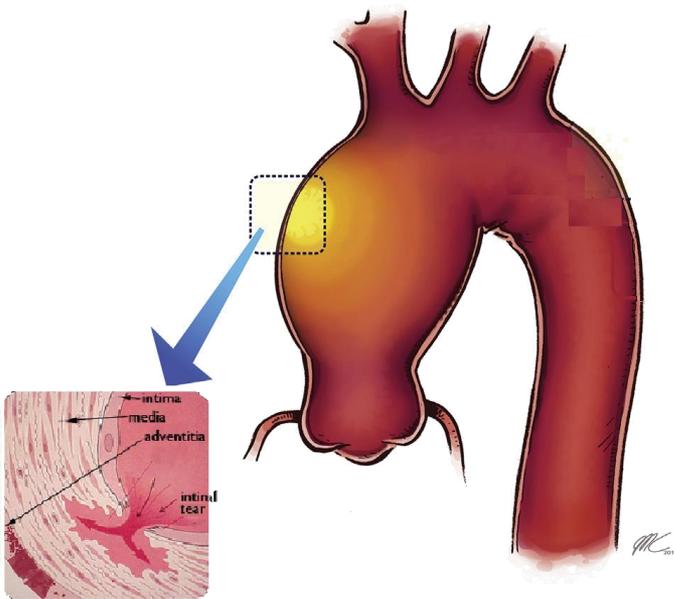


Biomechanics and mechanobiology of aneurysm progression: the journey towards better healthcare





OUTLINE

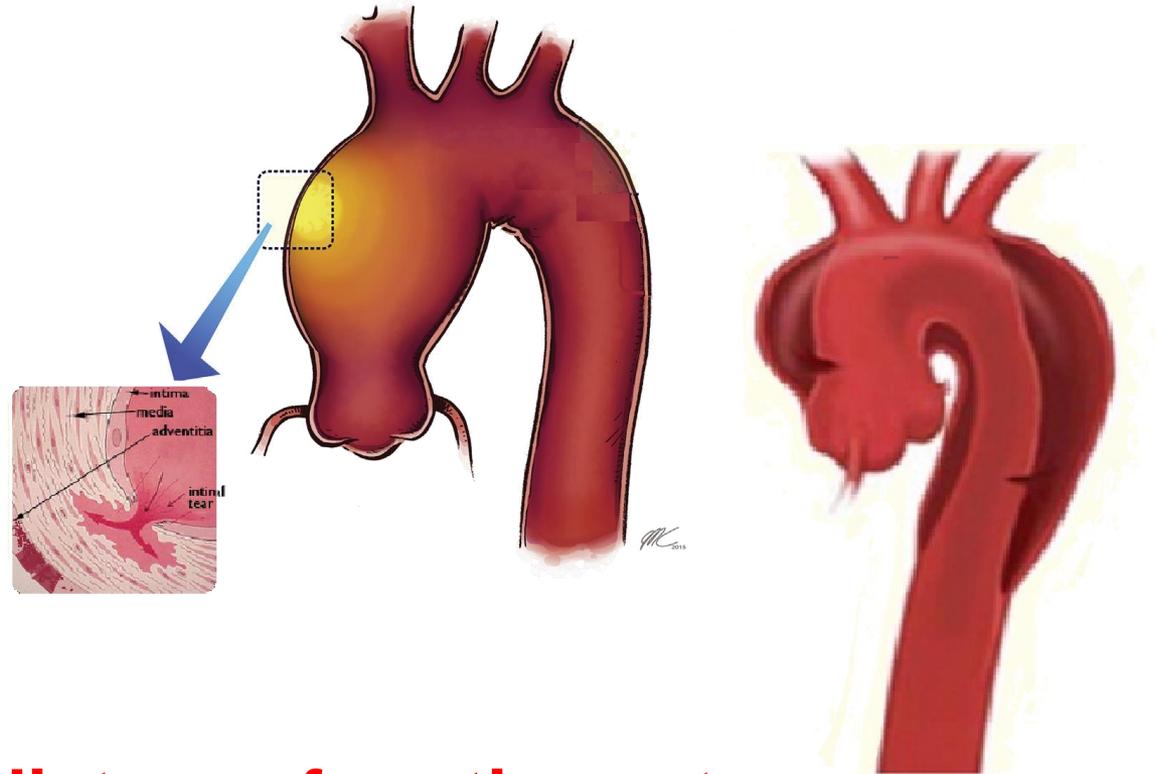
- ❑ PART I: Material stiffness is a predictor for aortic rupture
- ❑ PART II: Tensional homeostasis of collagen controls aneurysm progression
- ❑ PART III: How SMCs can establish a link between tensional homeostasis and material stiffness?



OUTLINE

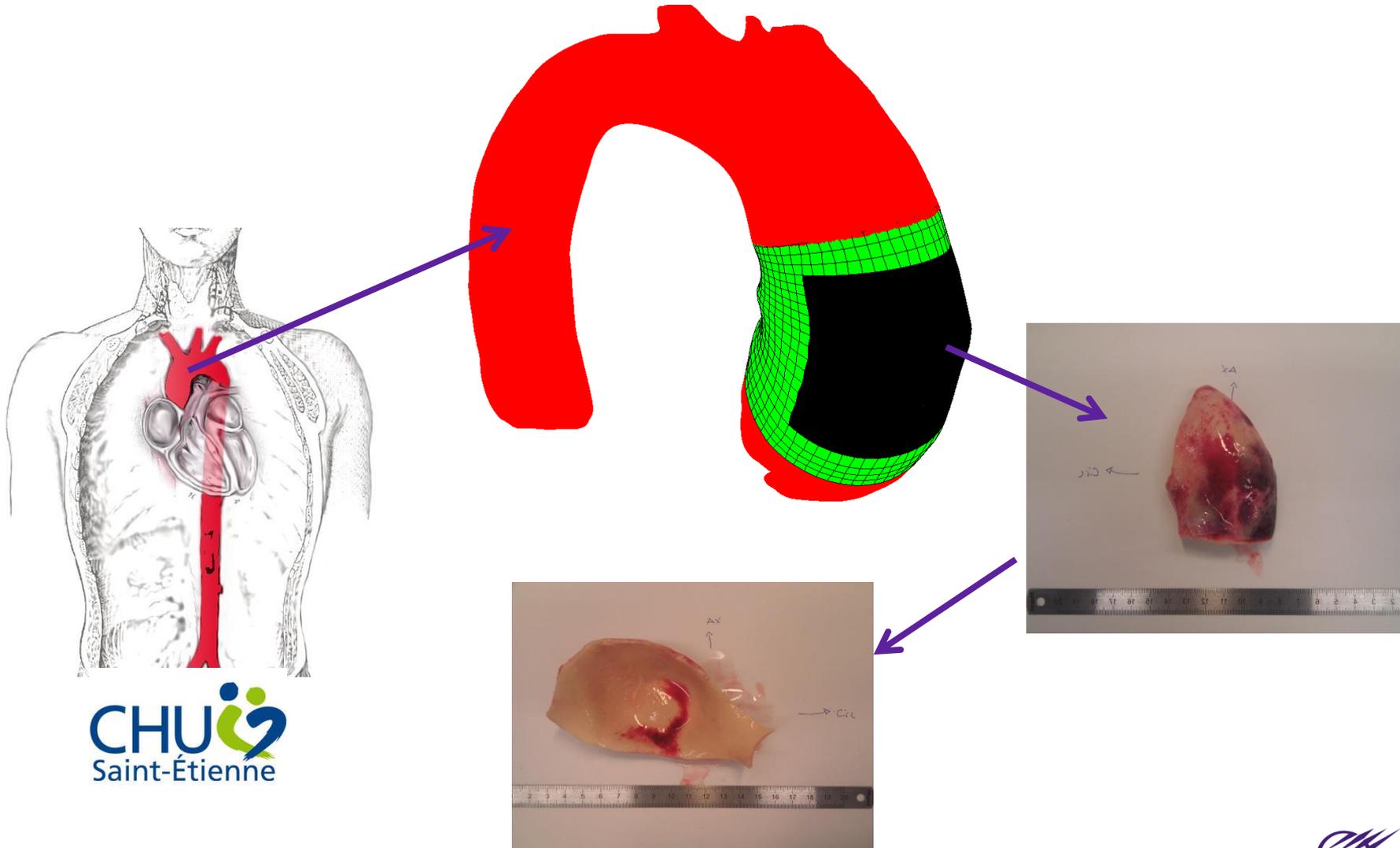
- ❑ **PART I: Material stiffness is a predictor for aortic rupture**
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Aneurysms and Dissections of the ascending thoracic aorta



