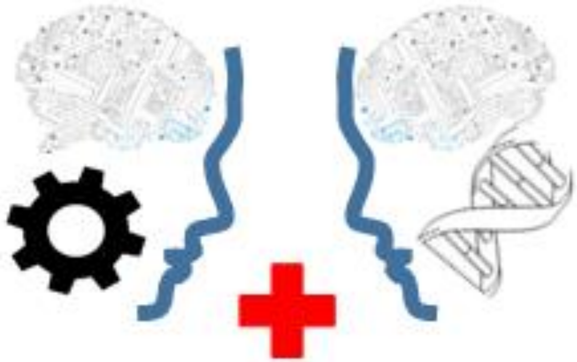

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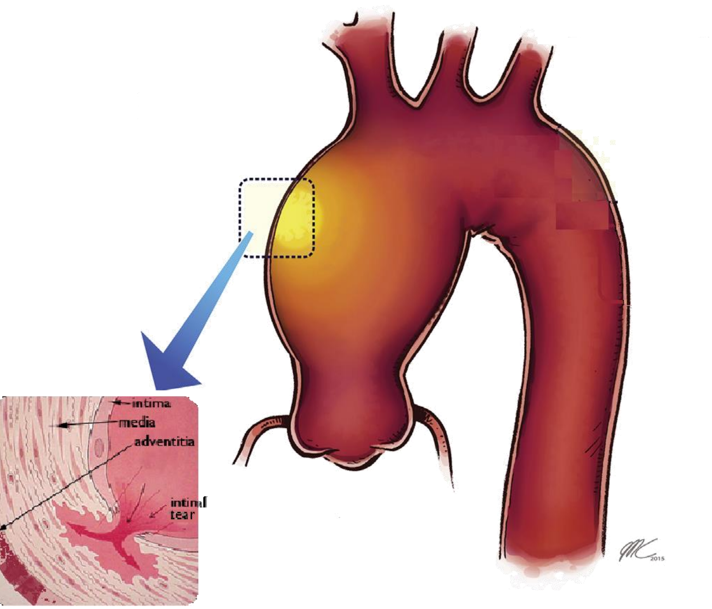

Coupling continuum mechanics and biology to assist clinicians in the management of aortic aneurysms

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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: Can continuum mechanics models predict human health?
- PART II: The need of combining data driven and continuum mechanics models in cardiovascular mechanobiology
- PART III: Continuum mechanics of tensional homeostasis down to the subcellular level

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OUTLINE

- **PART I: Can continuum mechanics models predict human health**
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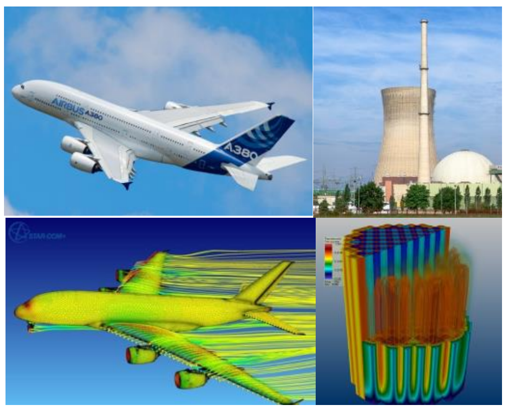
Numerical simulation was commonplace in automotive and aeronautics industry

In any other industrial sector



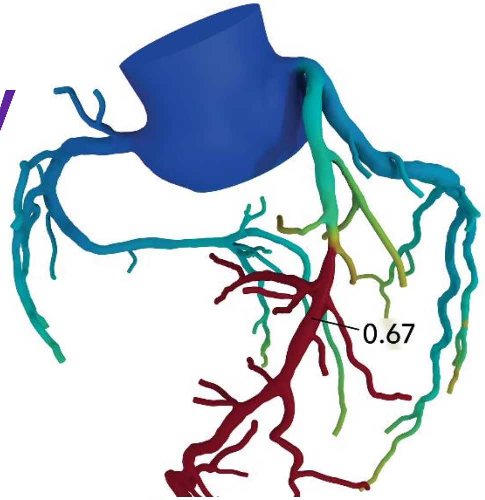
Testing is now done mostly with computer simulation

In healthcare

X X X X X X X X
X X X X X X X X
X X X X X X X ✓

Standard test for safety and efficacy of new products is by trial and error

Since 1989: a 30+ years journey

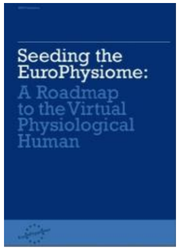


HeartFlow

Physiome Project

1993: Physiome

2005:
VPH


Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human

2007: STEP

VPH Institute
Building the Virtual Physiological Human

2010: VPH Institute

In these 30 years the idea of an In Silico Medicine with Digital Twins for each patient, and In Silico Trials to test new products, moved from science fiction to an industrial reality


in silico
Clinical Trials:

2016: Avicenna

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

2013: Sensome

2014: Sim&Cure

2017: Predisurge

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My own experience on aortic aneurysms is the result of strong and historical collaborations with clinicians

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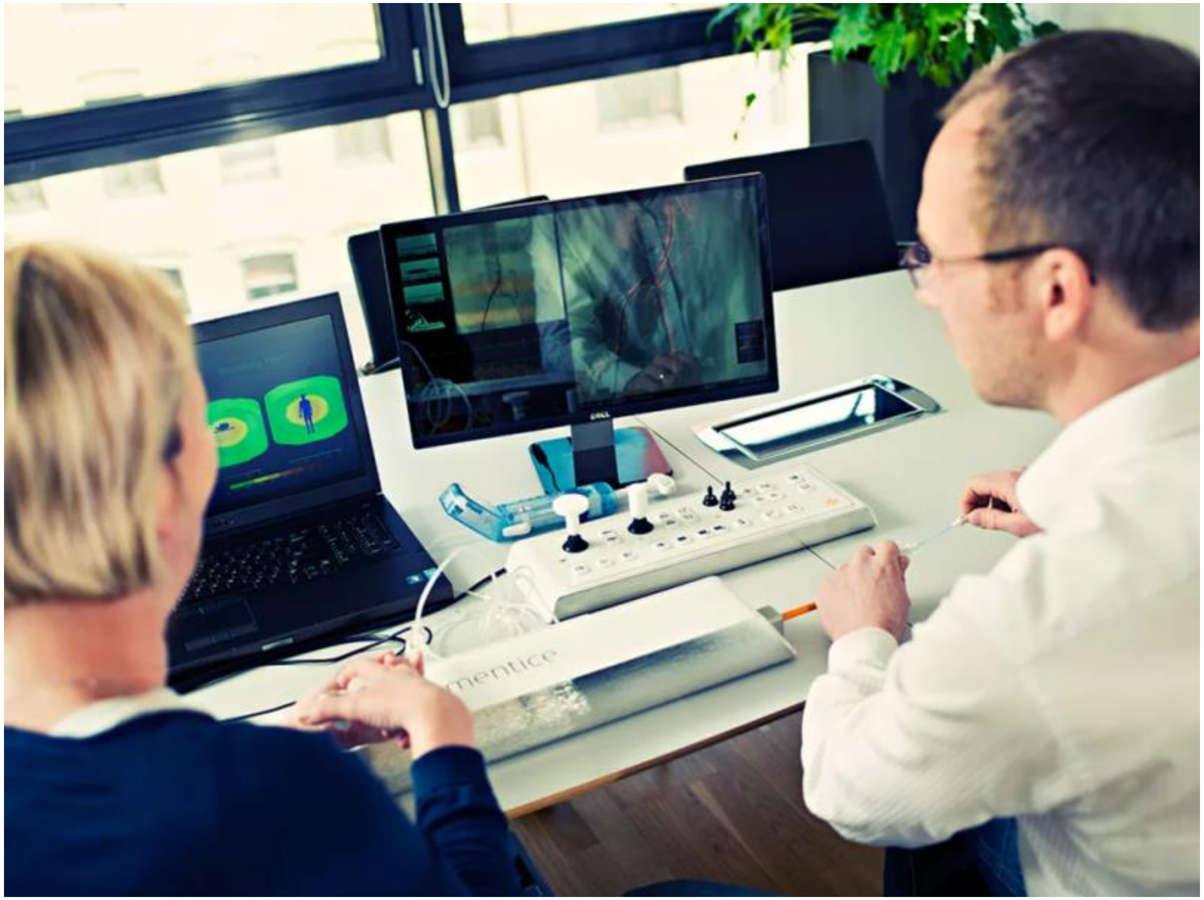
PrediSurge



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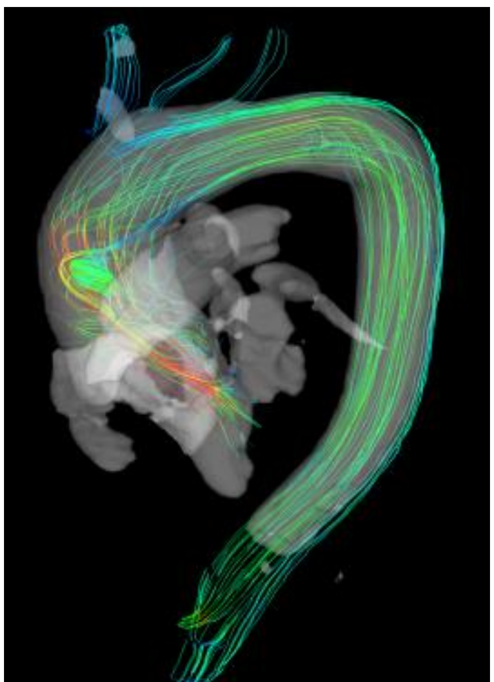
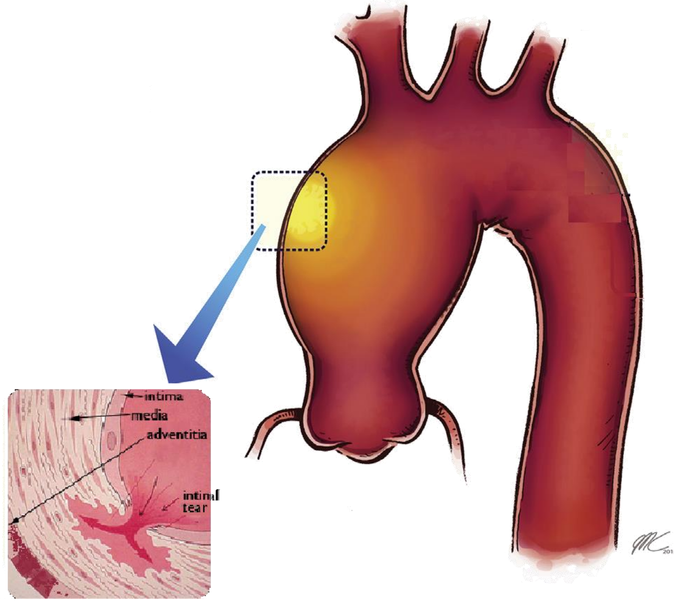
Aneurysms and Dissections of the aorta





== Devastating complications!

