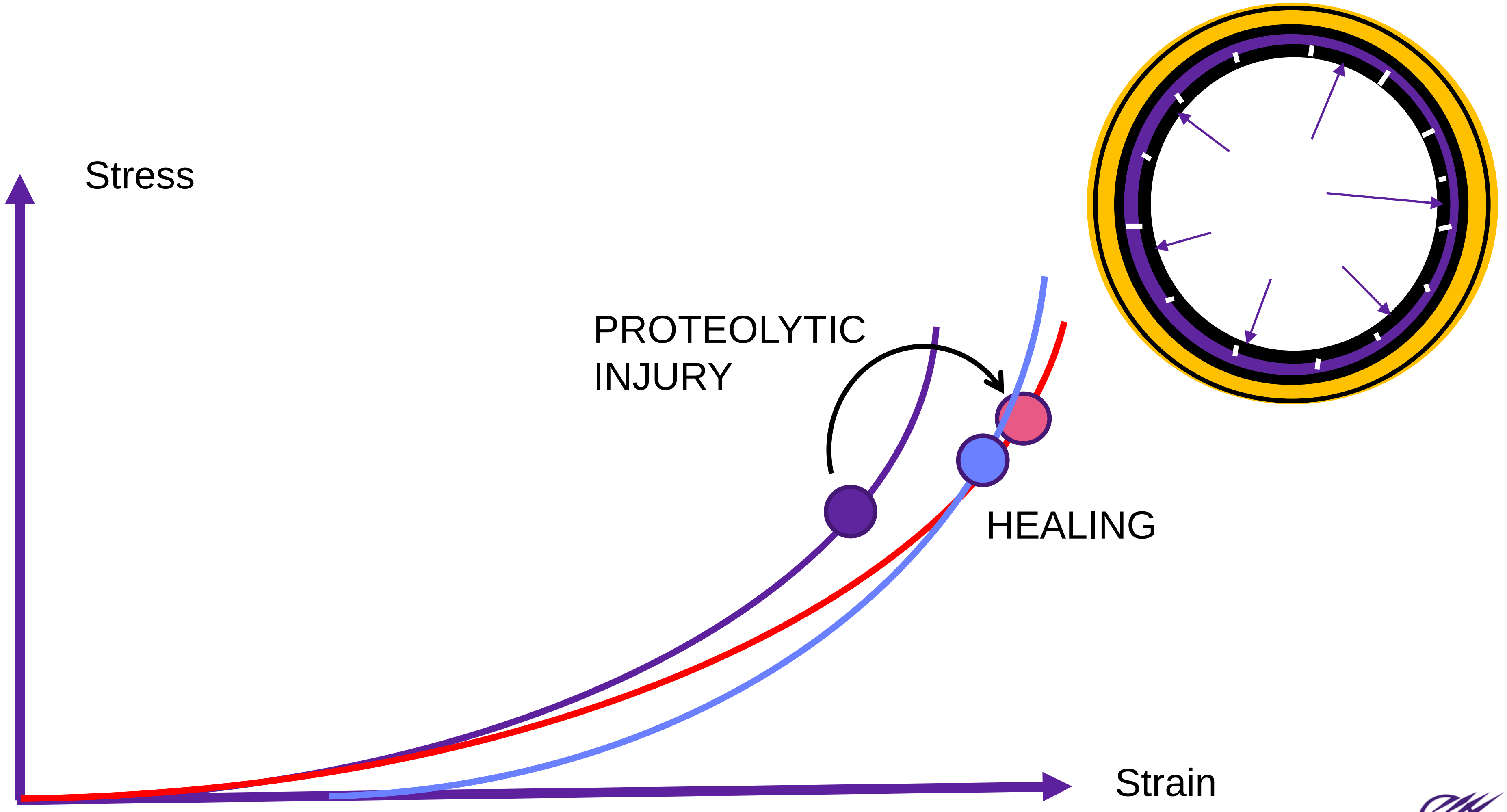
Proteolytic injury and tissue adaptation

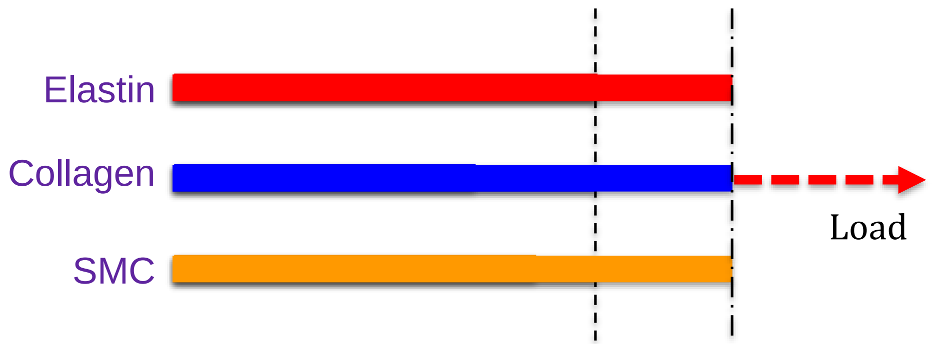


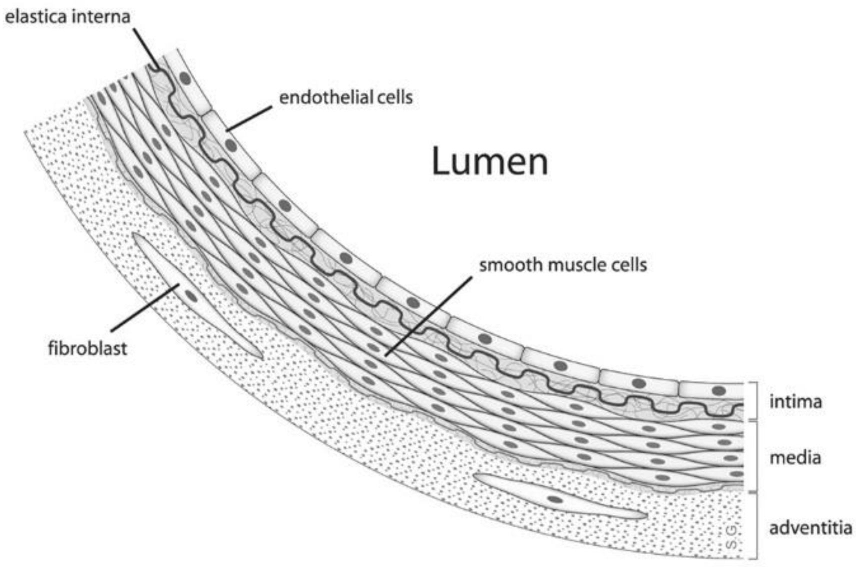
Layer-specific constitutive model

Strain-energy function based on the constrained mixture theory

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

Deposition stretch of each constituent:





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

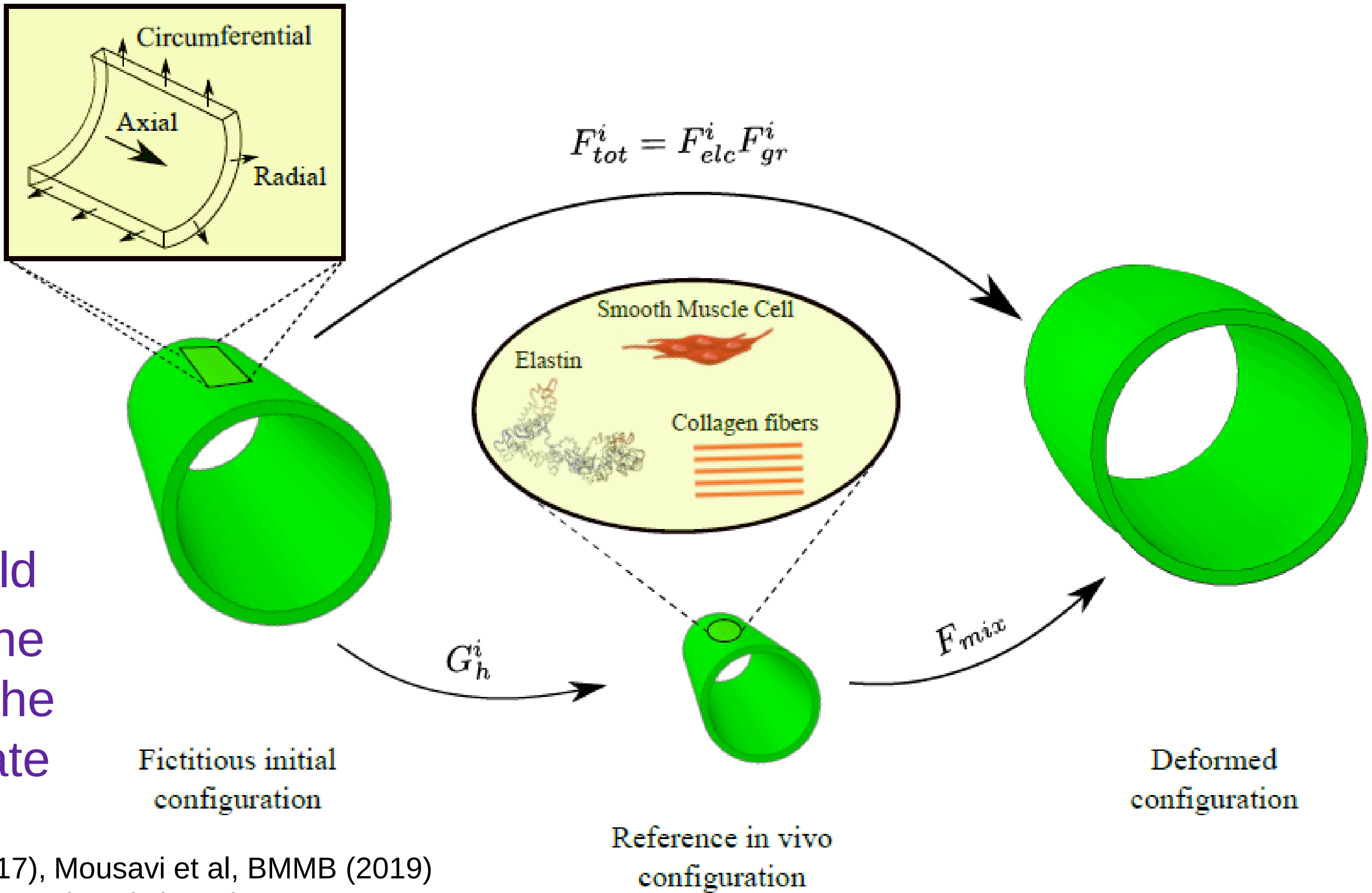
Layer-specific constitutive model

Elastic and inelastic decomposition of deformation gradient

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

$$\mathbf{F}^{j}_{\mathrm{gr}} = \mathbf{F}^{j}_{\mathrm{r}}\mathbf{F}^{j}_{\mathrm{g}}$$

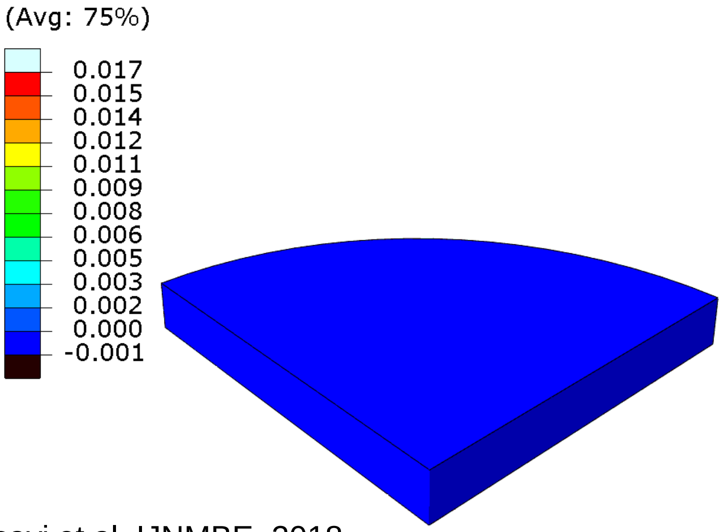
$\mathbf{F}^{j}_{\mathrm{r}}$ and $\mathbf{F}^{j}_{\mathrm{g}}$ should be **updated** if the artery is not in the homeostatic state



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, θ, z)
- ✓ Two different layers (media and adventitia)



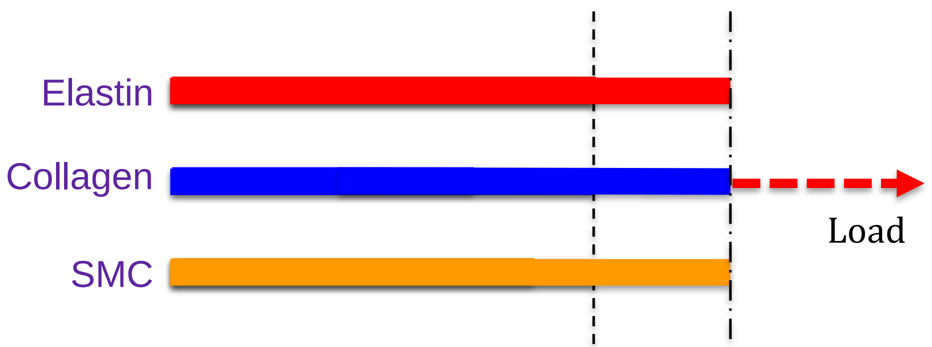
Mousavi et al, IJNMBE, 2018

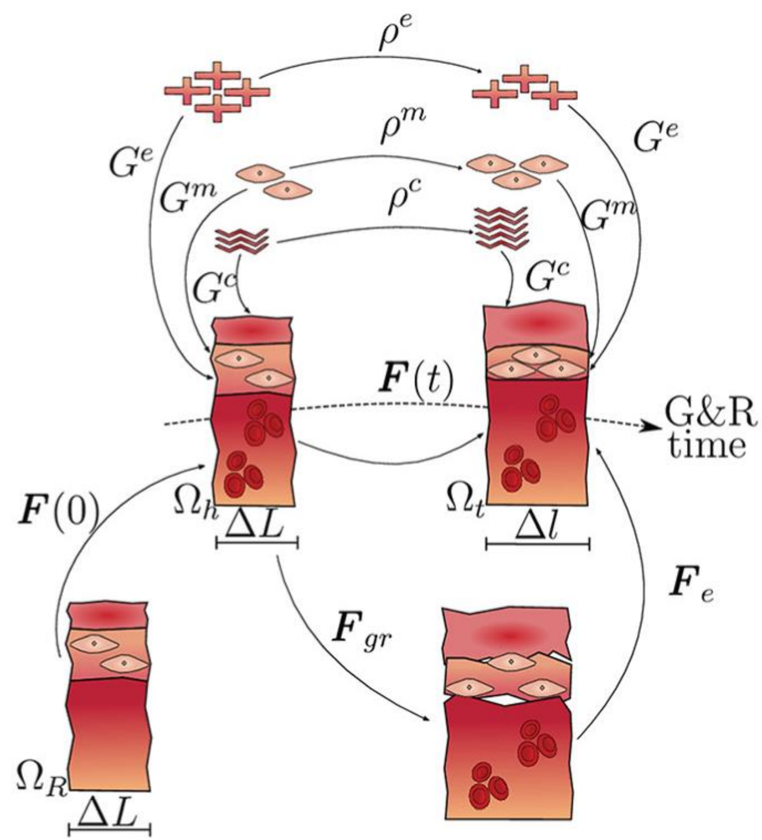
Growth and Remodeling in homogenized constrained mixture

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)

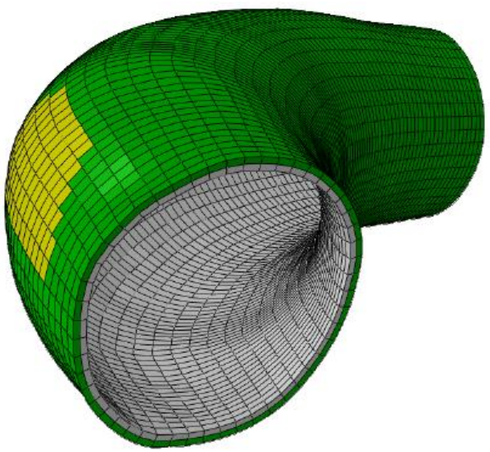
Patient-specific predictions

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

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

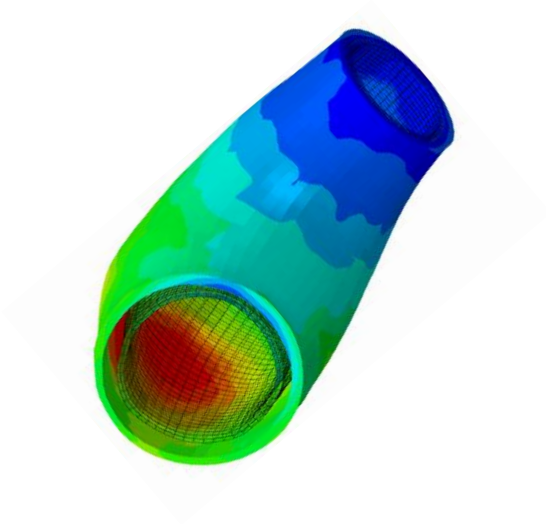
$$\dot{\varrho}^{\mathrm{e}} = -\frac{\varrho^{\mathrm{e}}(\mathbf{X},t)}{T^{\mathrm{e}}} - \frac{D_{\max}}{t_{\mathrm{dam}}}\varrho^{\mathrm{e}}(\mathbf{X},0)e^{-0.5\left(\frac{X_3}{L_{\mathrm{dam}}}\right)^2 - \frac{t}{t_{\mathrm{dam}}}}$$