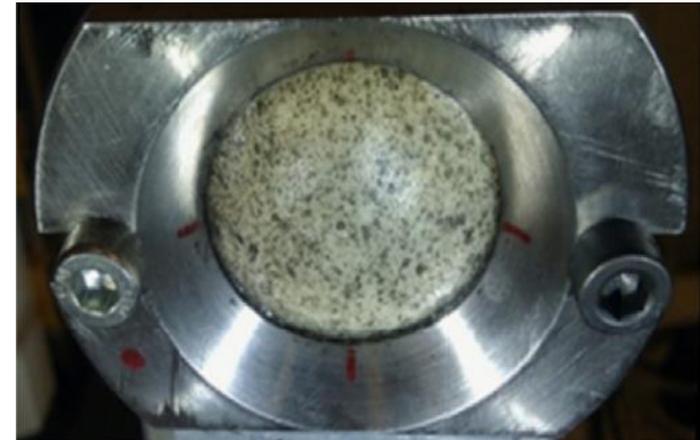
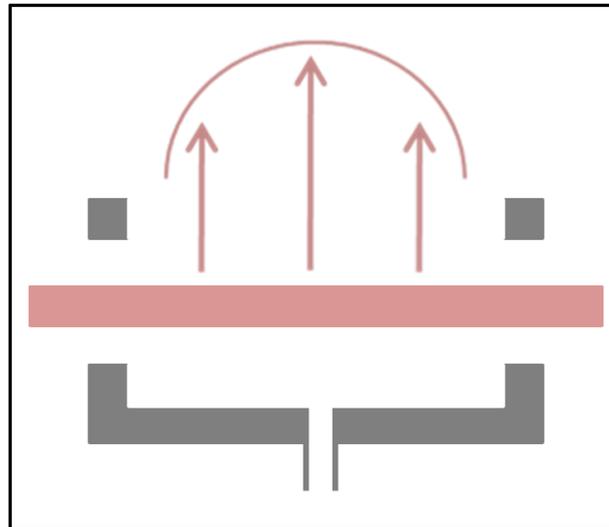
Goal: find predictors of aortic rupture

Collection of human samples

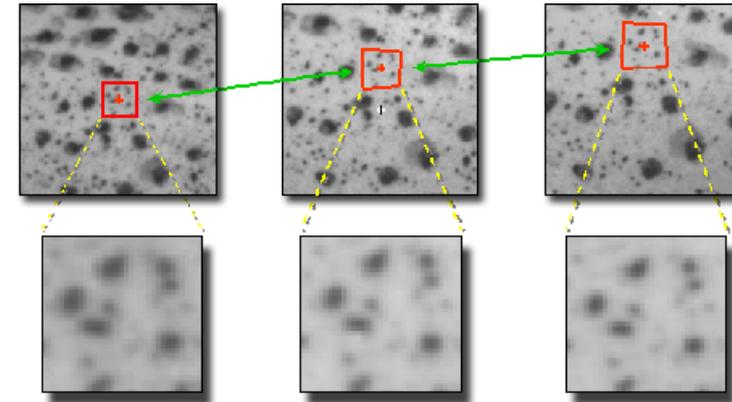


Bulge inflation test

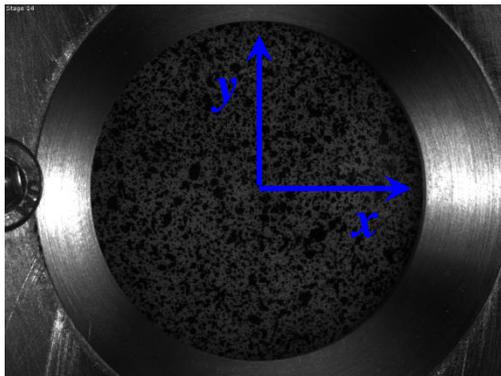
Romo et al. Journal of Biomechanics -2014.



Full-field measurements using sDIC



Undeformed



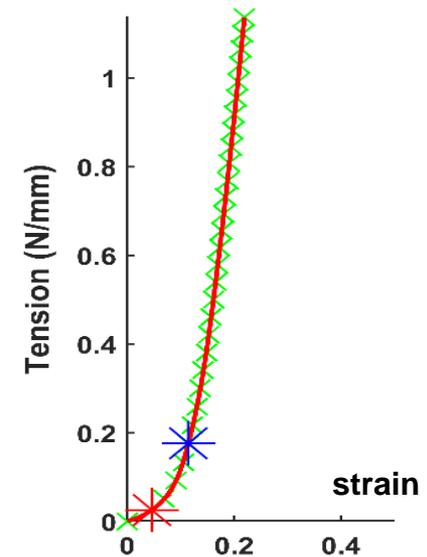
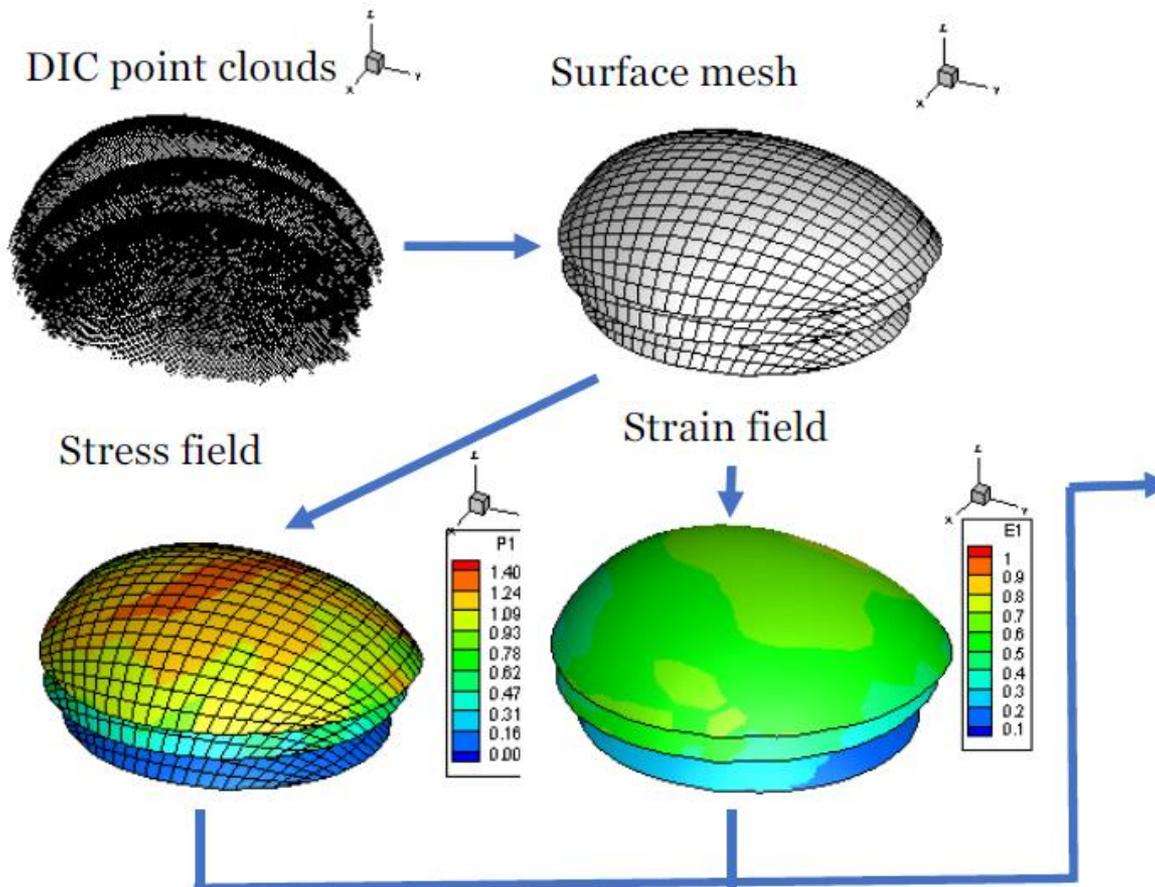
Deformed