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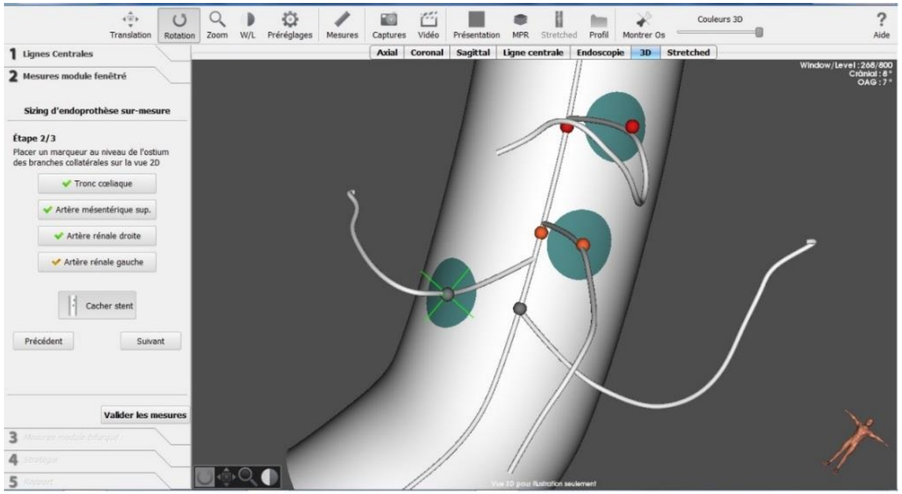
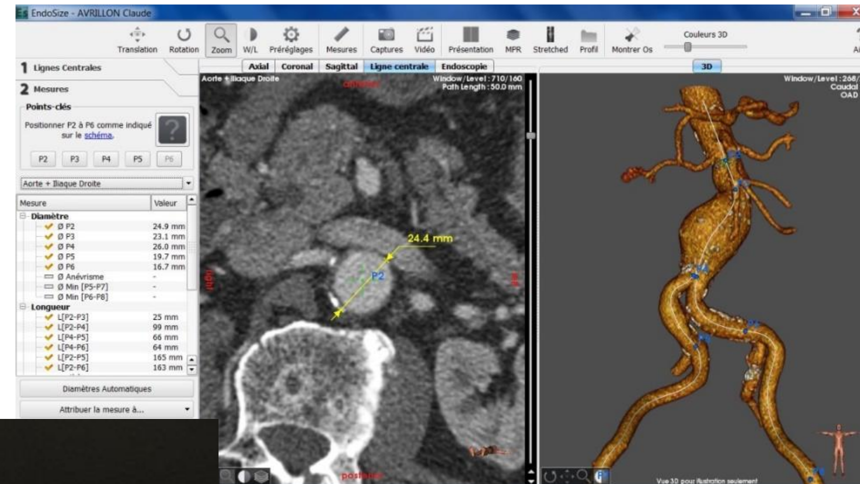
Planification / sizing of fenestrated stent grafts in EVAR procedures





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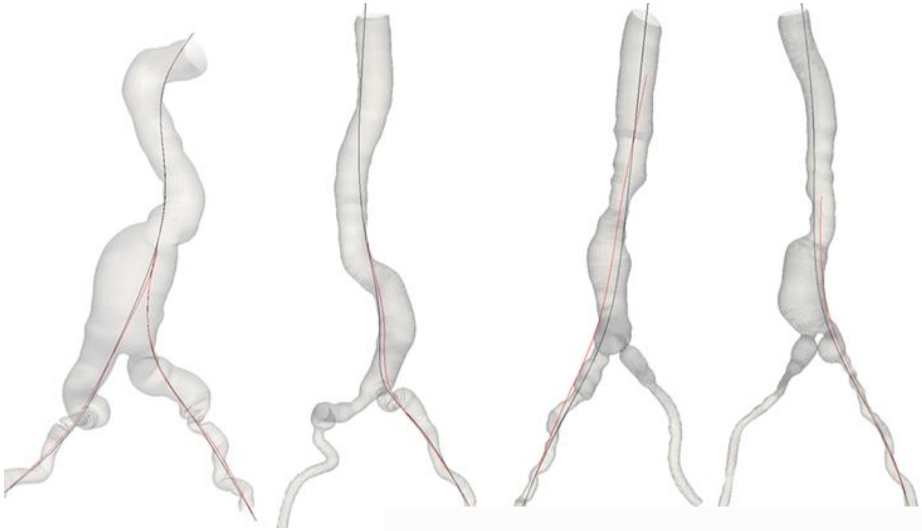
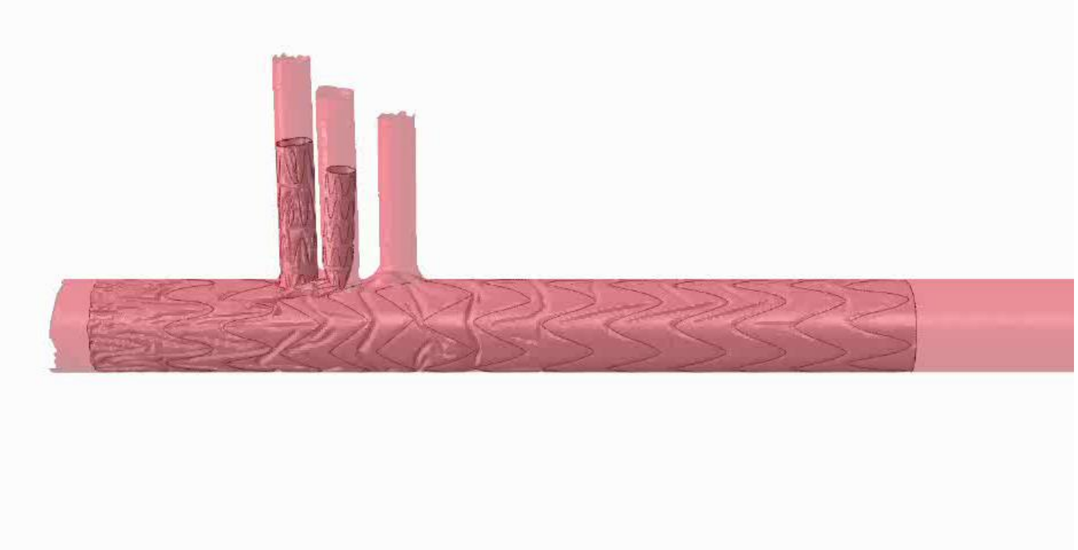
Simulation of stent-graft deployment





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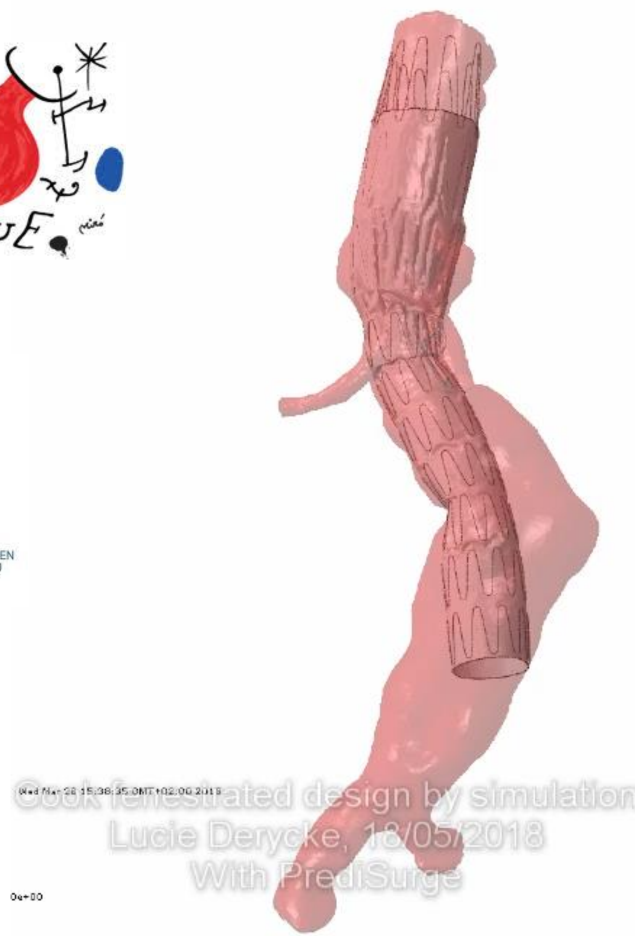
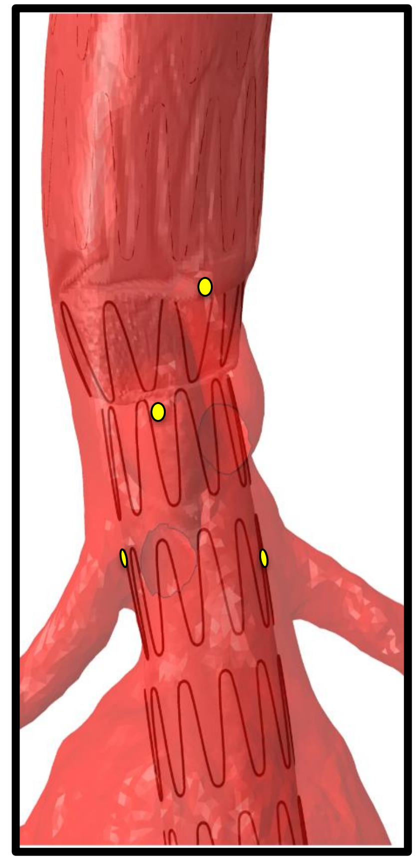
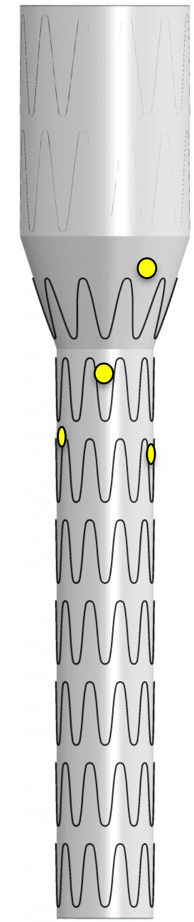
Clinically validated for FEVAR Zenith® Cook Medical







SUMMARY

- Computational models using continuum mechanics are now used commonly in healthcare for developing medical devices

- Major challenges still need to be overcome to go beyond the virtual patient and establish digital twins of oneself integrating **time evolutions**.

- Challenges are related to **biology**.