Localization function around the point of TAWSS max



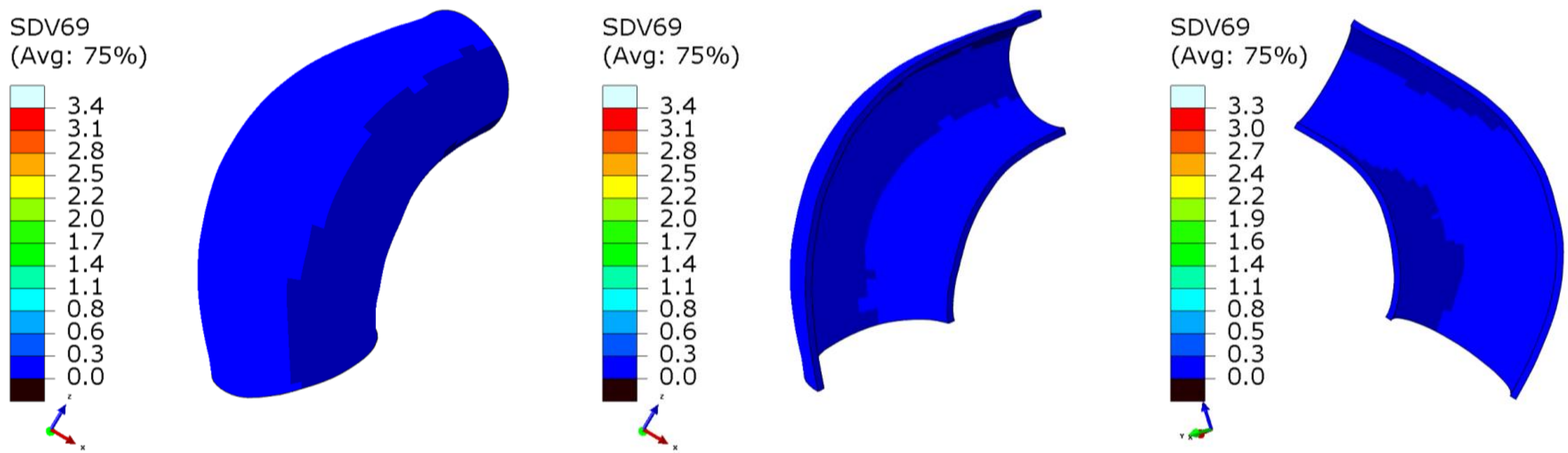
Mousavi et al, BMMB (2019)

Patient-specific predictions



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

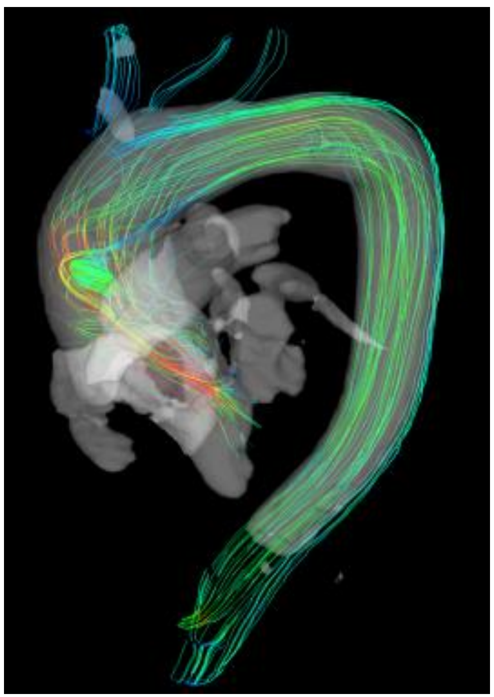
Small growth parameter

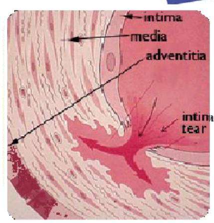


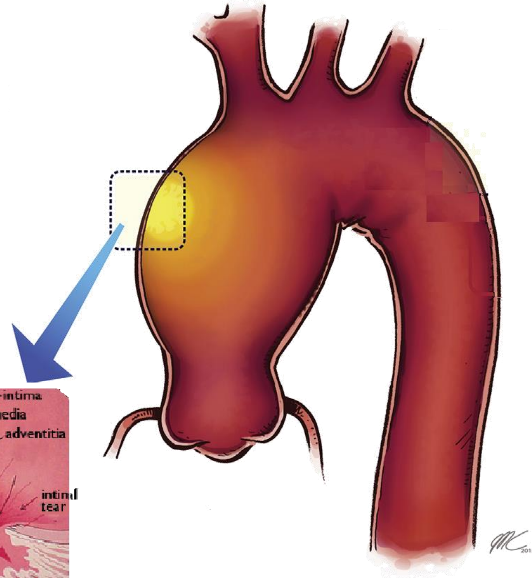
Normalized Thickness

Mousavi et al, BMMB (2019)