Identification of local material properties



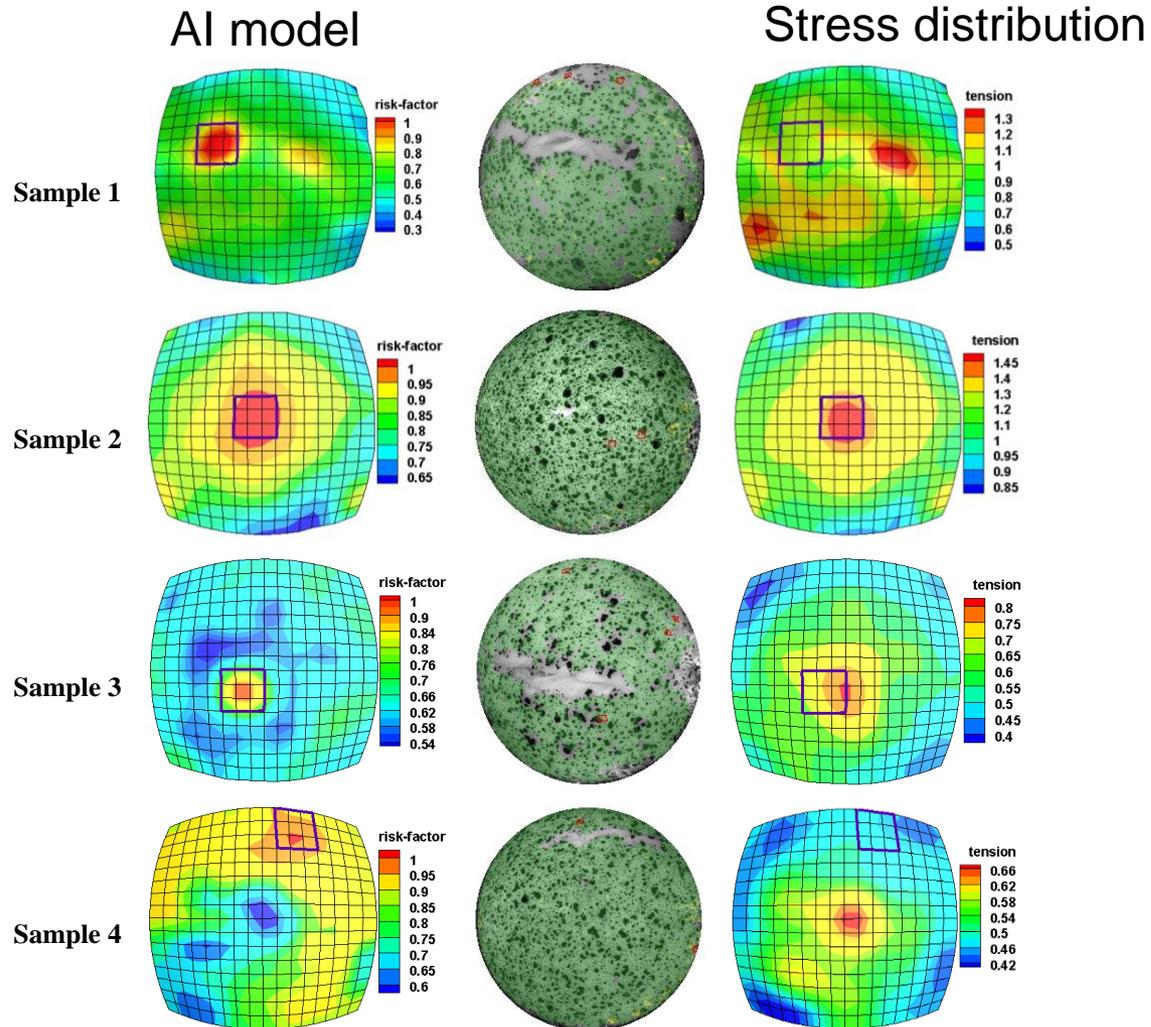
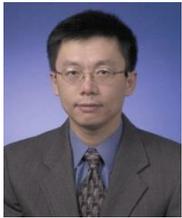
The
WHITAKER
Foundation



Davis et al. BMMB – 2015.
Davis et al. JMBS – 2016
Zhao et al. 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



Cardiovascular Engineering and Technology, Vol. 9, No. 4, December 2018 (© 2018) pp. 707–722
<https://doi.org/10.1007/s13239-018-00385-z>

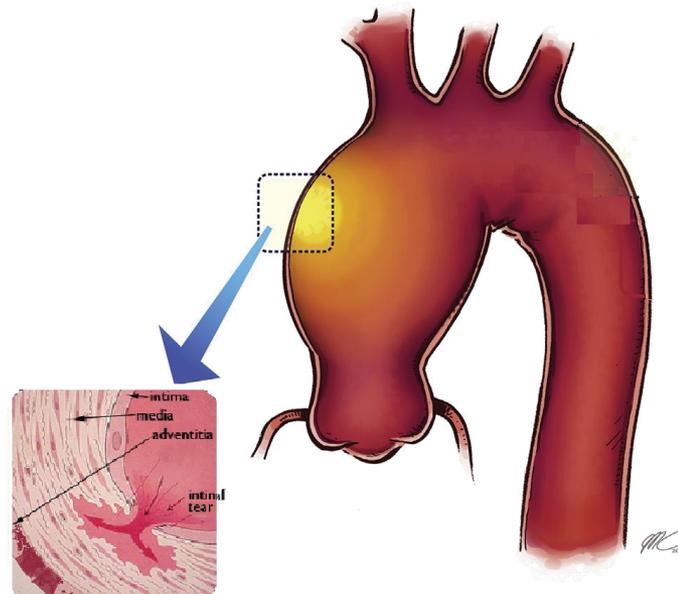
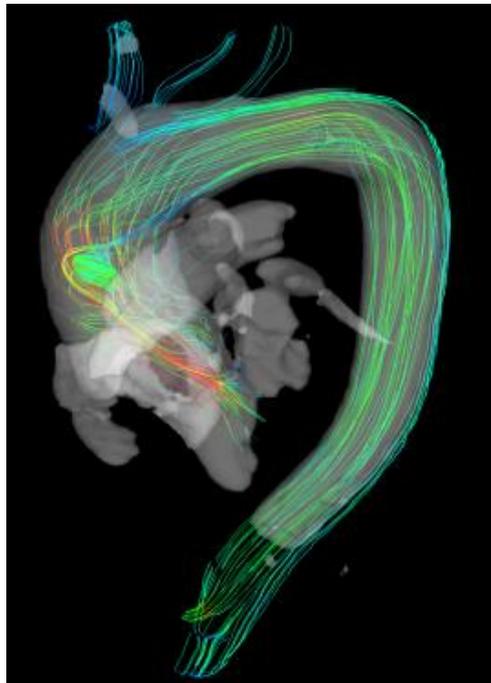
Evaluation of Peak Wall Stress in an Ascending Thoracic Aortic Aneurysm Using FSI Simulations: Effects of Aortic Stiffness and Peripheral Resistance



OUTLINE

- PART I: Material stiffness is a predictor for aortic rupture
- **PART II: Tensional homeostasis of collagen controls aneurysm progression**
- PART III: How SMCs can establish a link between tensional homeostasis and material stiffness?

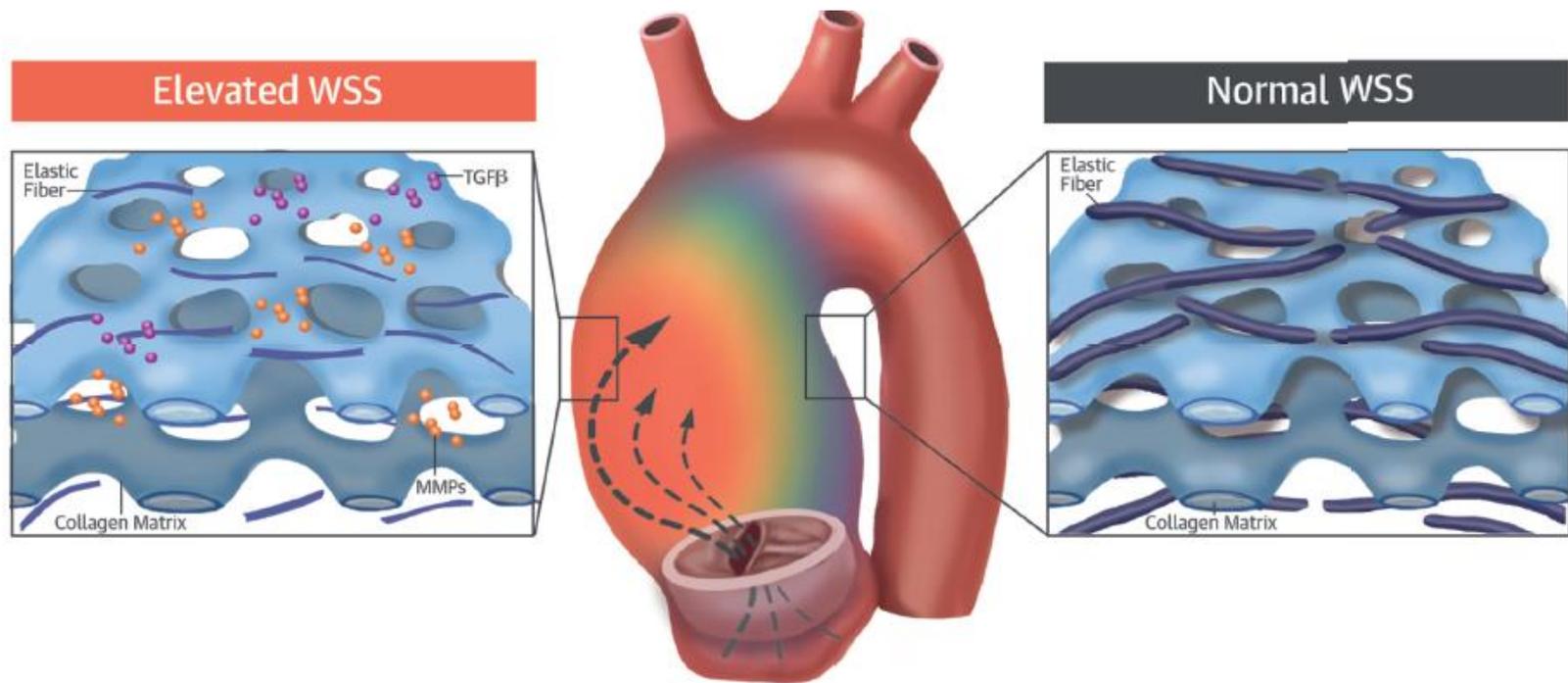
Aneurysms and Dissections of the ascending thoracic aorta