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OUTLINE

- PART I: Can continuum mechanics models predict human health

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

- PART III: From computer models to digital twins enabling precision medicine

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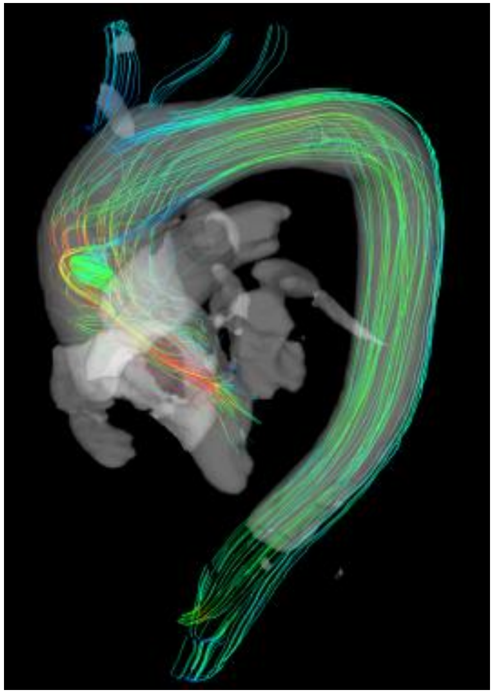
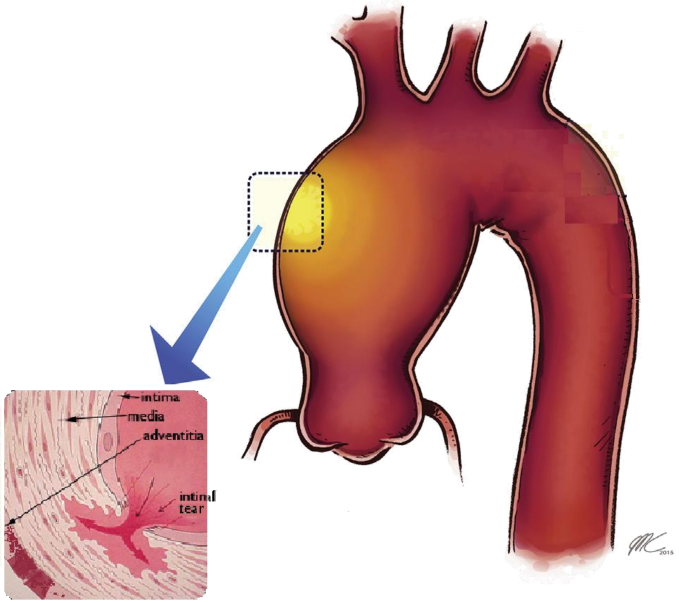
Aneurysms and Dissections of the aorta





Challenge: decision making to avoid aortic dissections!

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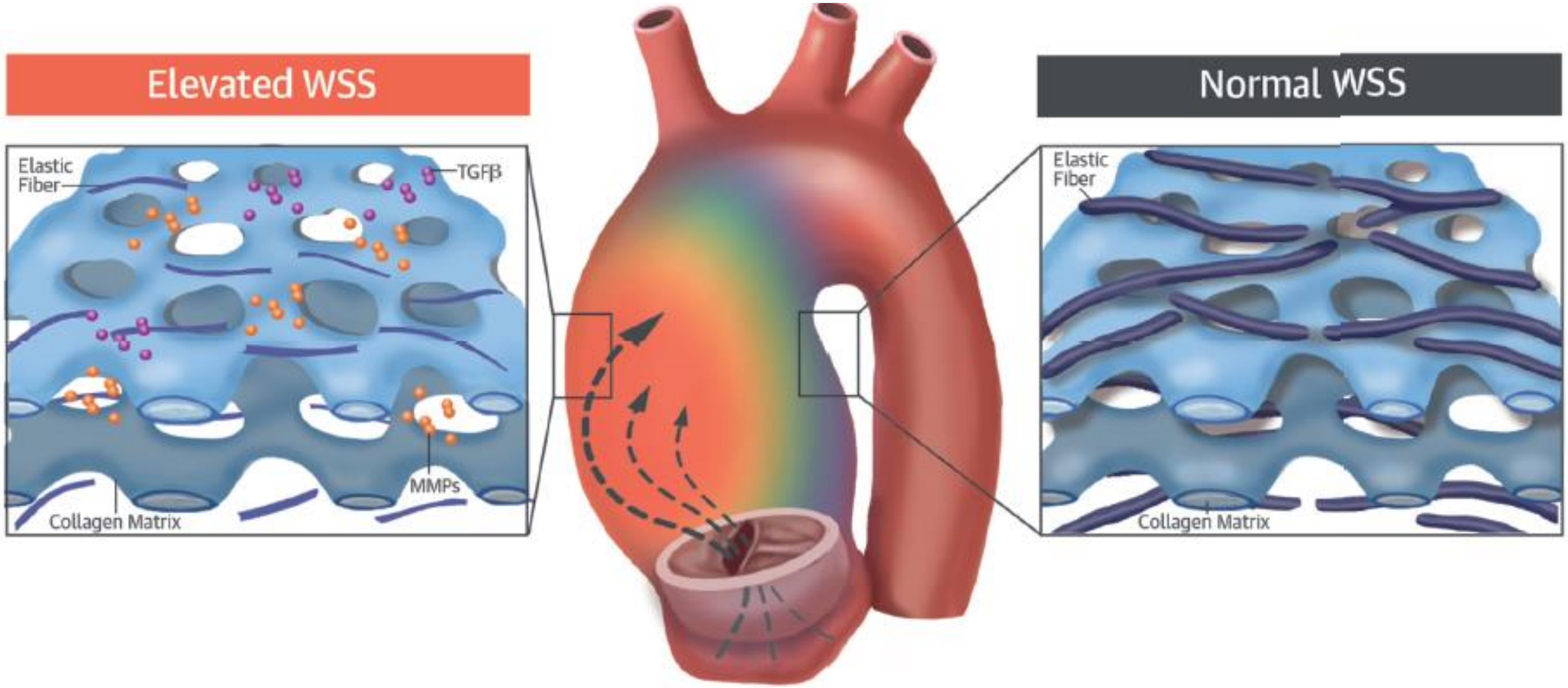
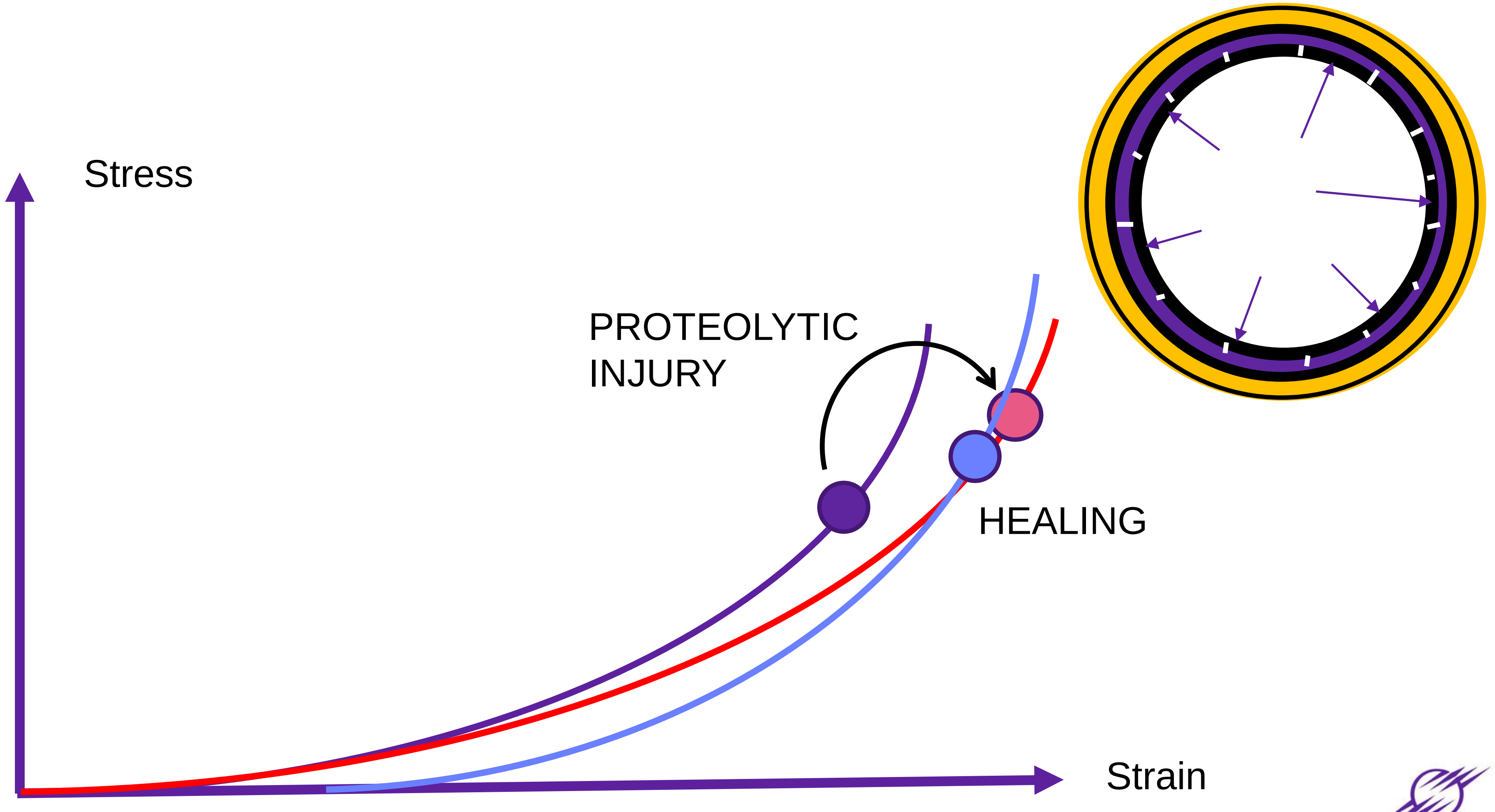
Continuum mechanics approach

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



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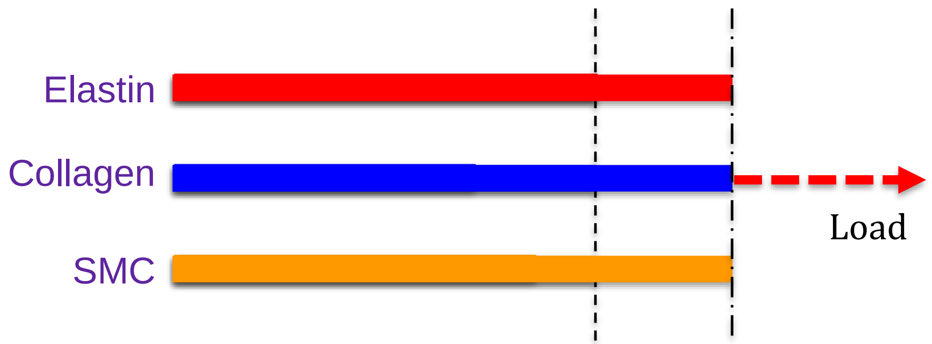
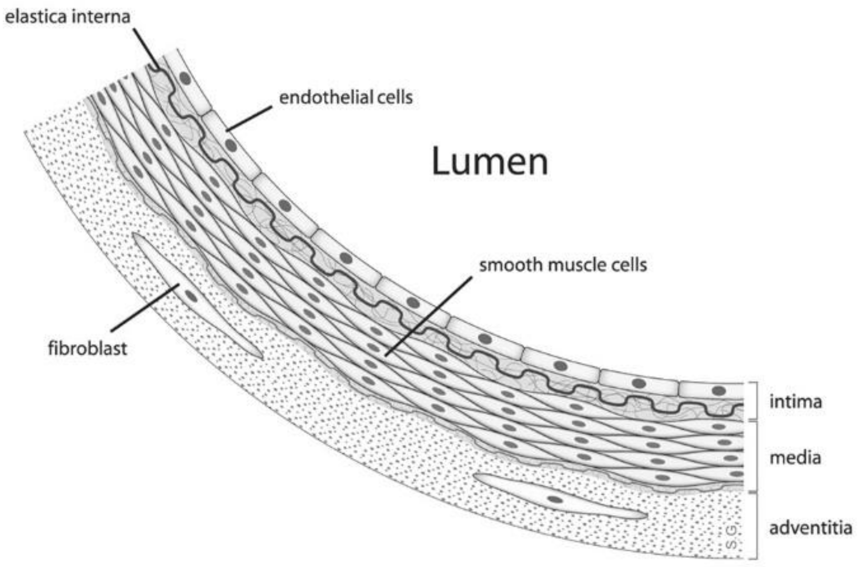
Layer-specific constitutive model