Background: Aneurysms and Dissections of the ascending thoracic aorta







dissection

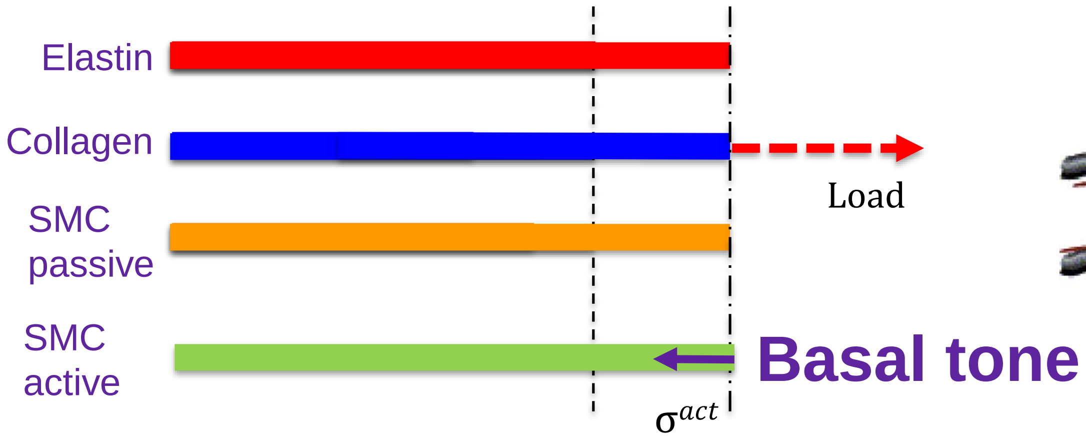
vSMC

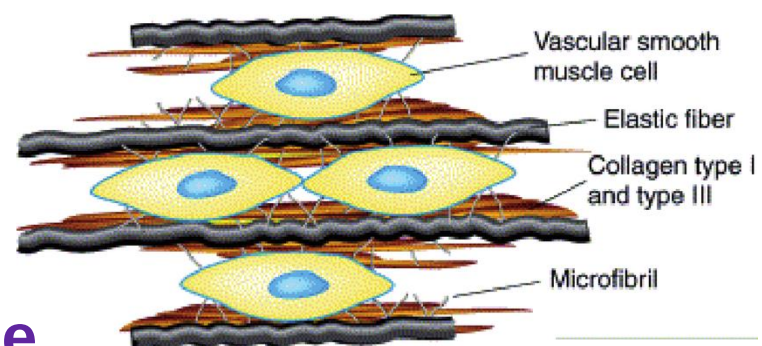
Humphrey et al, Science, 2014

Effects of active SMC contraction

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

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

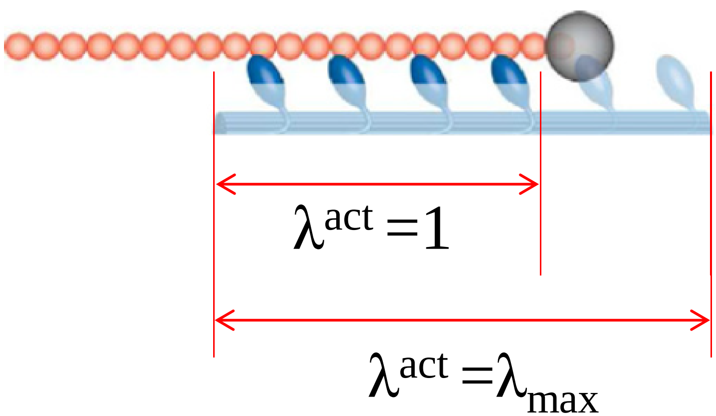


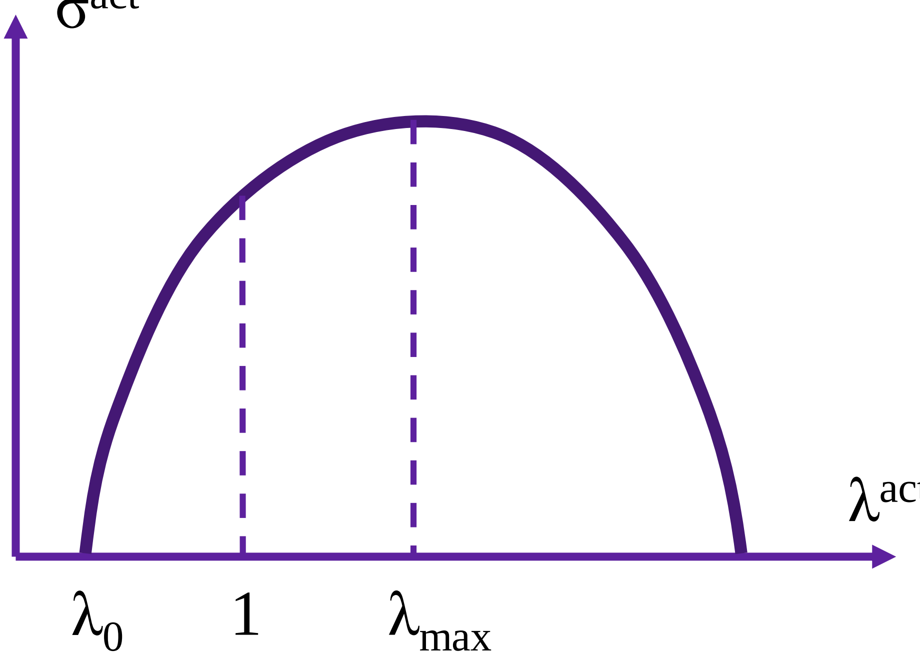


Length-tension relationship of SMCS

$$\sigma^{act} = \frac{\sigma_{actmax}}{\varrho_0(0)\left[C^{m} : (\boldsymbol{a}_0^{m} \otimes \boldsymbol{a}_0^{m})\right]}\left(1 - \frac{(\lambda_{max}^{m} - \lambda_{act})^2}{(\lambda_{max}^{m} - \lambda_0^{m})^2}\right)$$

Basal tone ~50kPa



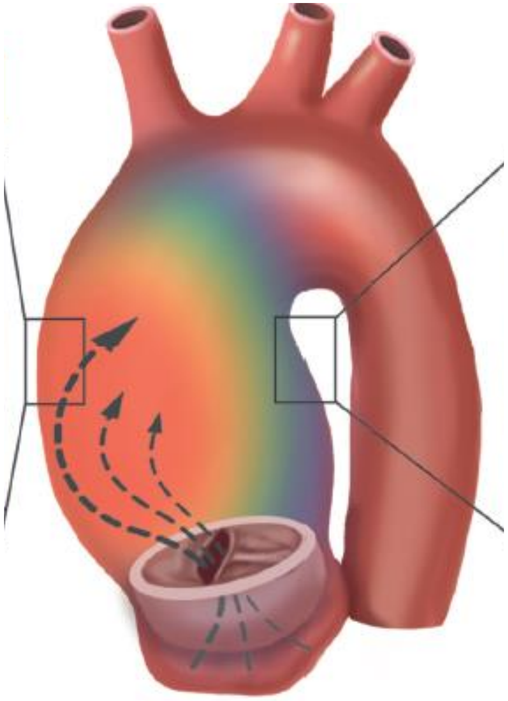


Murtada et al, J Theor Biol 2012, Ghavamian et al, Front Bioeng Biotech (2020)

Future work: test other assumptions

Combination of local decrease of SMC active stress and proteolytic injury

Large WSS resulting in reduced SMC contractility

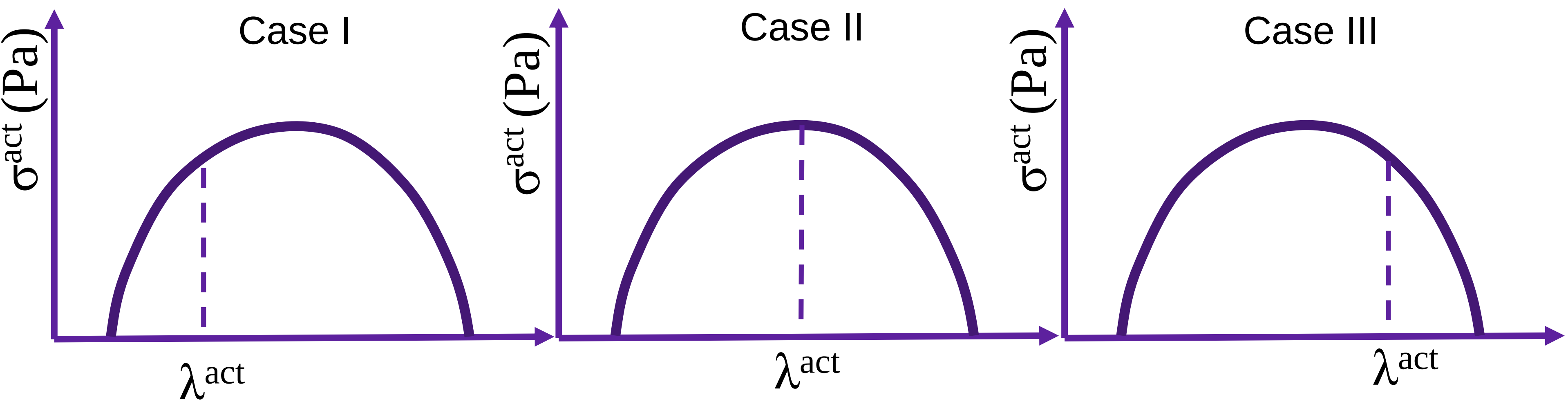


Large RRT resulting in possibly increased proteolytic effects

Mousavi et al, ABME (2020, submitted)