Goal: Predict weakening in the aortic wall

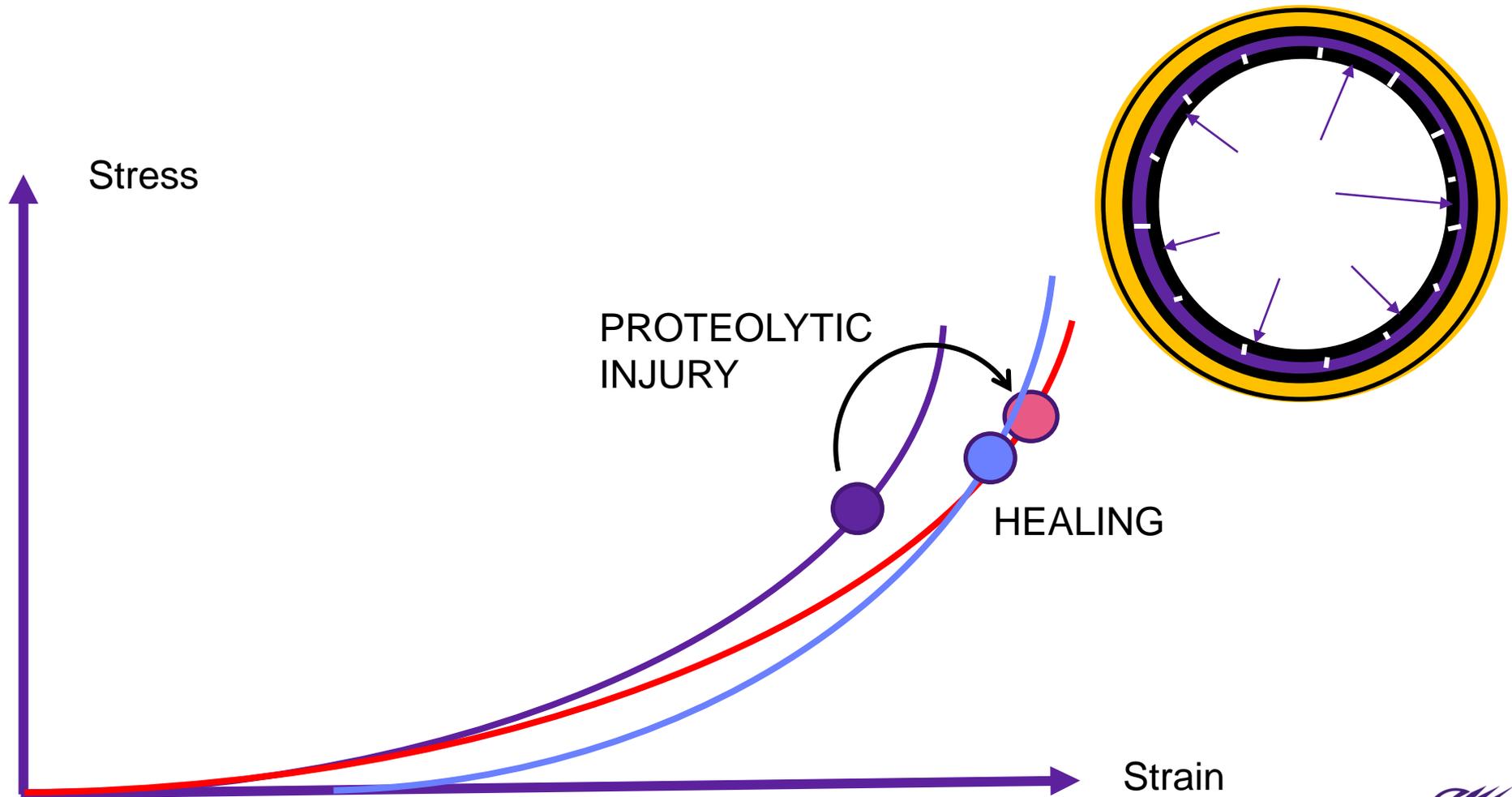
Introduction - Assumption

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

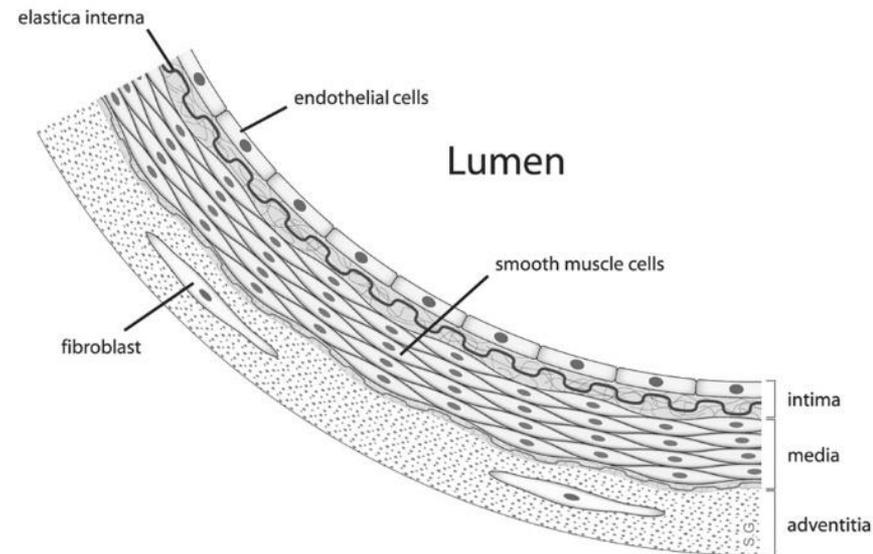
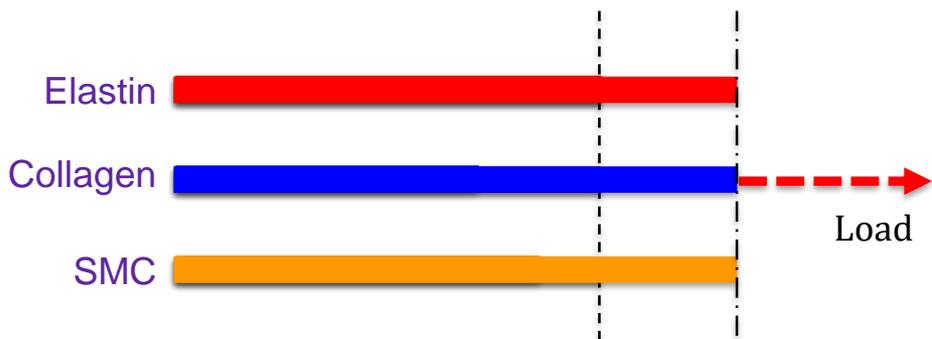


Layer-specific constitutive model

Strain-energy function based on the constrained mixture theory

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

Deposition stretch of each constituent:

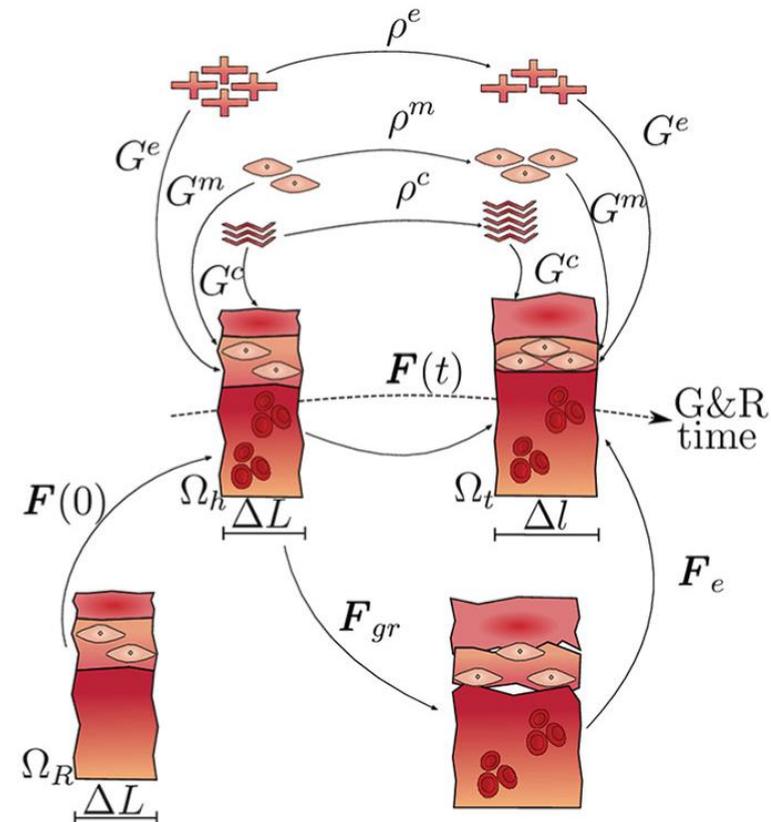
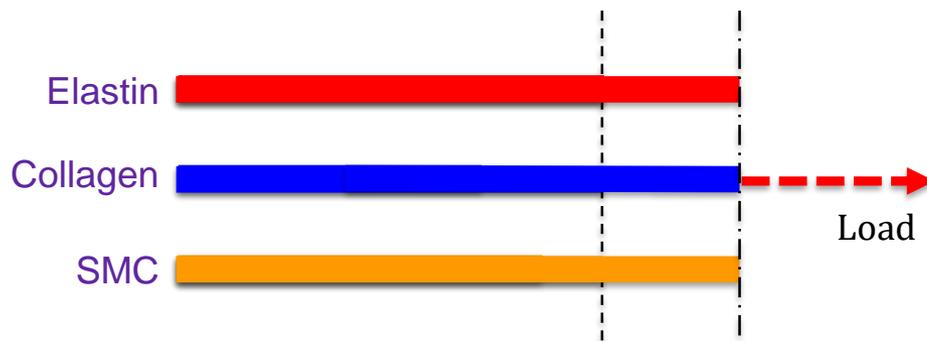