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:



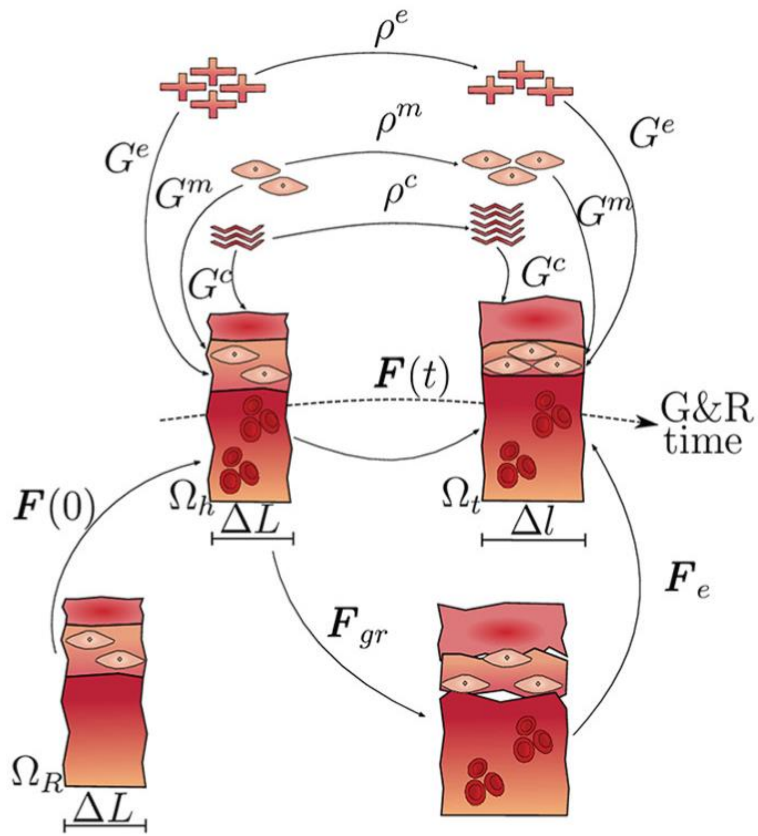


Humphrey & Rajagopal, Math Models Methods Appl Sci. (2002) ; Bellini et al, ABME (2014), Mousavi & Avril, BMMB (2017)

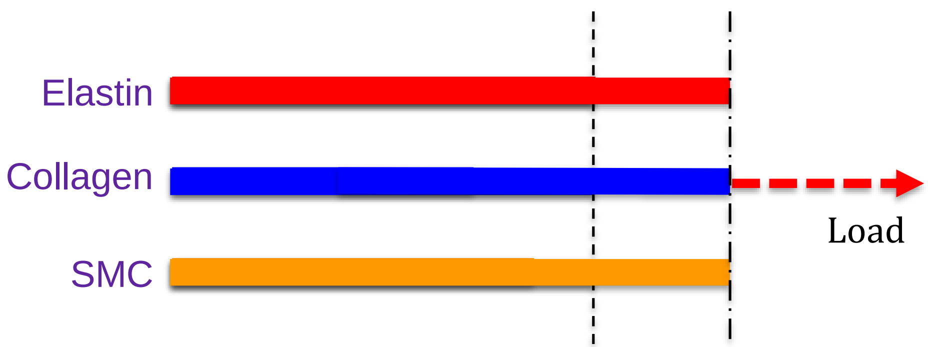
Growth and Remodeling in homogenized constrained mixture

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)

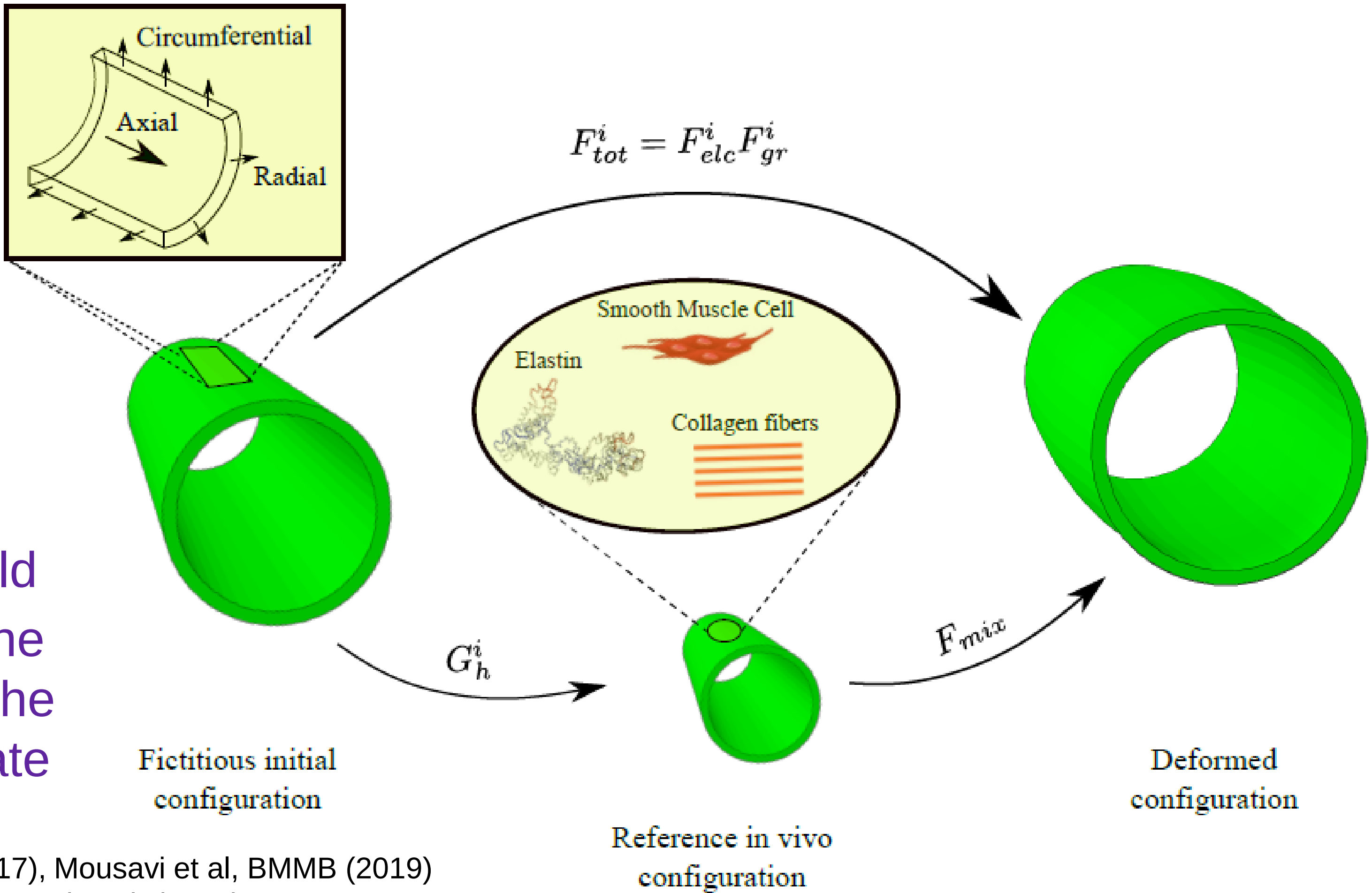
Continuum mechanics approach

Elastic and inelastic decomposition of deformation gradient

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

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

$\mathbf{F}_{\mathrm{r}}^{j}$ and $\mathbf{F}_{\mathrm{g}}^{j}$ 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)

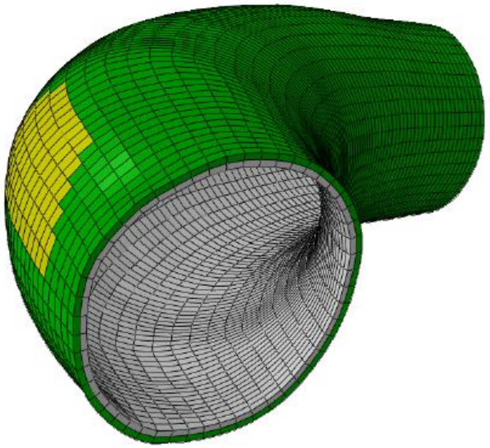
Continuum mechanics approach

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

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

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

Localization function around the point of TAWSS max



Mousavi et al, BMMB (2019)

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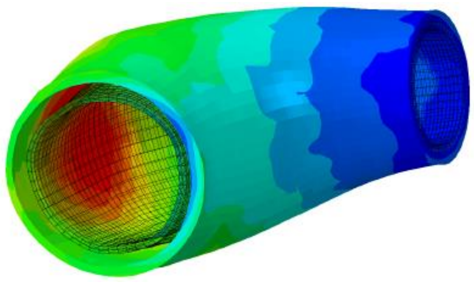
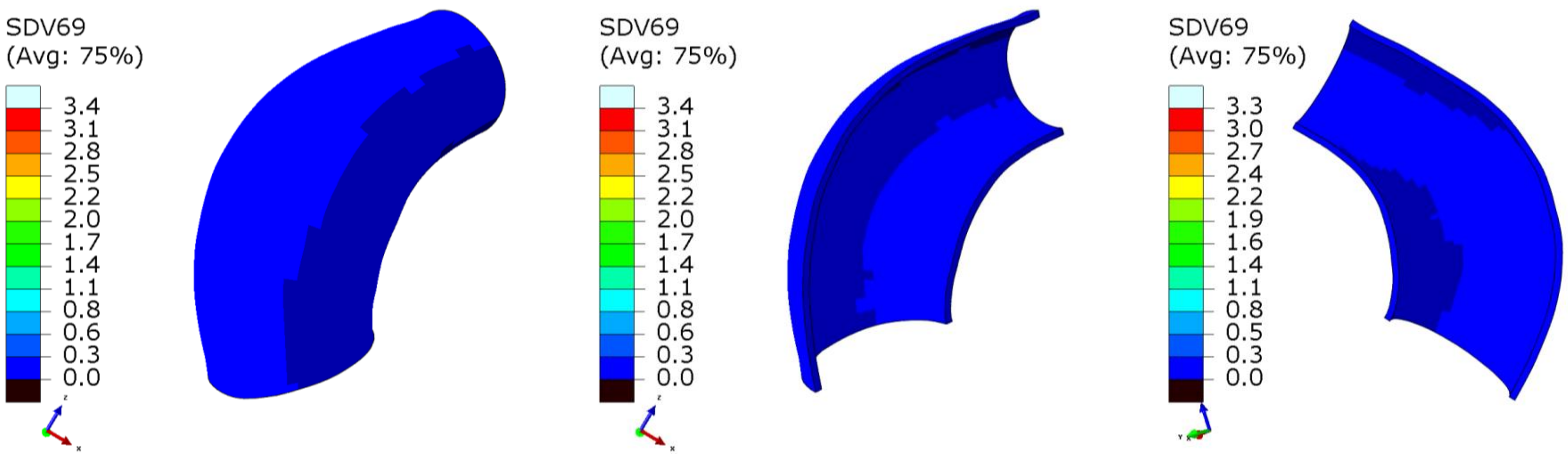
Patient-specific predictions