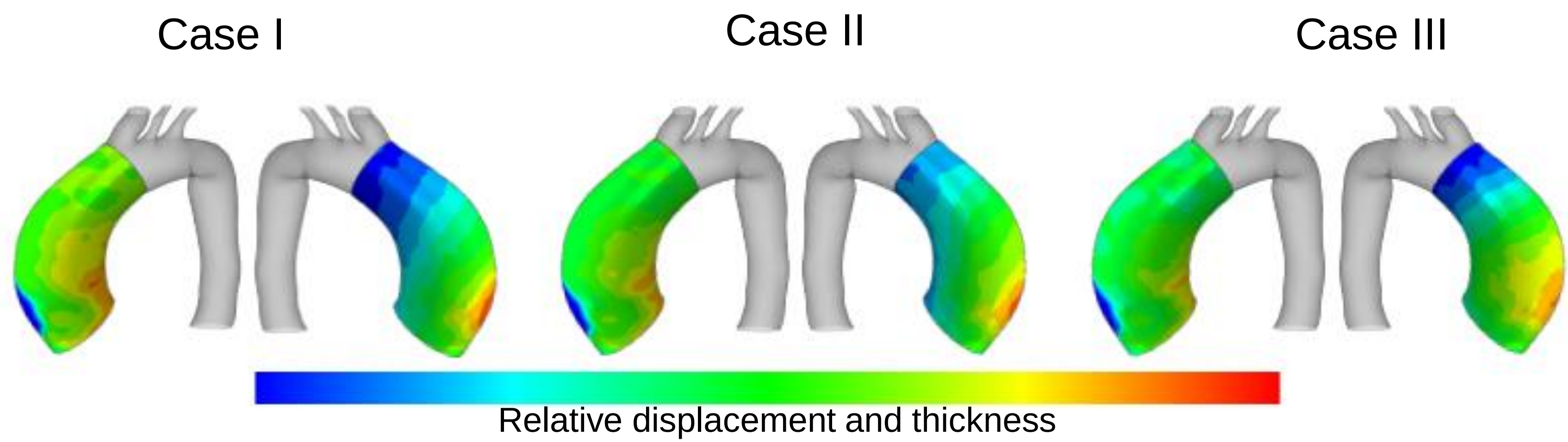
Sensitivity analysis

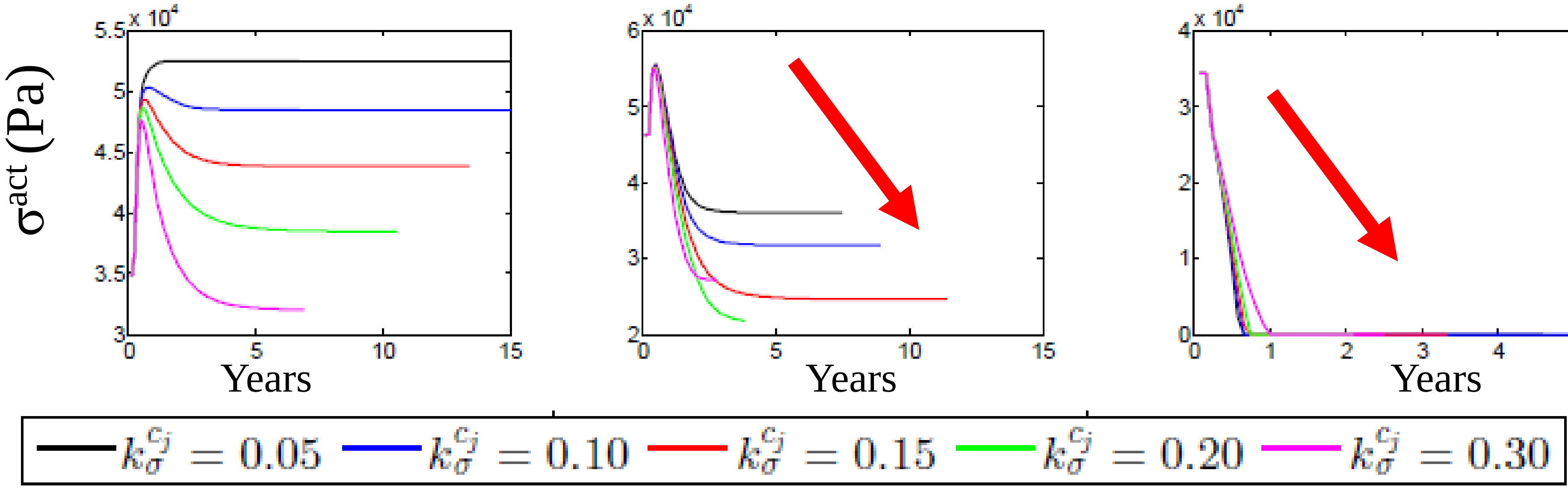
- The time of which the artery is maximally damaged (t_{dam}),
- The rate of collagen deposition ($k_\sigma^{c_j}/T^{c_j}$),
- The maximum contractility of SMCs ($\lambda_{\text{max}}^{\text{m}}$).



Ghavamian et al, Front Bioeng Biotech (2020)

Evolution of the active stress of SMCs





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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

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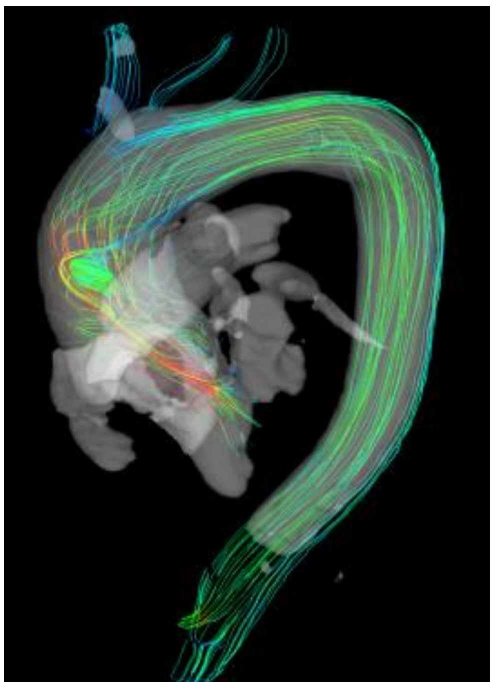
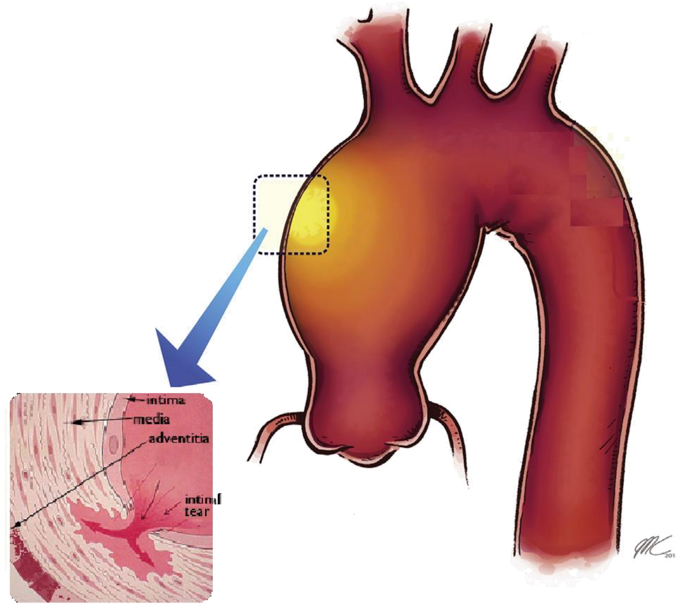
The major role of SMCs in Aneurysms and Dissections of the ascending thoracic aorta





vSMC

Humphrey et al, Science, 2014

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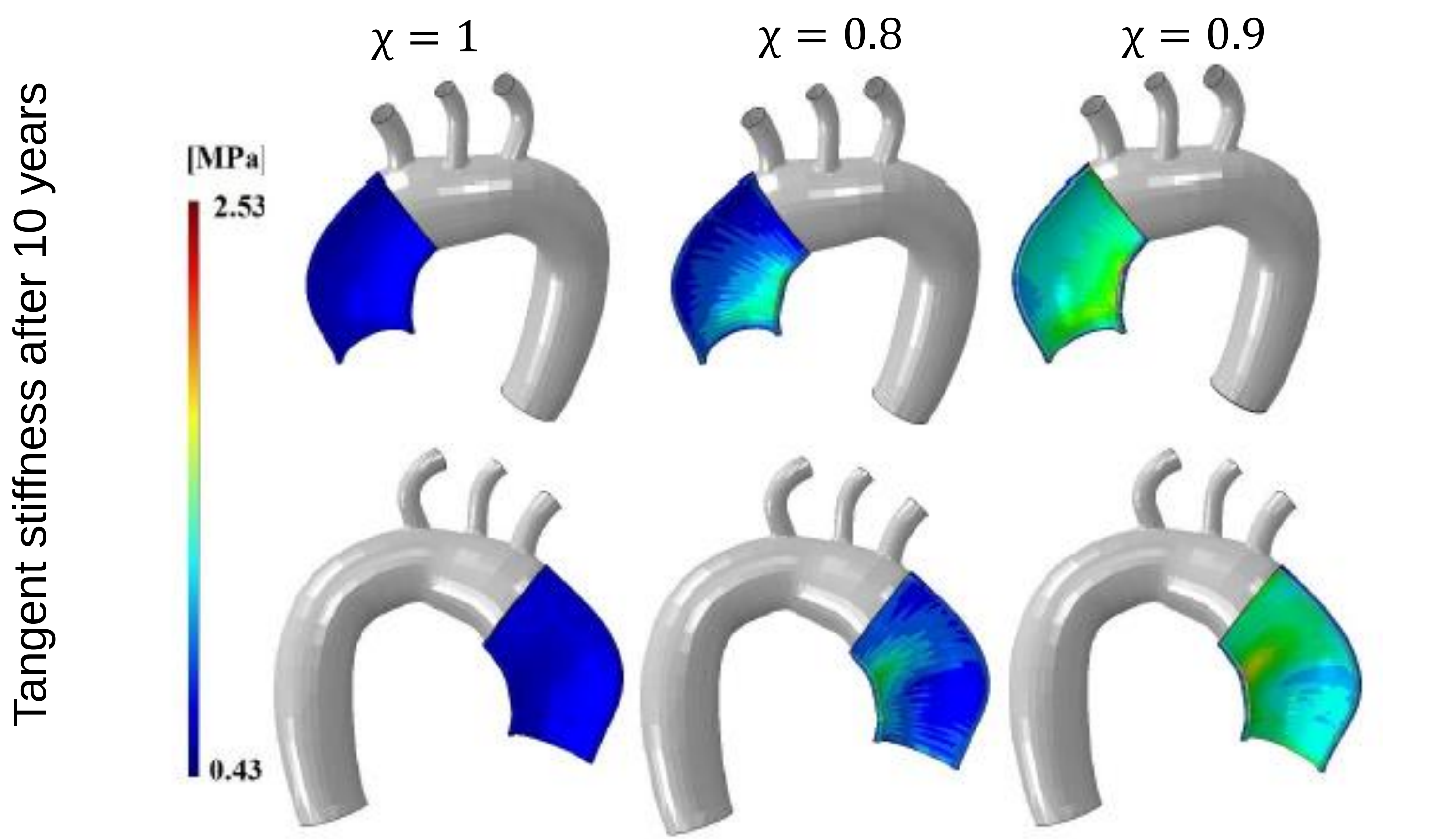
Future work: mechanosensitivity impairment