Growth and Remodeling in homogenized constrained mixture

Collagen mass production

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

Inelastic deformation due to remodeling



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

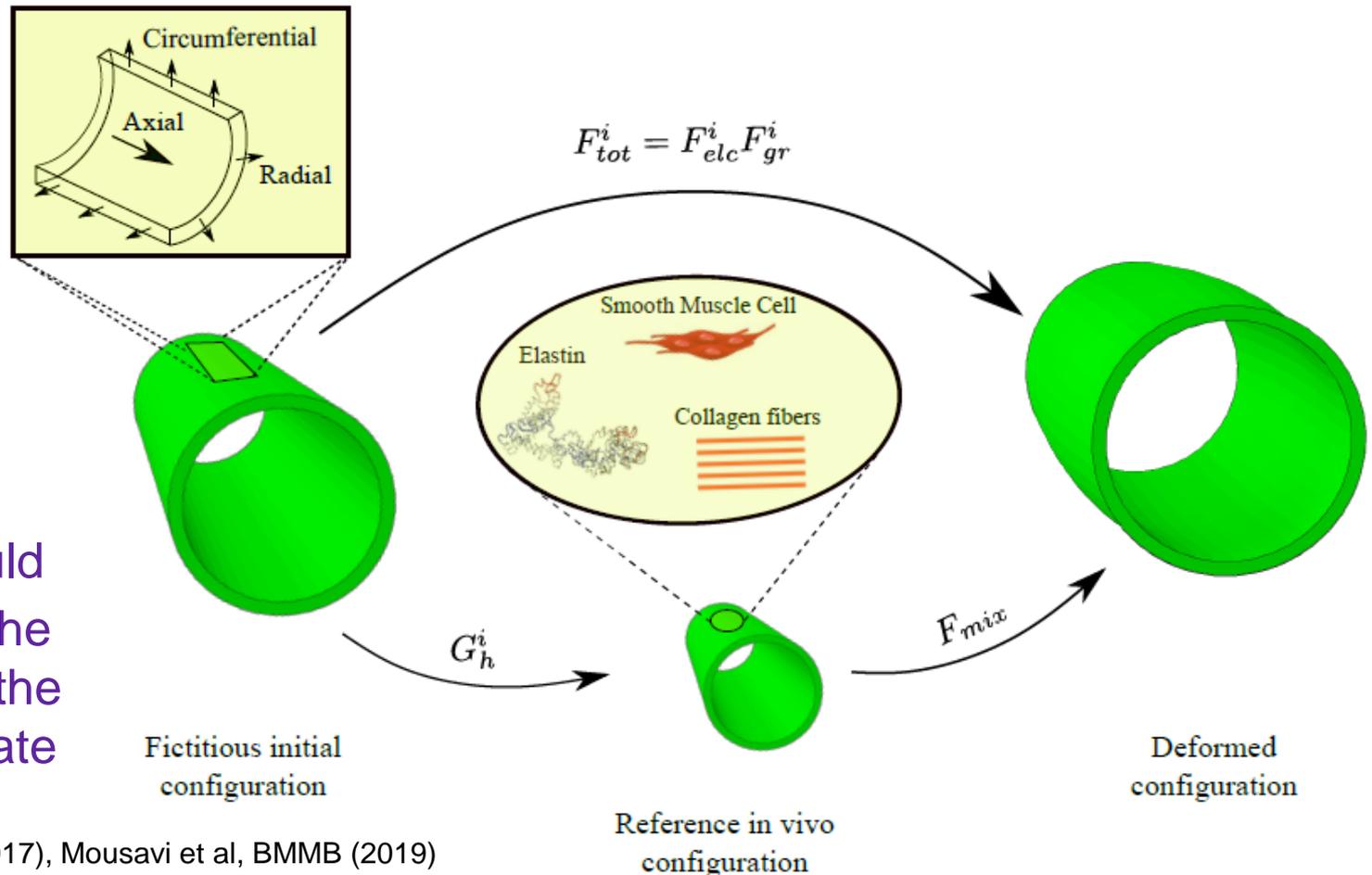
Layer-specific constitutive model

Elastic and inelastic decomposition of deformation gradient

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

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

\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)

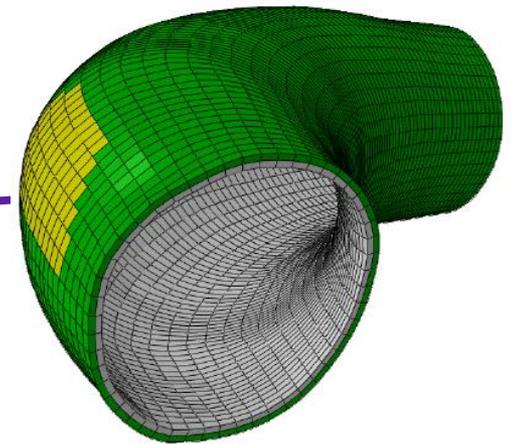
Patient-specific predictions

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

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

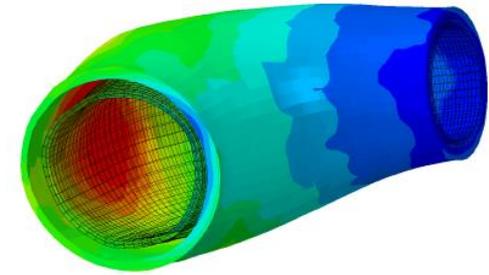
$$\dot{\varrho}^e = -\frac{\varrho^e(\mathbf{X}, t)}{T^e} - \frac{D_{\max}}{t_{\text{dam}}} \varrho^e(\mathbf{X}, 0) e^{-0.5 \left(\frac{X_3}{L_{\text{dam}}} \right)^2 - \frac{t}{t_{\text{dam}}}}$$

Localization function
around the point of
TAWSS max



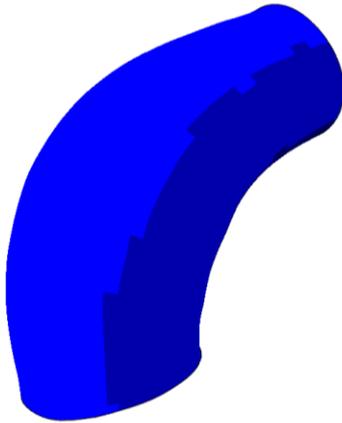
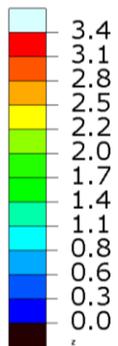
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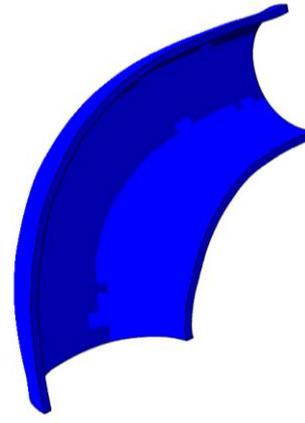
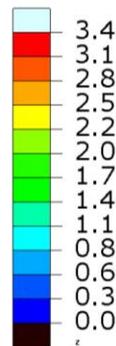


Small growth parameter

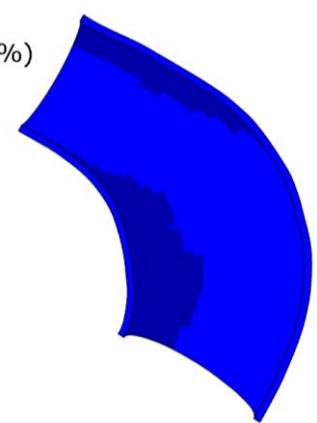
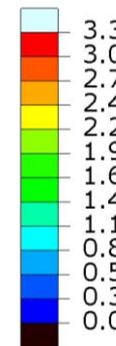
SDV69
(Avg: 75%)



SDV69
(Avg: 75%)



SDV69
(Avg: 75%)

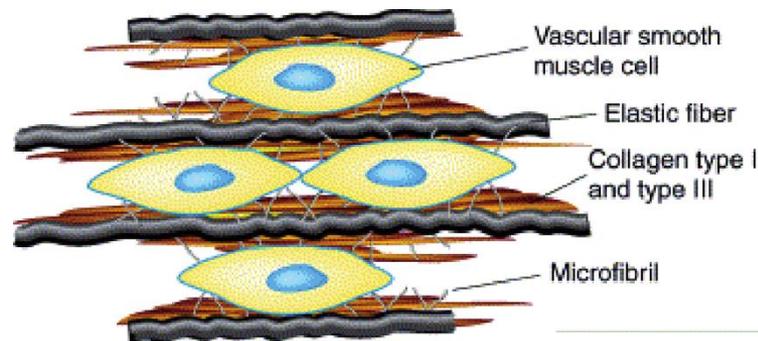


Normalized Thickness

Mousavi et al, BMMB (2019)

SUMMARY

- Patient-specific numerical model based on the constrained mixture theory including damage and G&R – coupling with CFD analyses, + active role of SMCs
- What is the role of SMCs in mechanoregulation?