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)

Difficulties related to the inter-individual variability of aortic dissections
=> uncertain boundary and initial conditions

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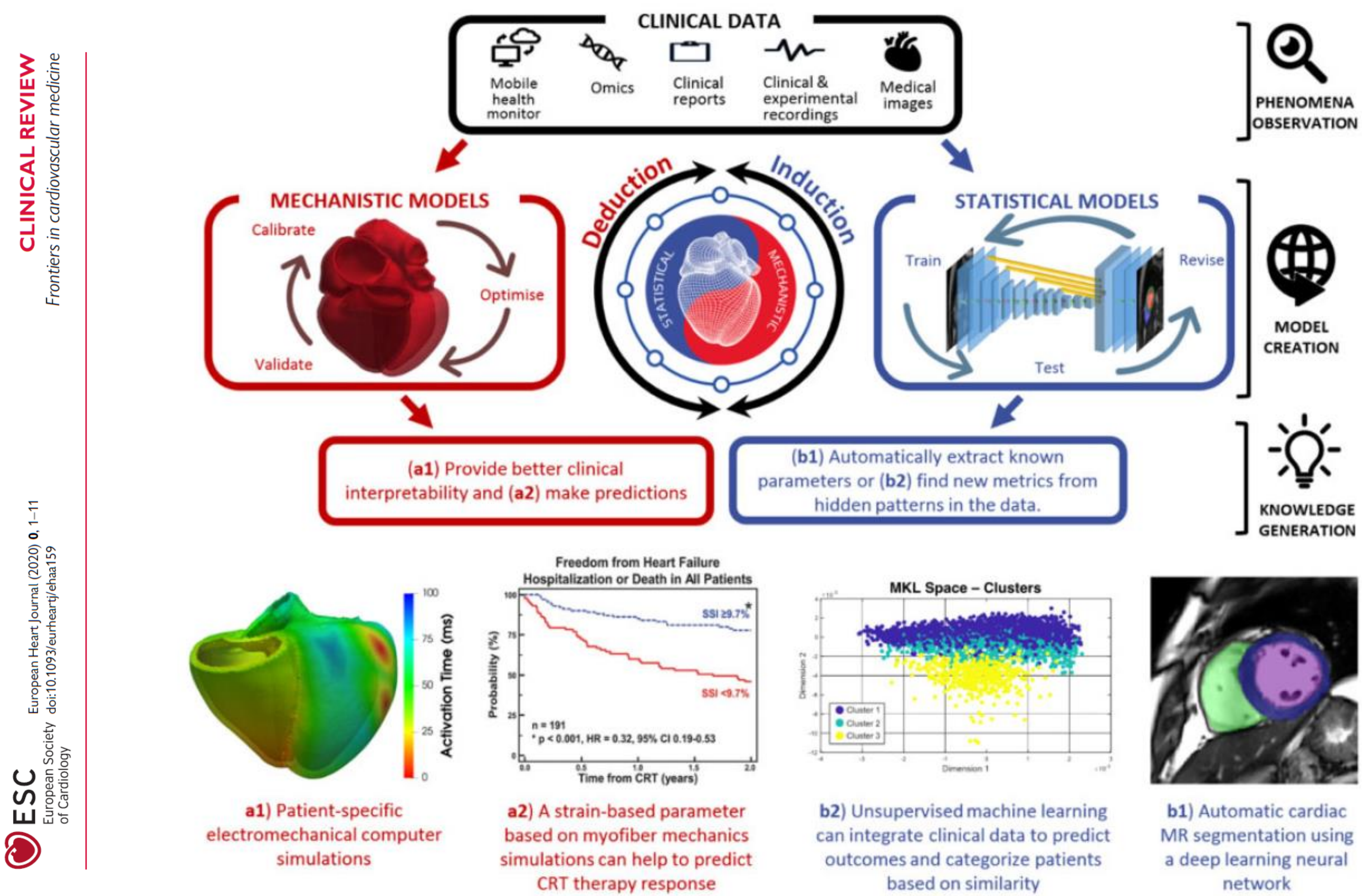
Solution: combining statistical models and the continuum mechanics approach



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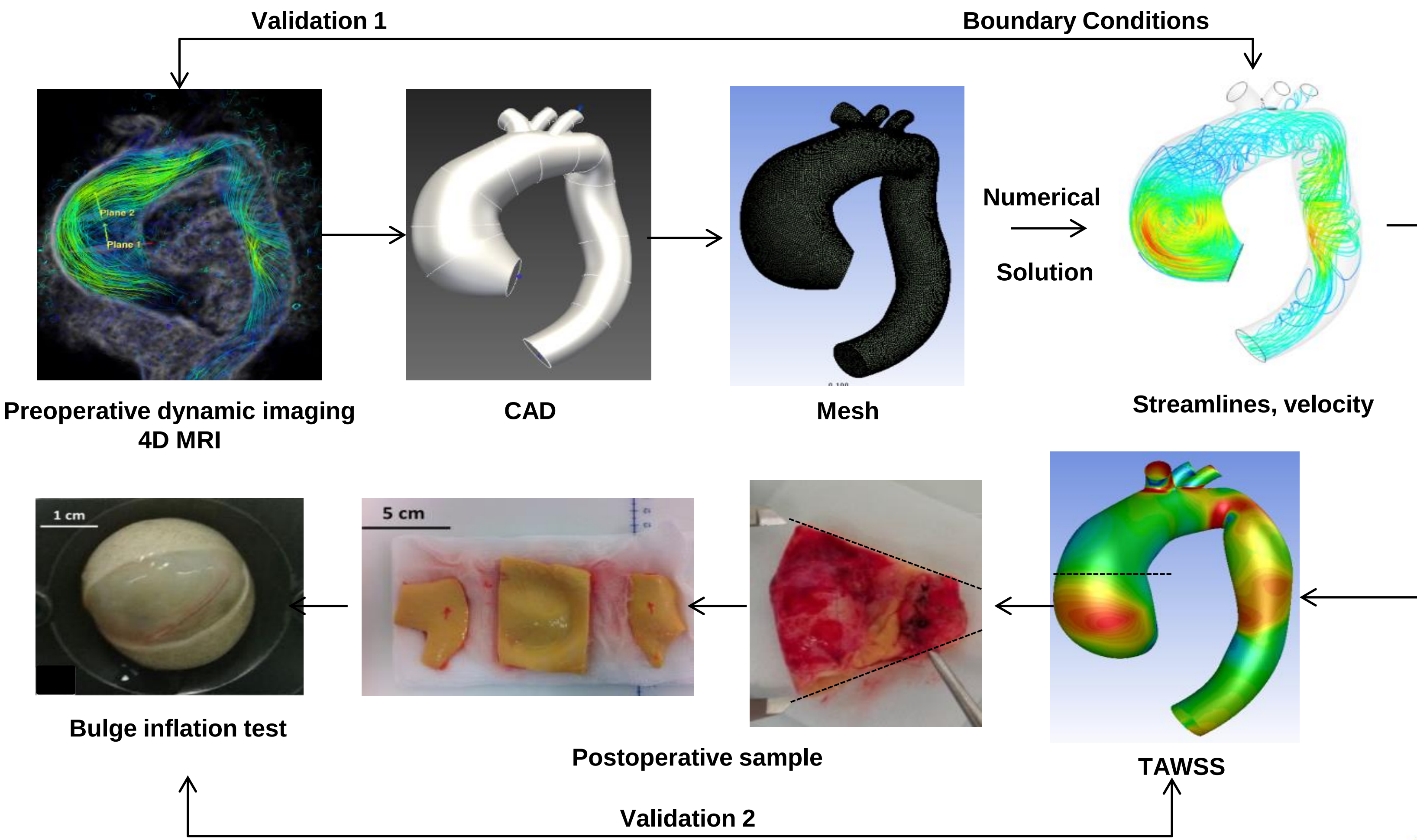
Learn boundary conditions, material properties and initial conditions from image analysis



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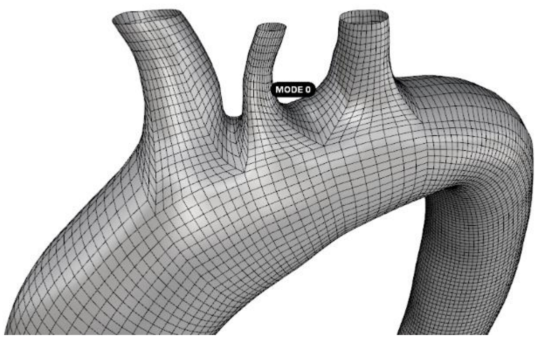
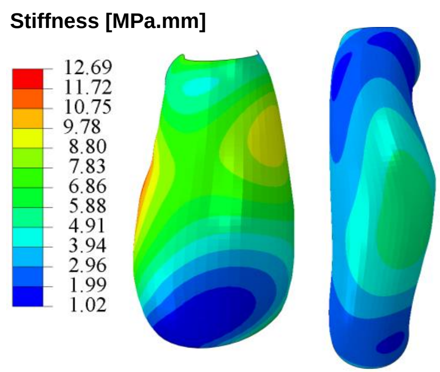
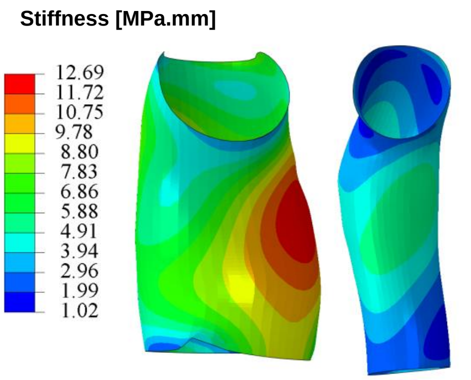
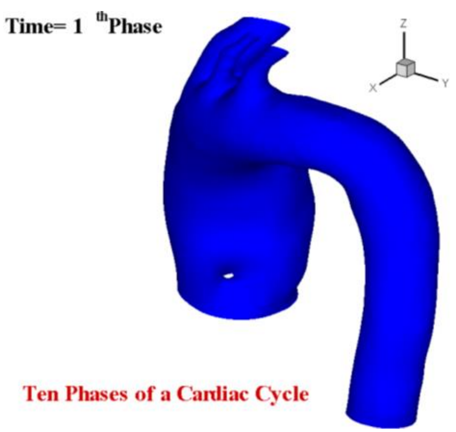
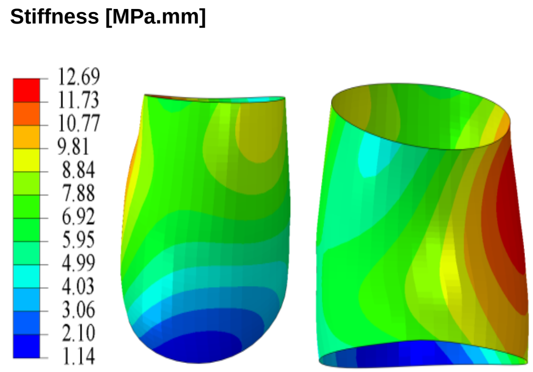
Learn boundary conditions, material properties and initial conditions from image analysis