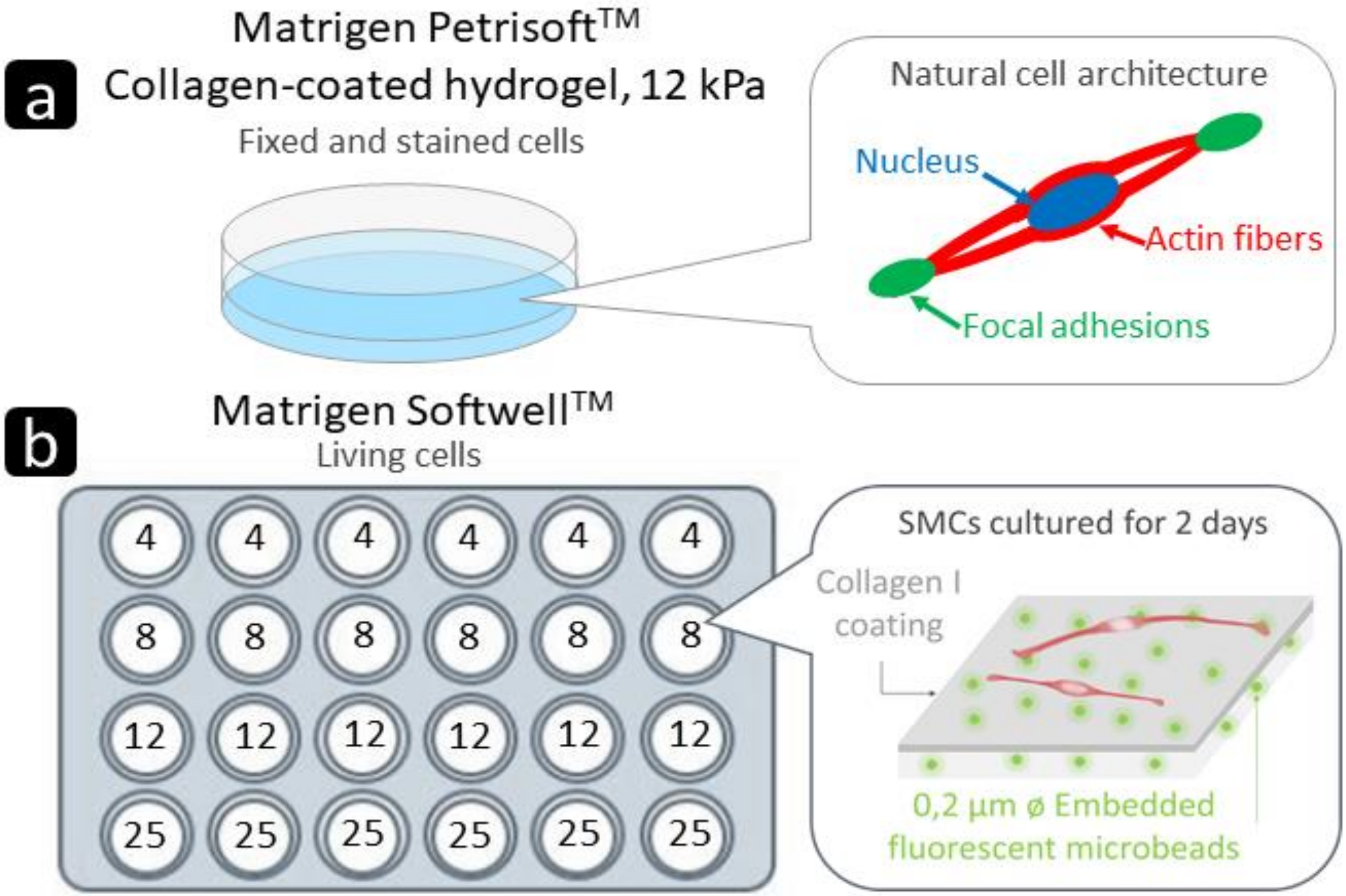
$$\dot{\varrho}^{j}(t) = \varrho^{j}(t) k_{\sigma}^{j} \frac{\chi * \sigma^{j}(t) - \sigma_{h}^{j}}{\sigma_{h}^{j}} + \dot{\xi}^{j}(t)$$

$0 \leq \chi \leq 1$: impairment coefficient



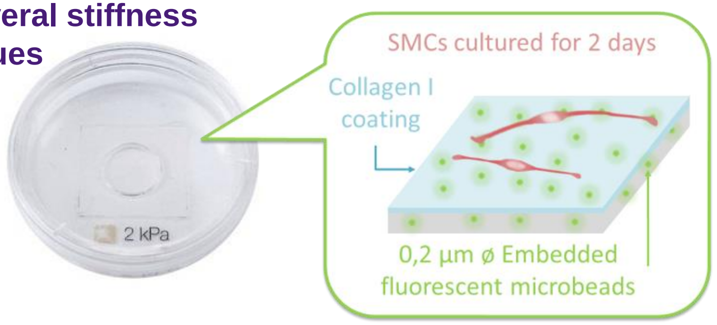
Mousavi et al, ABME (2020, submitted)

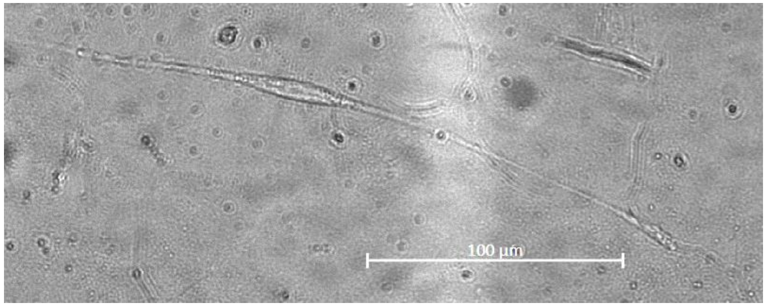
Traction force microscopy on aortic smooth muscle cells



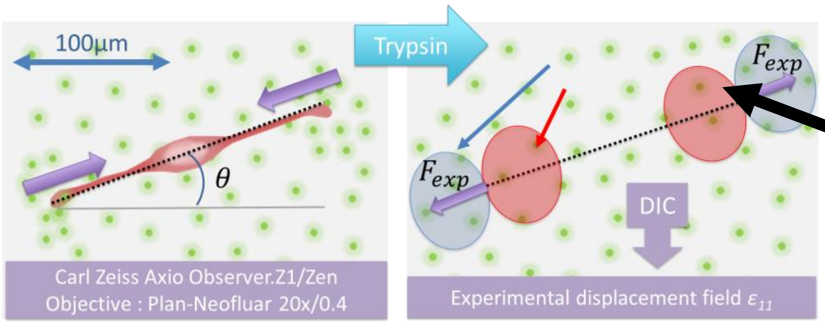
Traction force microscopy on aortic smooth muscle cells