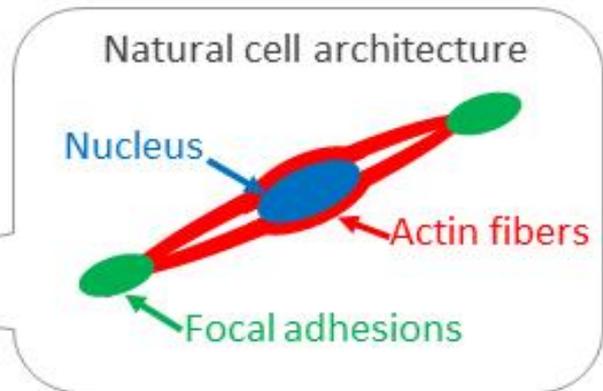
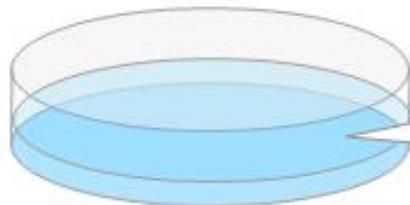


OUTLINE

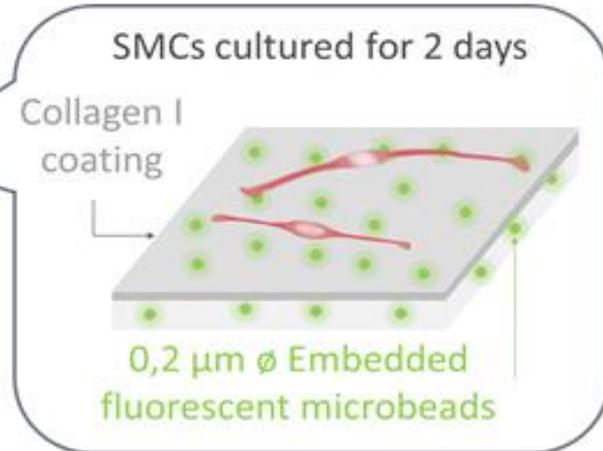
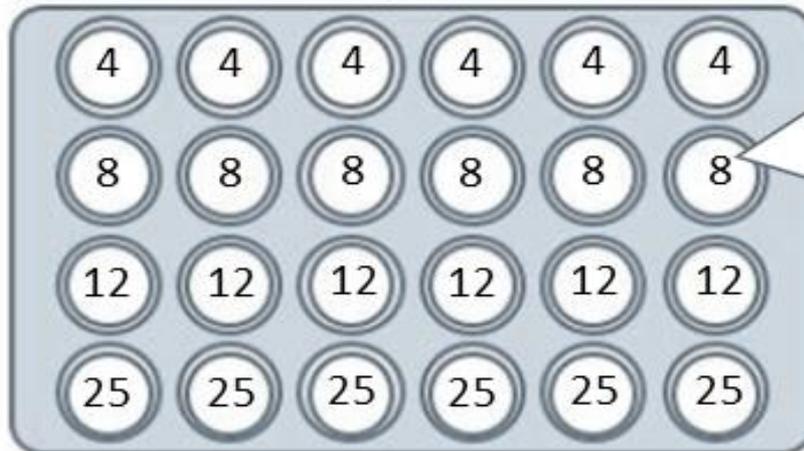
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Traction force microscopy on aortic smooth muscle cells