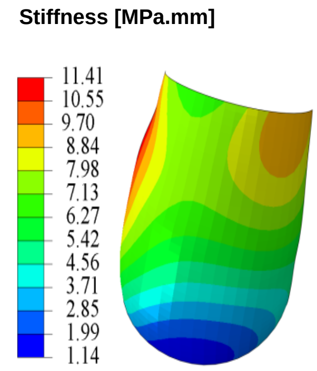






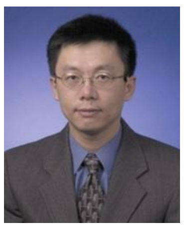


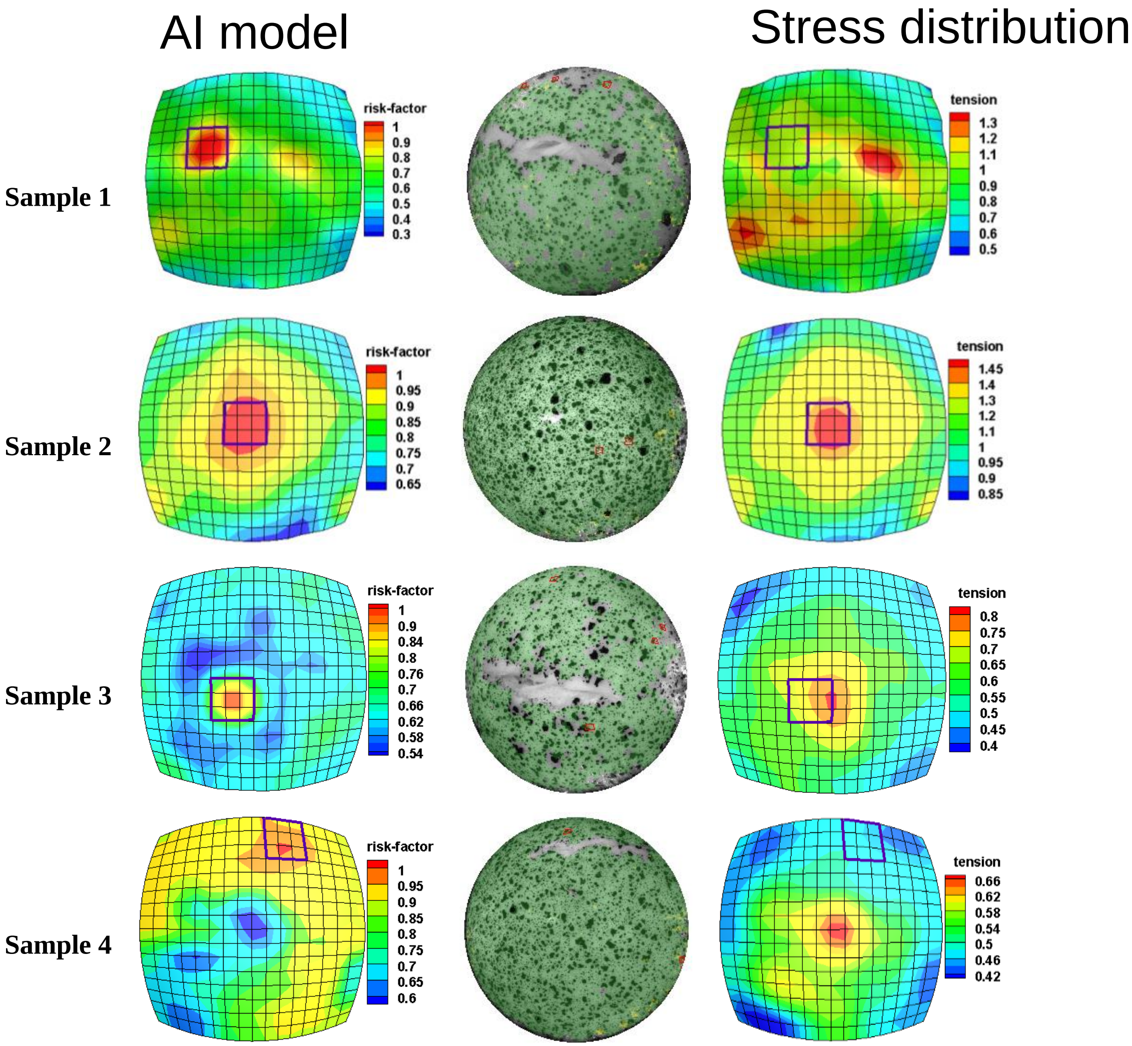




AI model of rupture criterion…

THE UNIVERSITY OF IOWA





He et al. BMMB – 2020
(Just accepted!)

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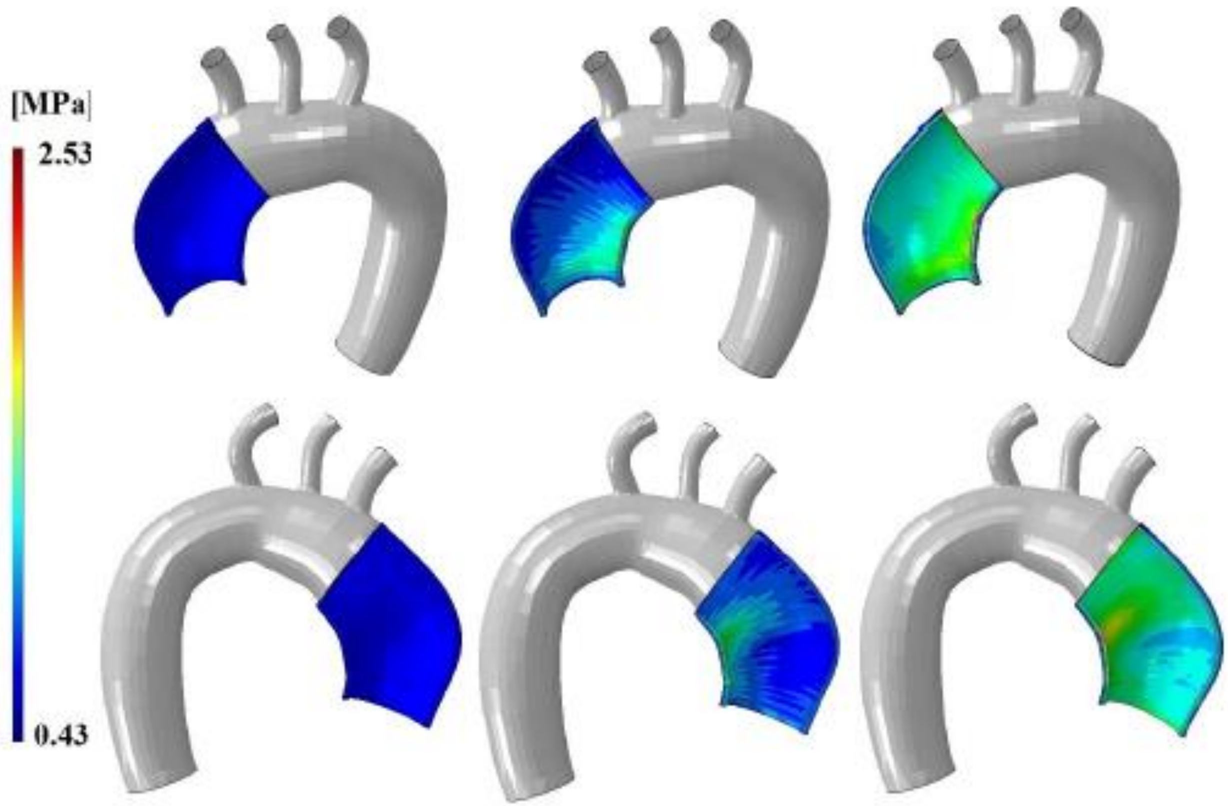
Defining patient subgroups depending on genetic factors

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

$\chi = 1$ $\chi = 1.1$ $\chi = 1.25$

Tangent stiffness after 10 years



Mousavi et al, CMPB (2021)