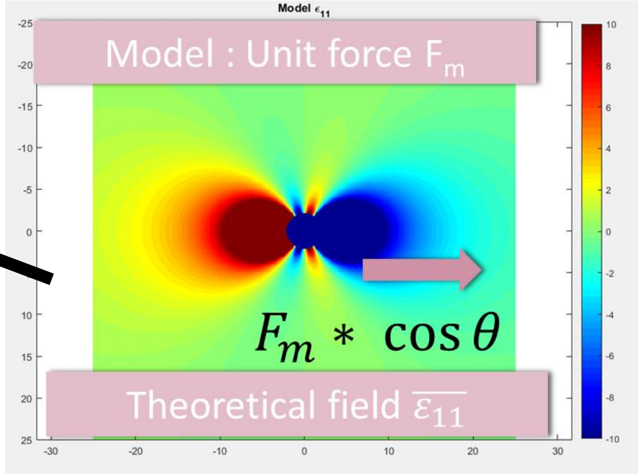
Several stiffness values





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

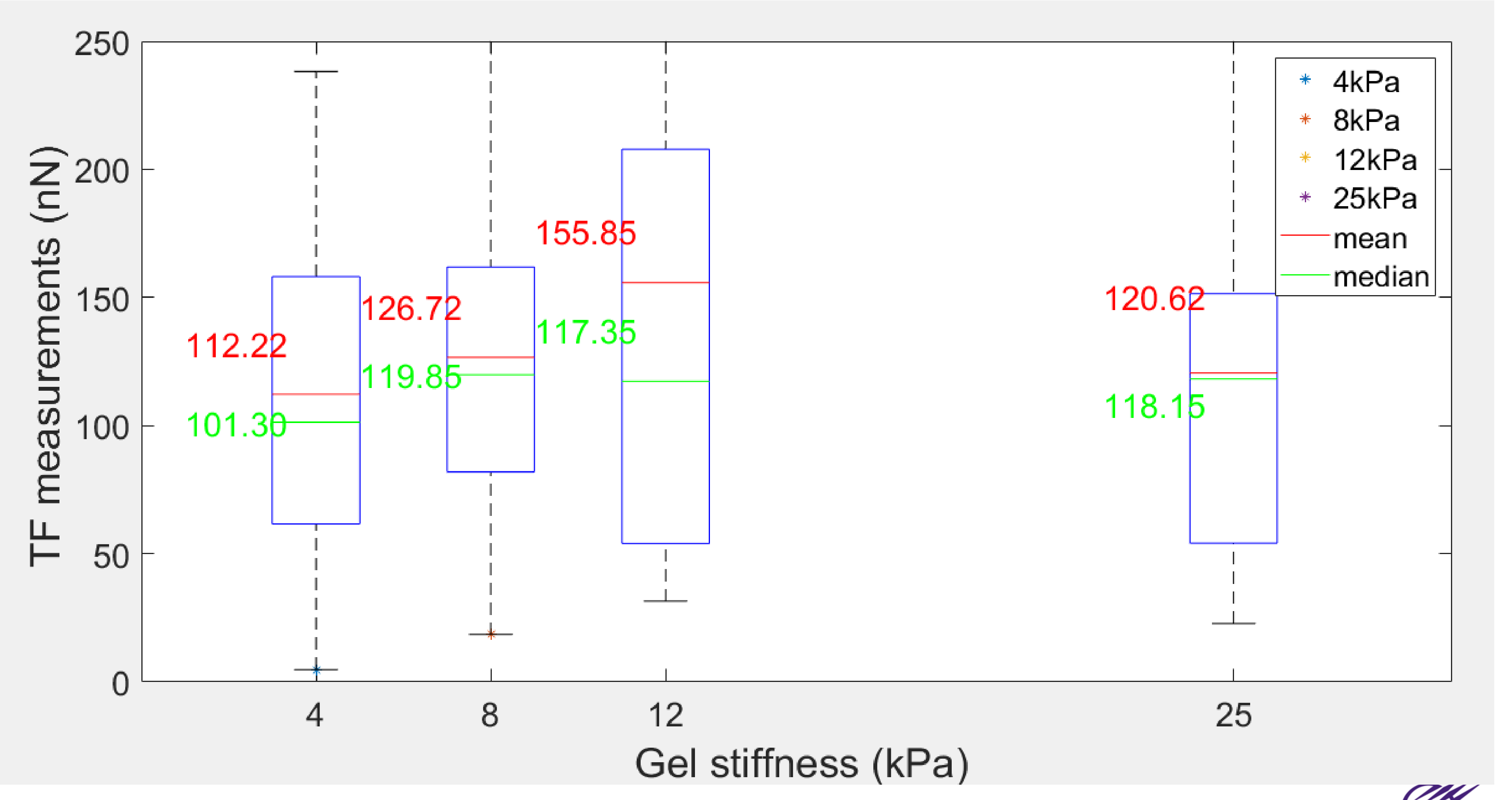




- **Fluorescent microscopy + DIC :** track the displacement of fluorescent microbeads
- **Cell unbinding method (with trypsin) :** assess the homeostatic state of single SMCs

$K = 2$

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



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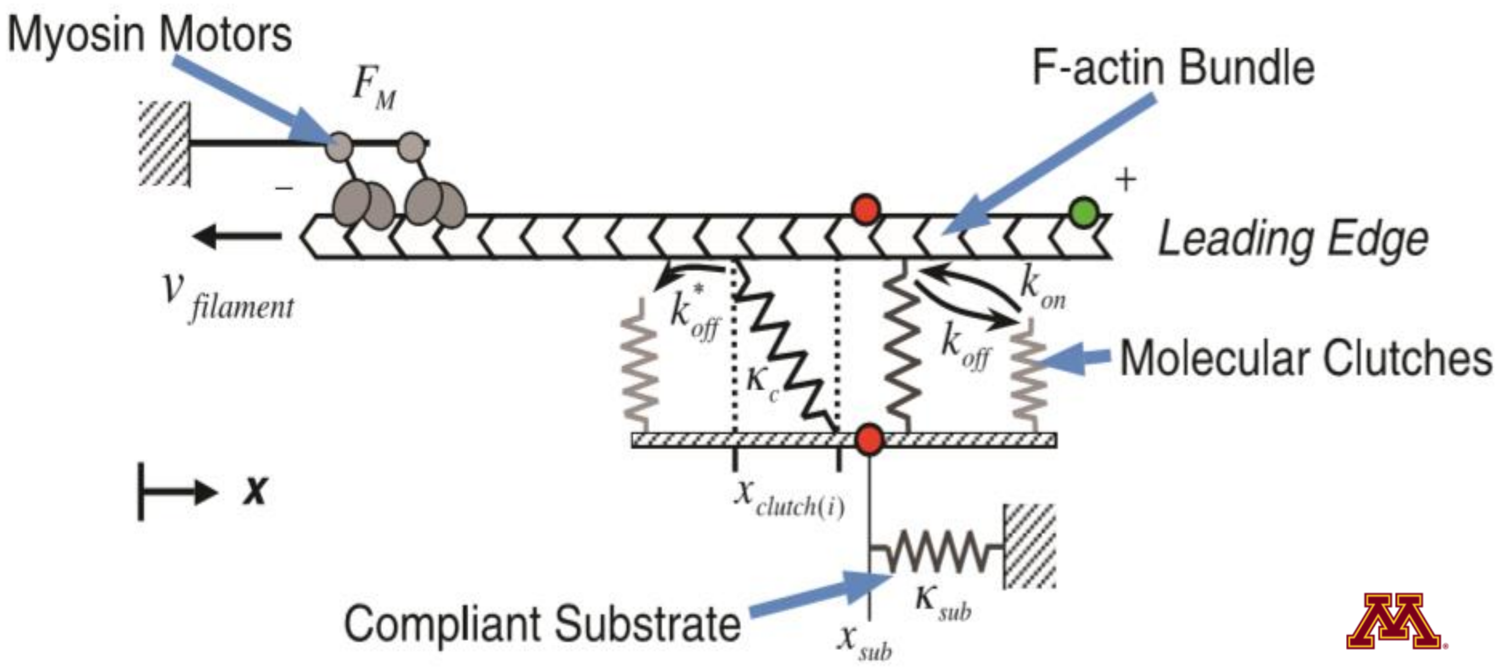
Modelling of SMCs cytoskeletal mechanics



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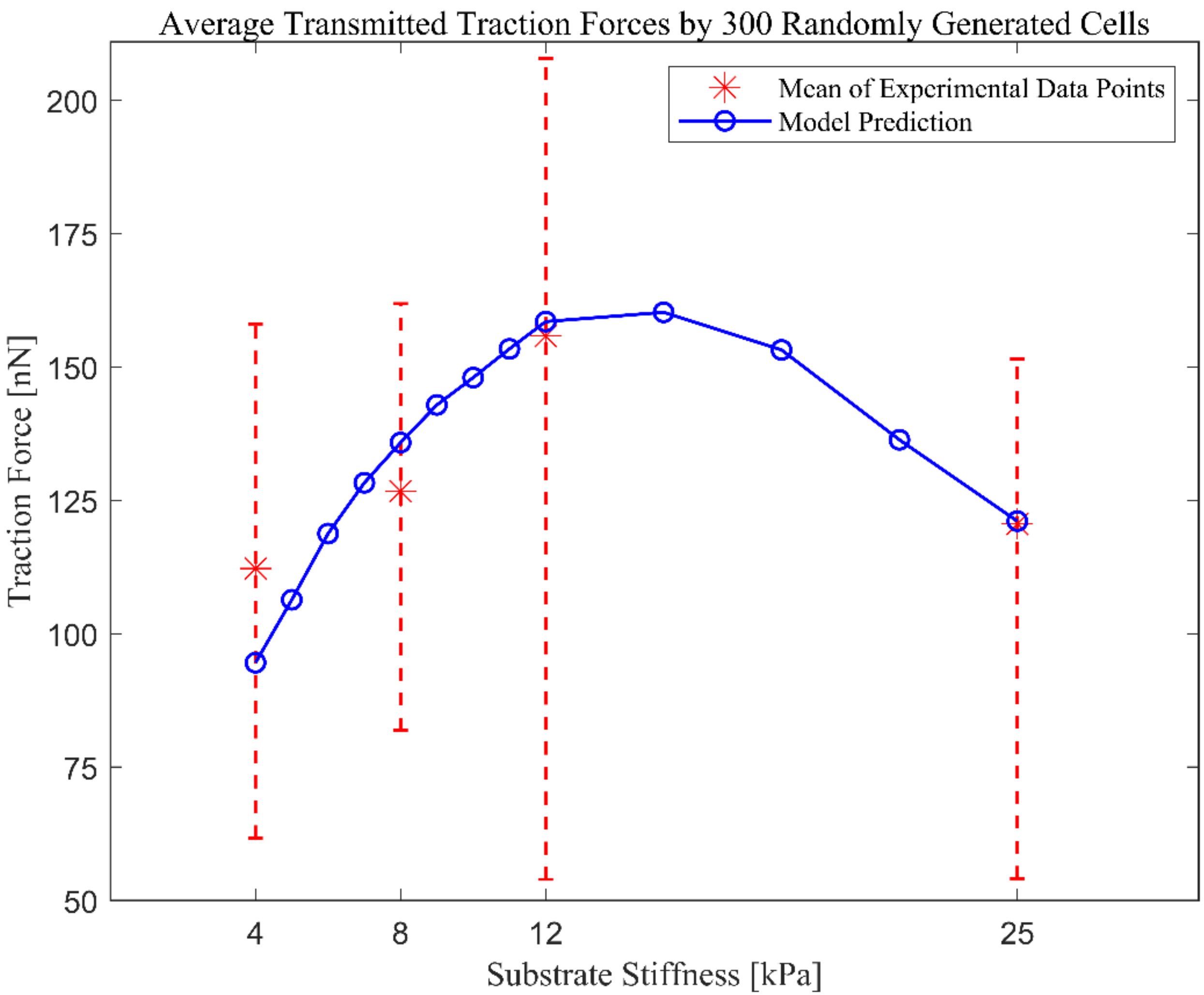
Chan, C. E., & Odde, D. J. (2008). Traction dynamics of filopodia on compliant substrates. *Science*, *322*(5908), 1687-1691.