a Matrigen Petrisoft™
Collagen-coated hydrogel, 12 kPa
Fixed and stained cells

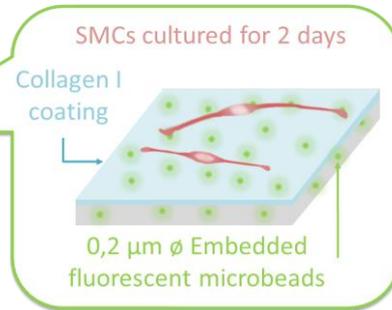


b Matrigen Softwell™
Living cells

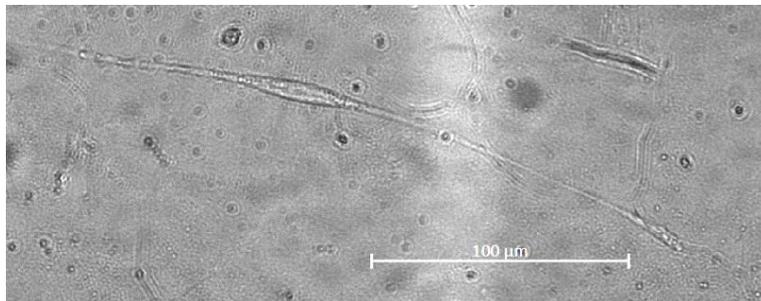


Traction force microscopy on aortic smooth muscle cells

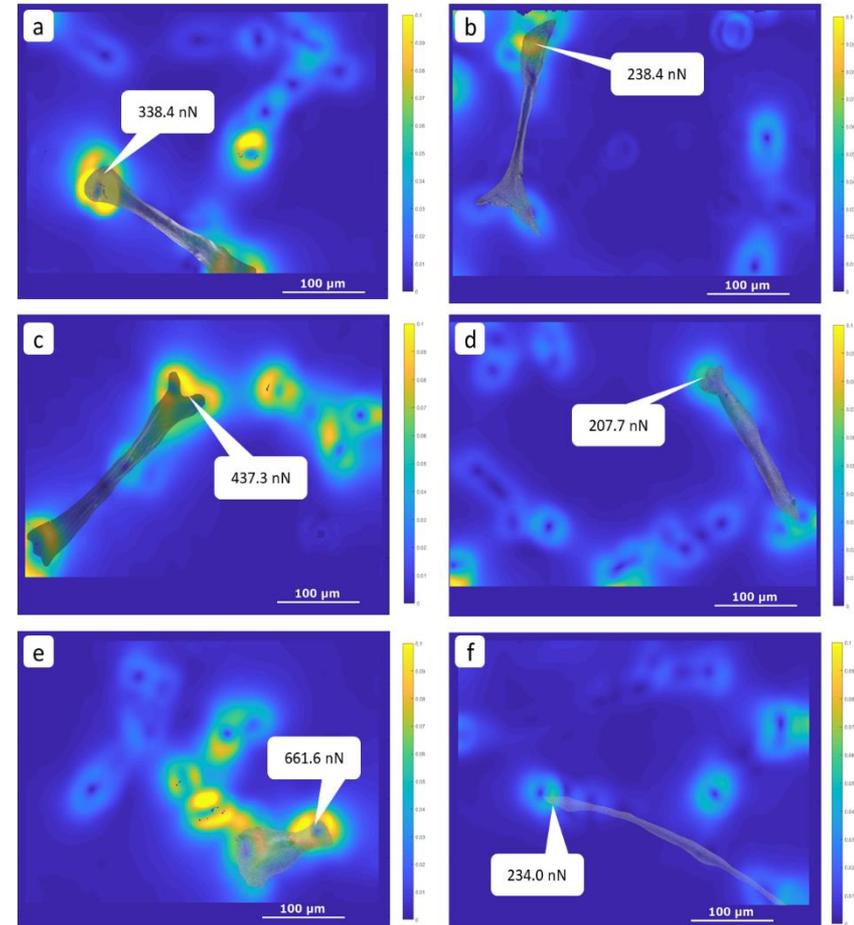
Several stiffness values



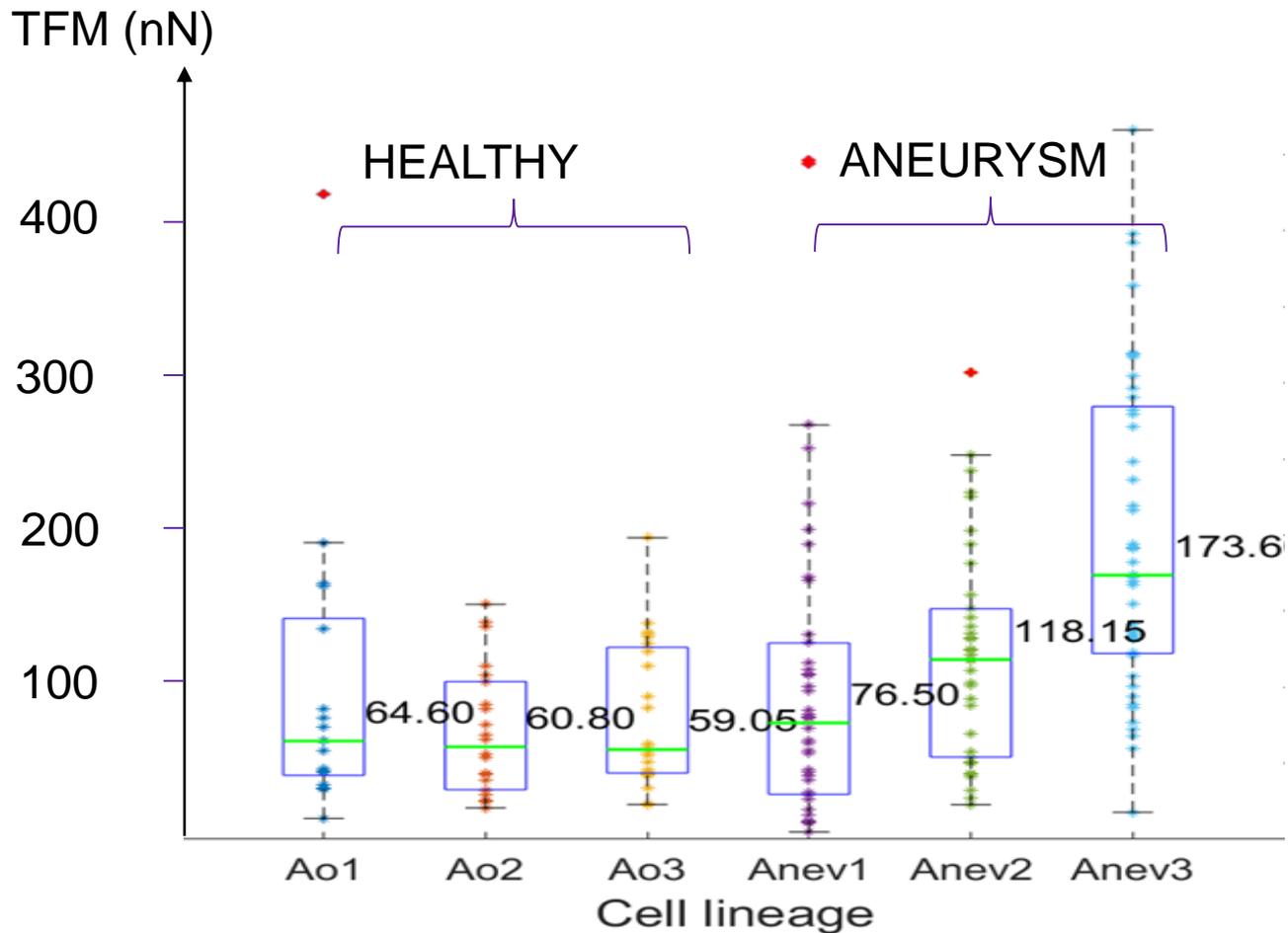
Aortic SMCs from human primary culture (AoSMC, Lonza), passages 5-7, cultured in a differentiating medium (SmBM, Lonza)



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



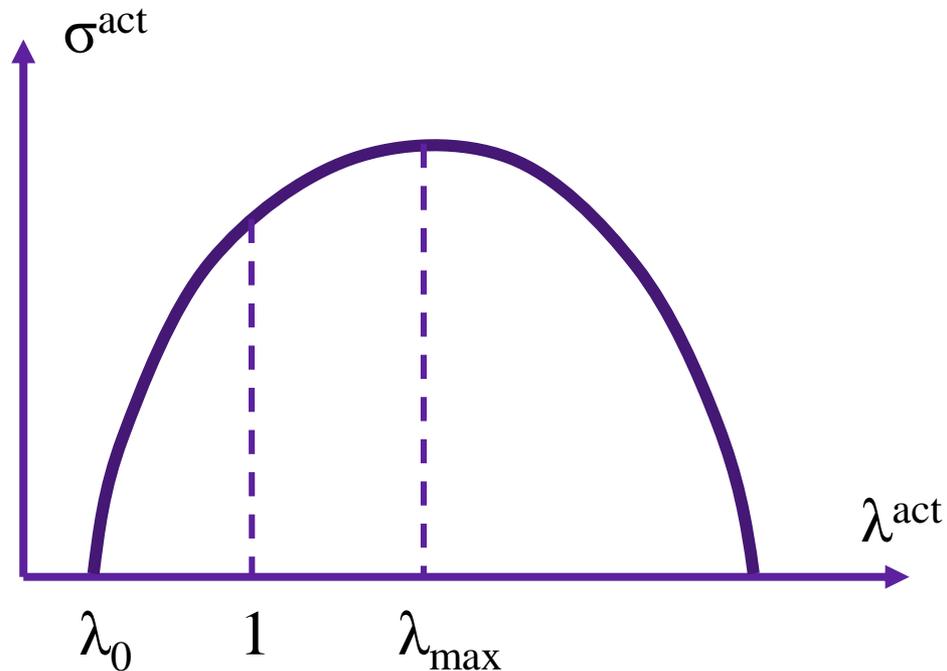
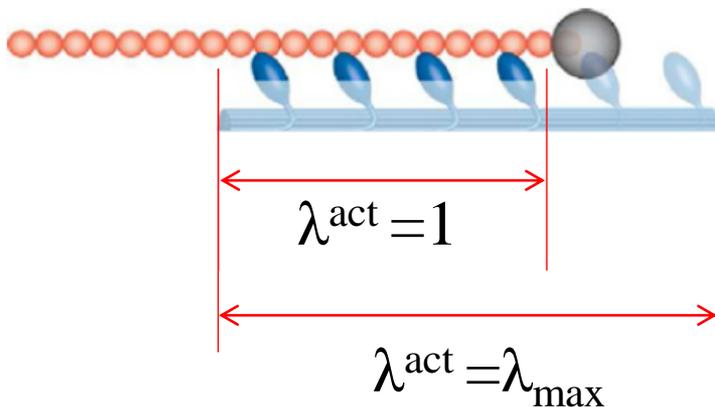
Aneurysmal SMCs tend to apply larger traction forces



Length-tension relationship of SMCS

$$\sigma^{\text{act}} = \frac{\sigma_{\text{actmax}}}{\rho_0(0) [C^{\text{m}} : (\mathbf{a}_0^{\text{m}} \otimes \mathbf{a}_0^{\text{m}})]} \left(1 - \frac{(\lambda_{\text{max}}^{\text{m}} - \lambda_{\text{act}})^2}{(\lambda_{\text{max}}^{\text{m}} - \lambda_0^{\text{m}})^2} \right)$$

Basal tone ~50kPa



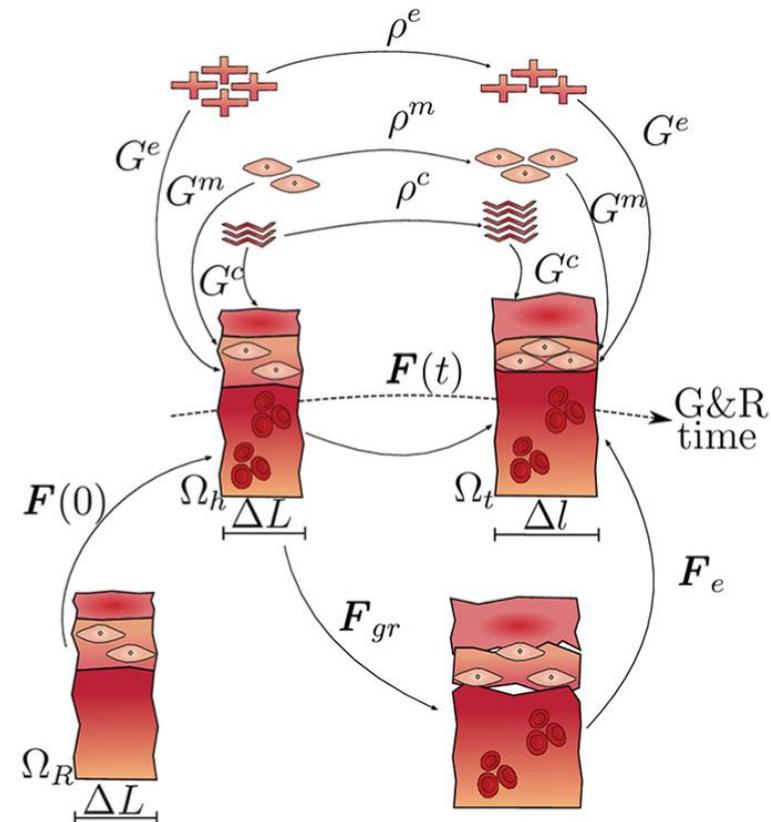
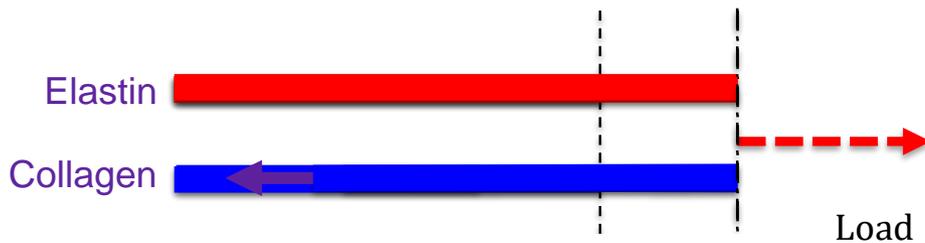
Murtada et al, J Theor Biol 2012, Ghavamian et al, Front Bioeng Biotech (2020)

Growth and Remodeling in homogenized constrained mixture

Collagen mass production

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

Inelastic deformation due to remodeling



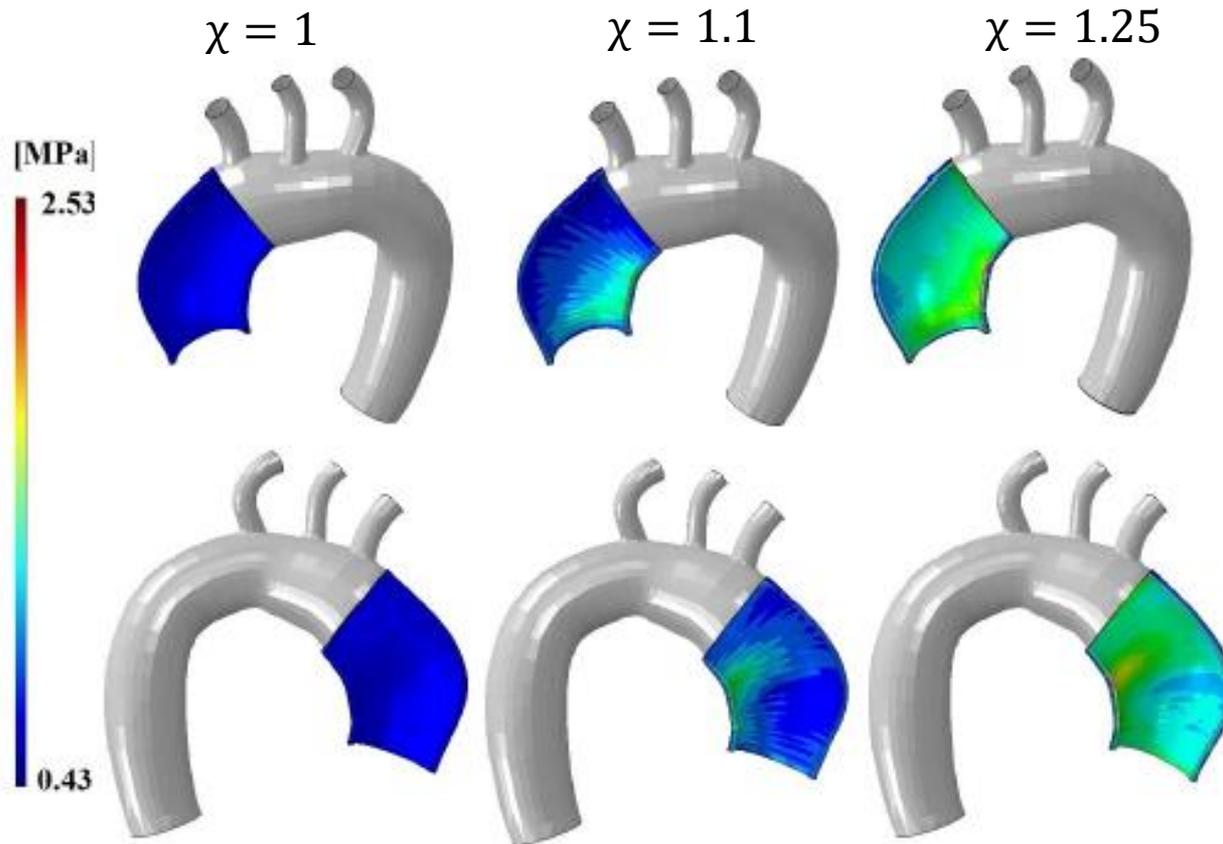
Cyron et al, BMBB (2016), Braeu et al, BMBB (2017), Laubrie et al, IJNMBE (2019)

Effect on mechanosensitivity impairment

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

$1 \leq \chi \leq 1.25$: impairment coefficient

Tangent stiffness after 10 years

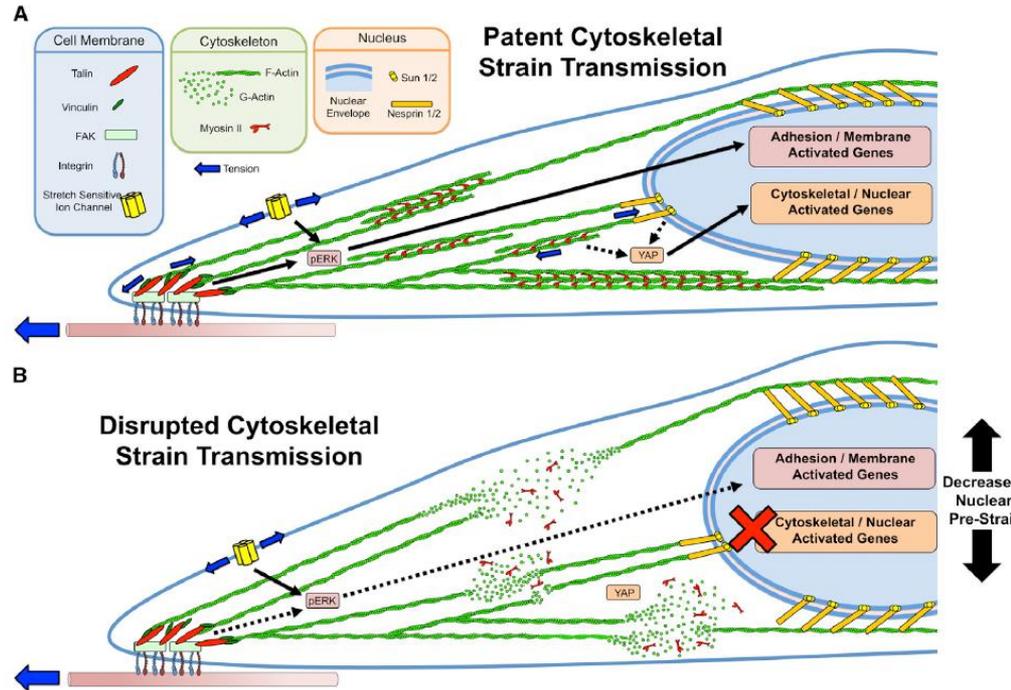
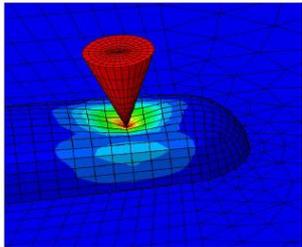
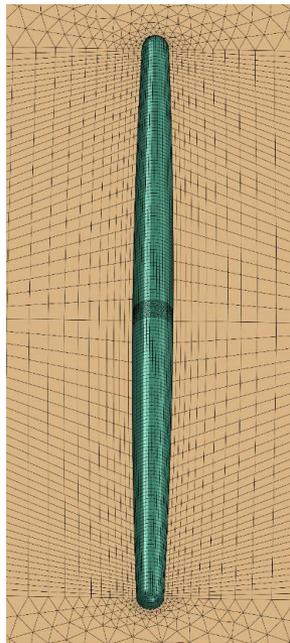
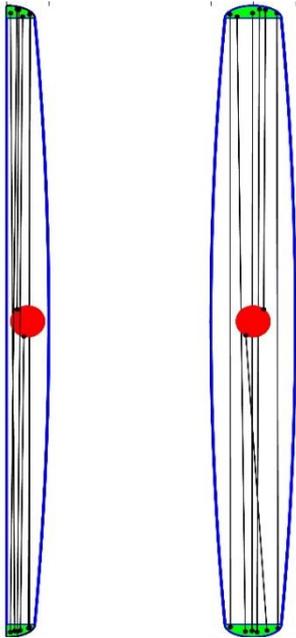


Mousavi et al, ABME (2020, submitted)

SUMMARY AND FUTURE WORK

- Include SMC tensional state into the computational models of aneurysm progression
- Towards clinical applications – drugs affecting SMCs locally
- Decipher the link between cytoskeletal SMC mechanics and mechanoregulation in aortic aneurysms

Finite-Element modelling of SMCs



Chan & Odde, Science 2008.
 Kharkaneh et al, ASME JBME 2020.

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- Claudie Petit
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