Modelling of SMCs cytoskeletal mechanics



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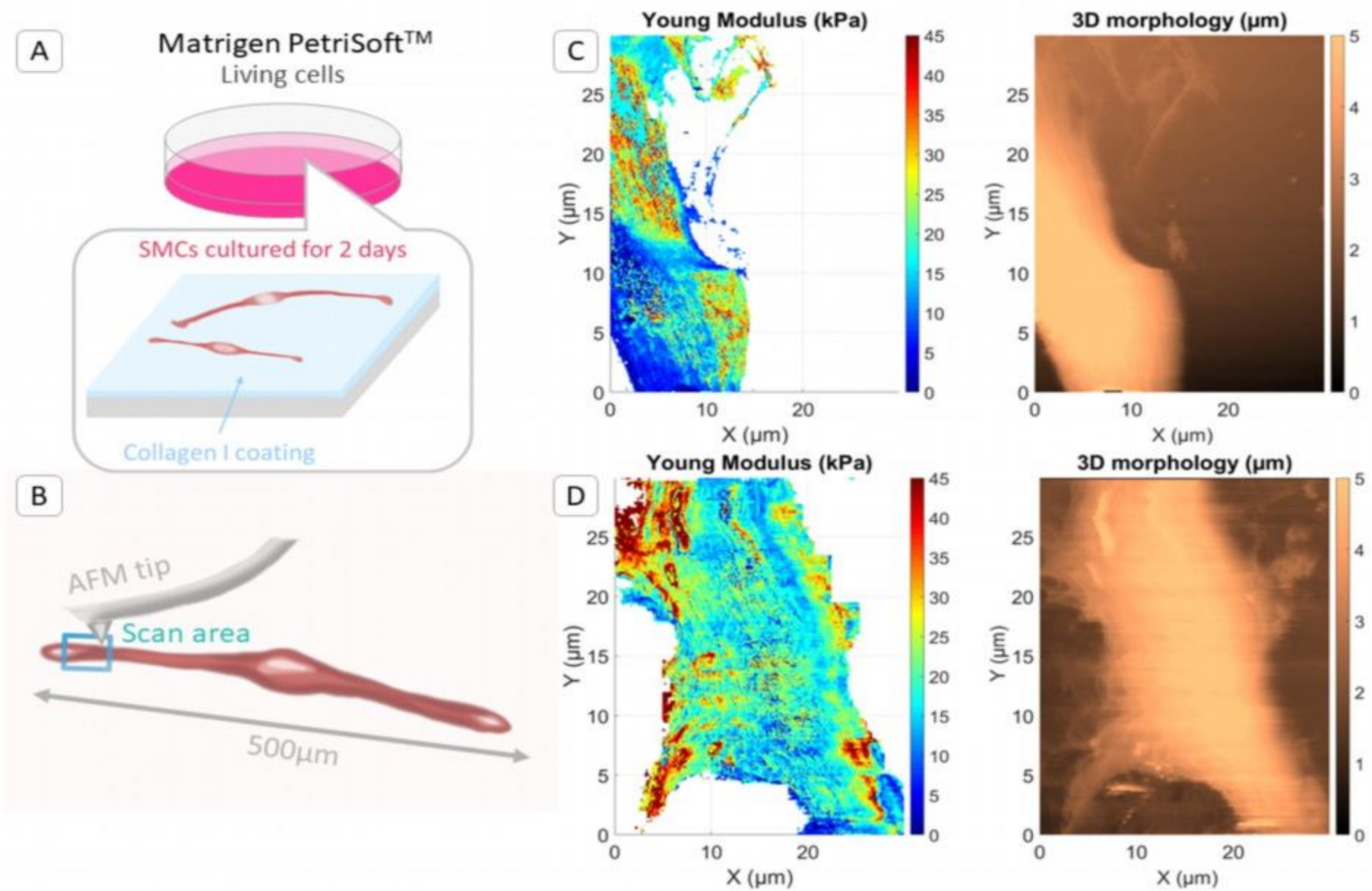
Stiffness characterization of aortic smooth muscle cells



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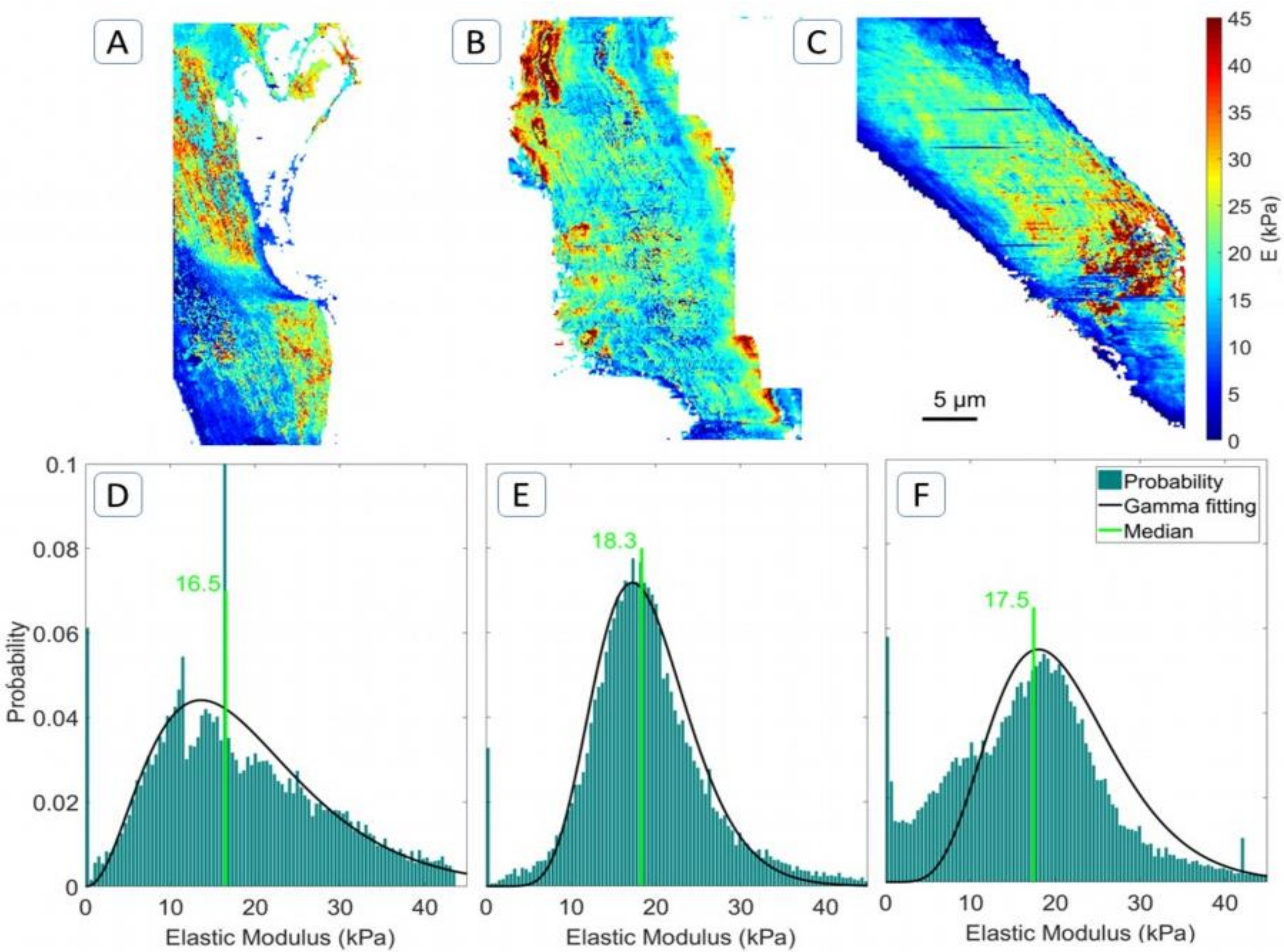

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SUMMARY AND FUTURE WORK

- 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

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Computational mechanics in the OR for vascular surgery?

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