SUMMARY

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

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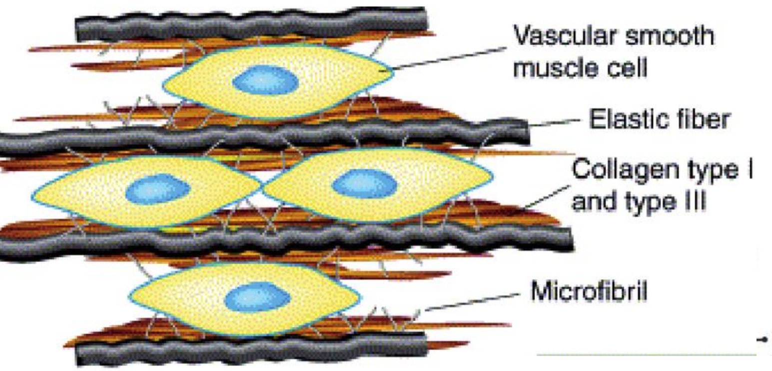
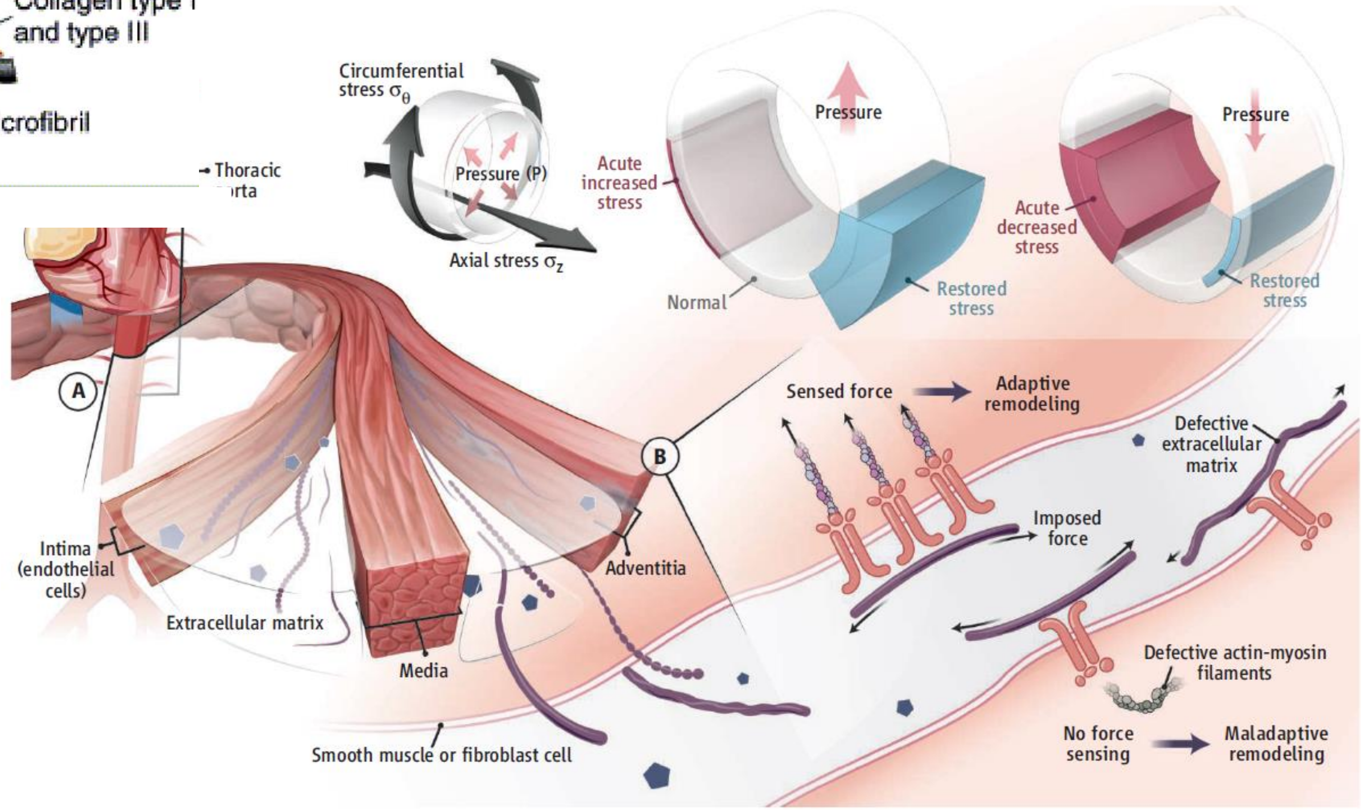
Challenges posed by molecular and cellular biology

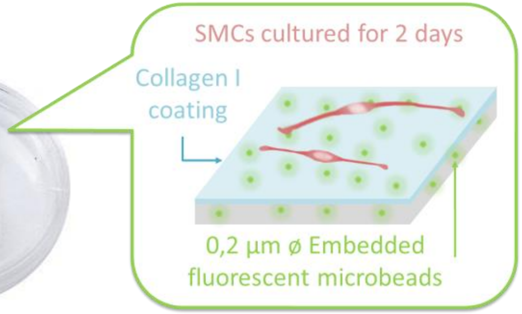




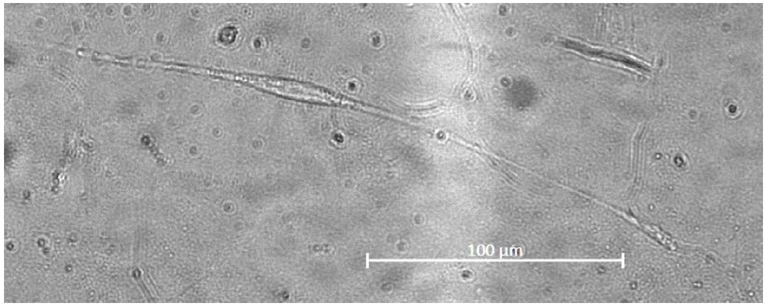
Humphrey et al, Science 2014

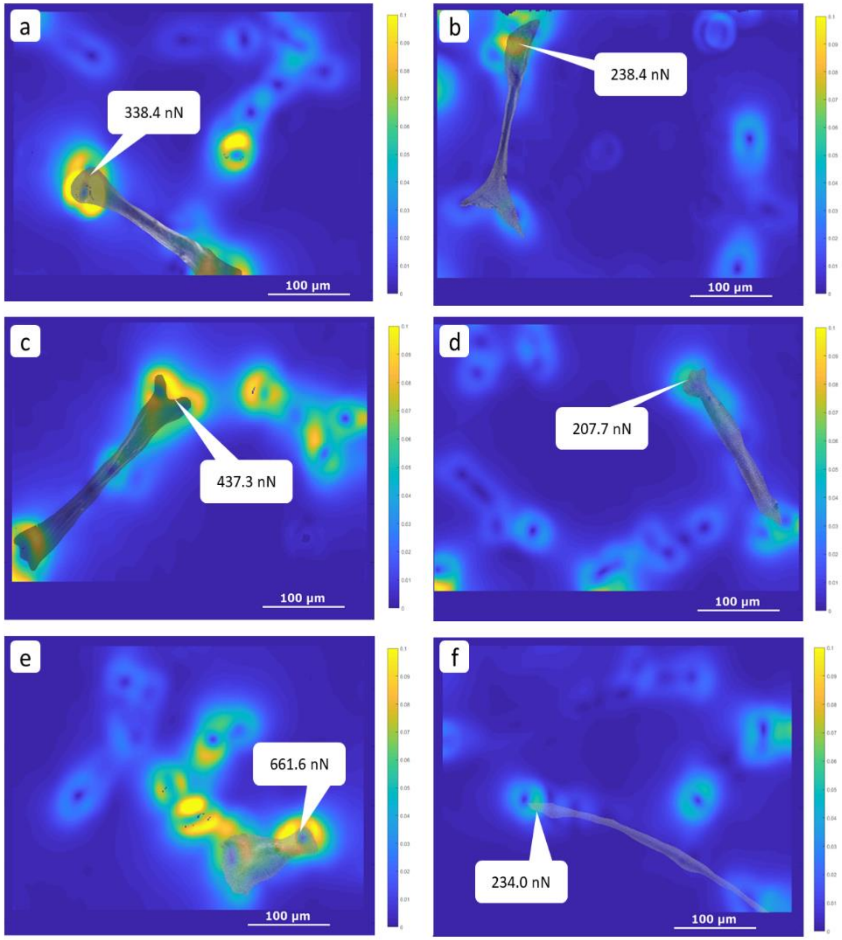
Monitoring mechanobiology *in vivo*

Several stiffness values



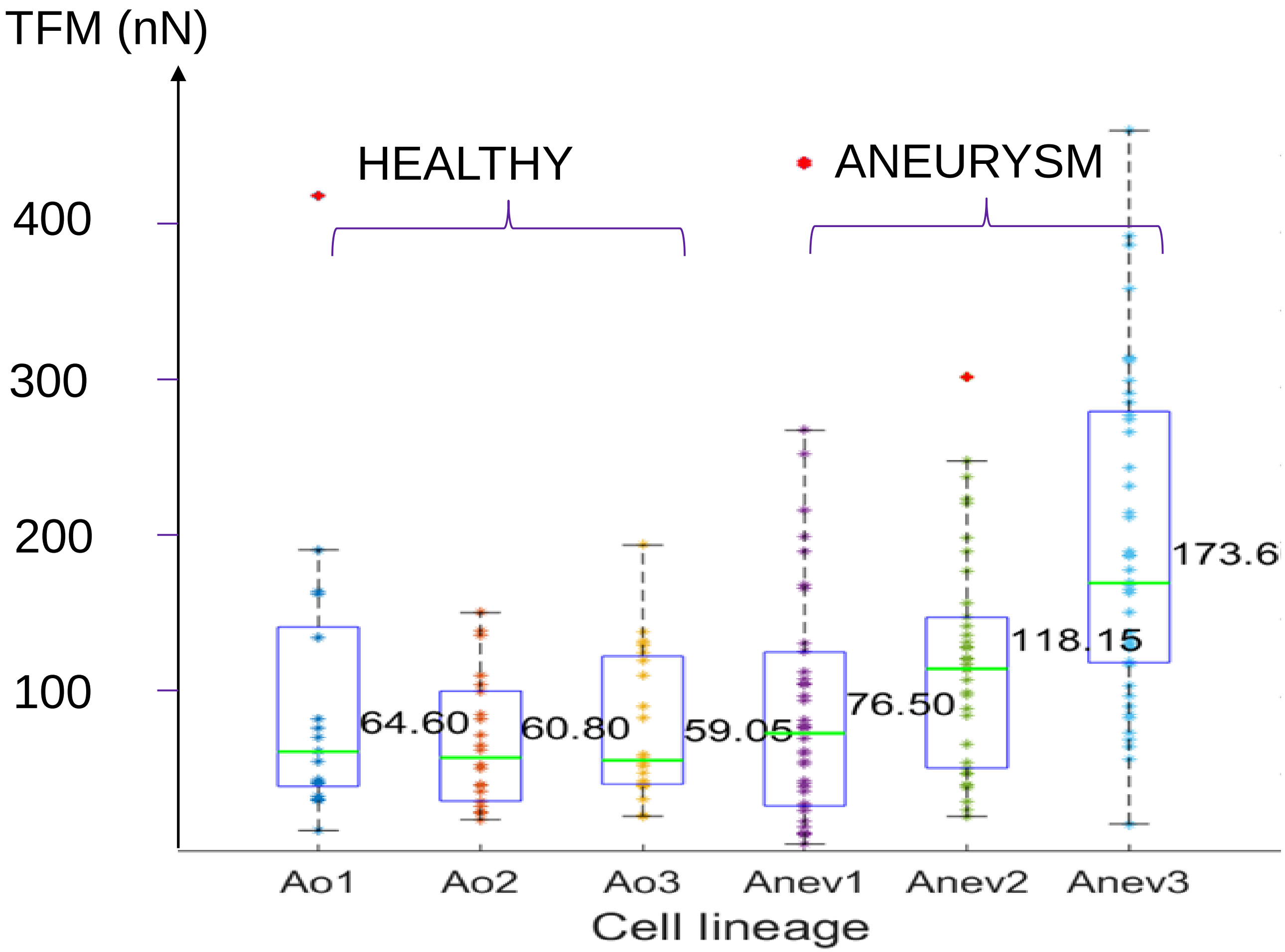
Aortic SMCs from human primary culture (AoSMC, Lonza), passages 5-7, cultured in a **differenciating medium** (SmBM, Lonza)





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

Aneurysmal SMCs tend to apply larger traction forces



Finite-Element model of the SMC

Stress fibers:

- $E_{SF} = 50$ MPa
- Truss-like elements, diameter = 0.2 µm

Cell membrane and nuclear envelope:

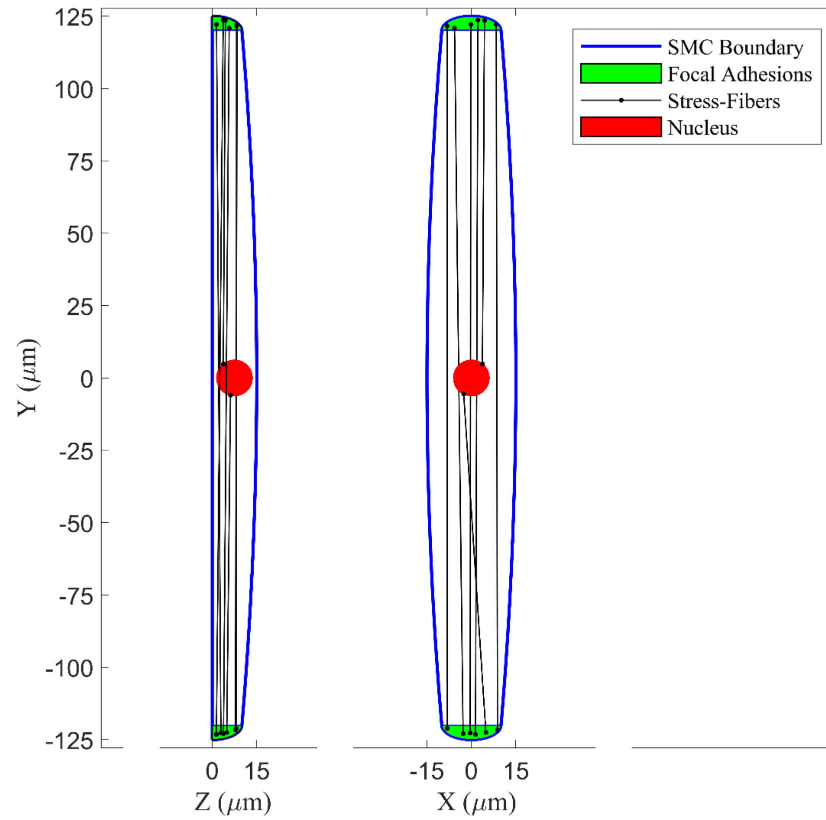
- Neo-Hookean, shear modulus = 600 kPa
- Poisson's ratio = 0.49

Cytoplasm and nucleus:

- Neo-Hookean, shear modulus = 100 Pa
- Poisson's ratio = 0.49

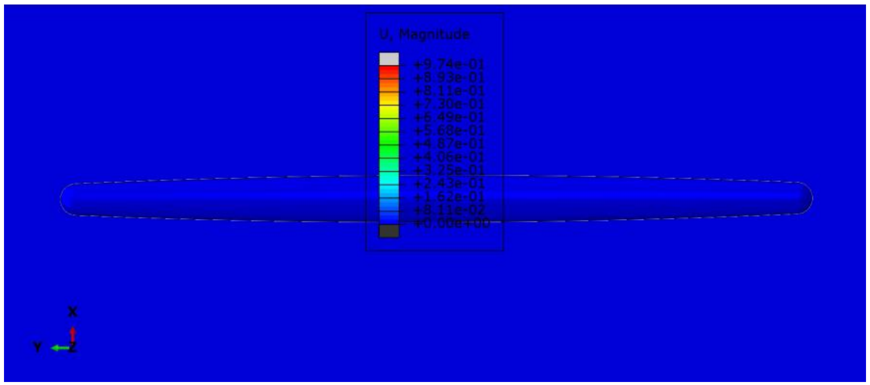
Substrate:

- Linear elastic, $E = \{4,8,12,25\}$ kPa and $\nu = 0.45$

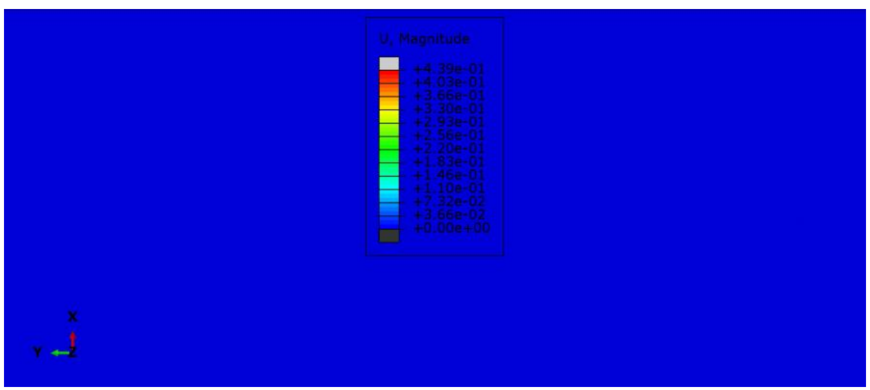


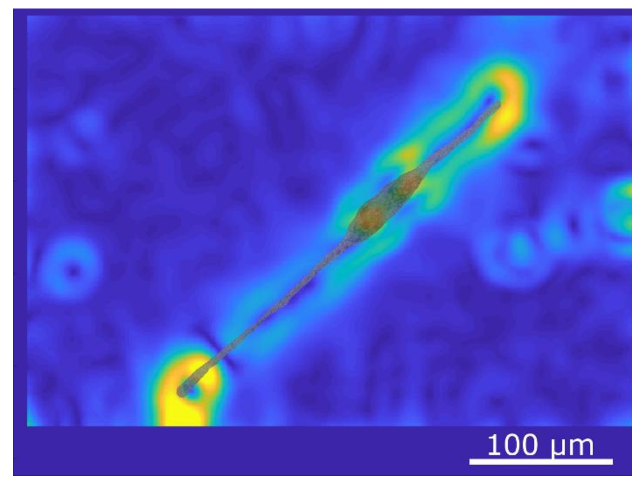
Gouget et al., BMMB (2016)

Simulating the cytoskeleton tension



$$\Delta T = 0.132$$
$$\alpha = 0.034$$
$$\xi = 0.68$$
$$E'_{SF} = -19.9\ \mathrm{MPa}$$





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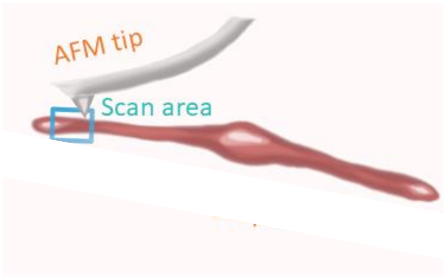
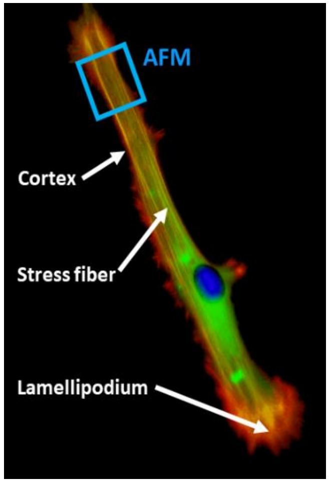
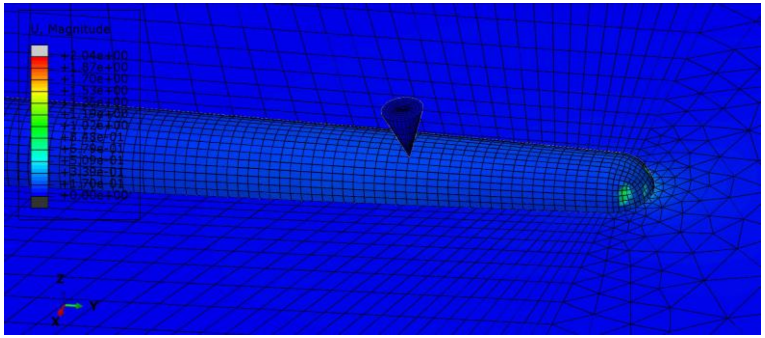
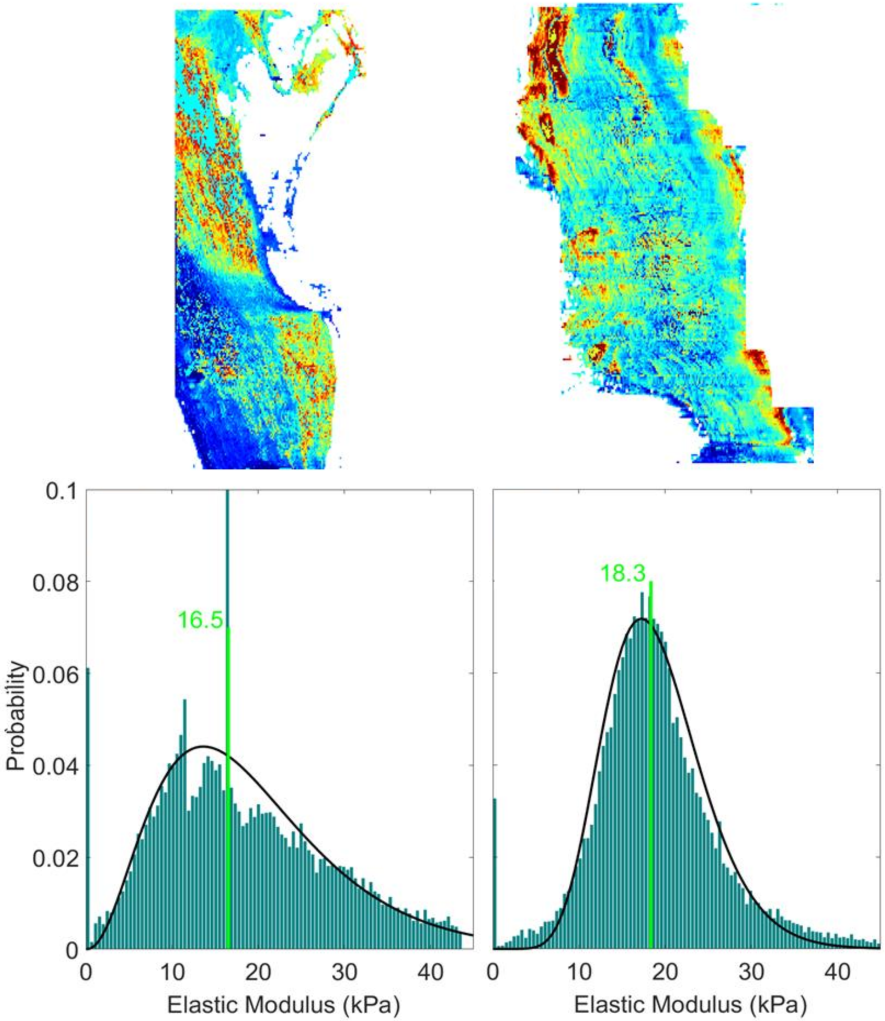
AFM nanoindentation of the cytoskeleton



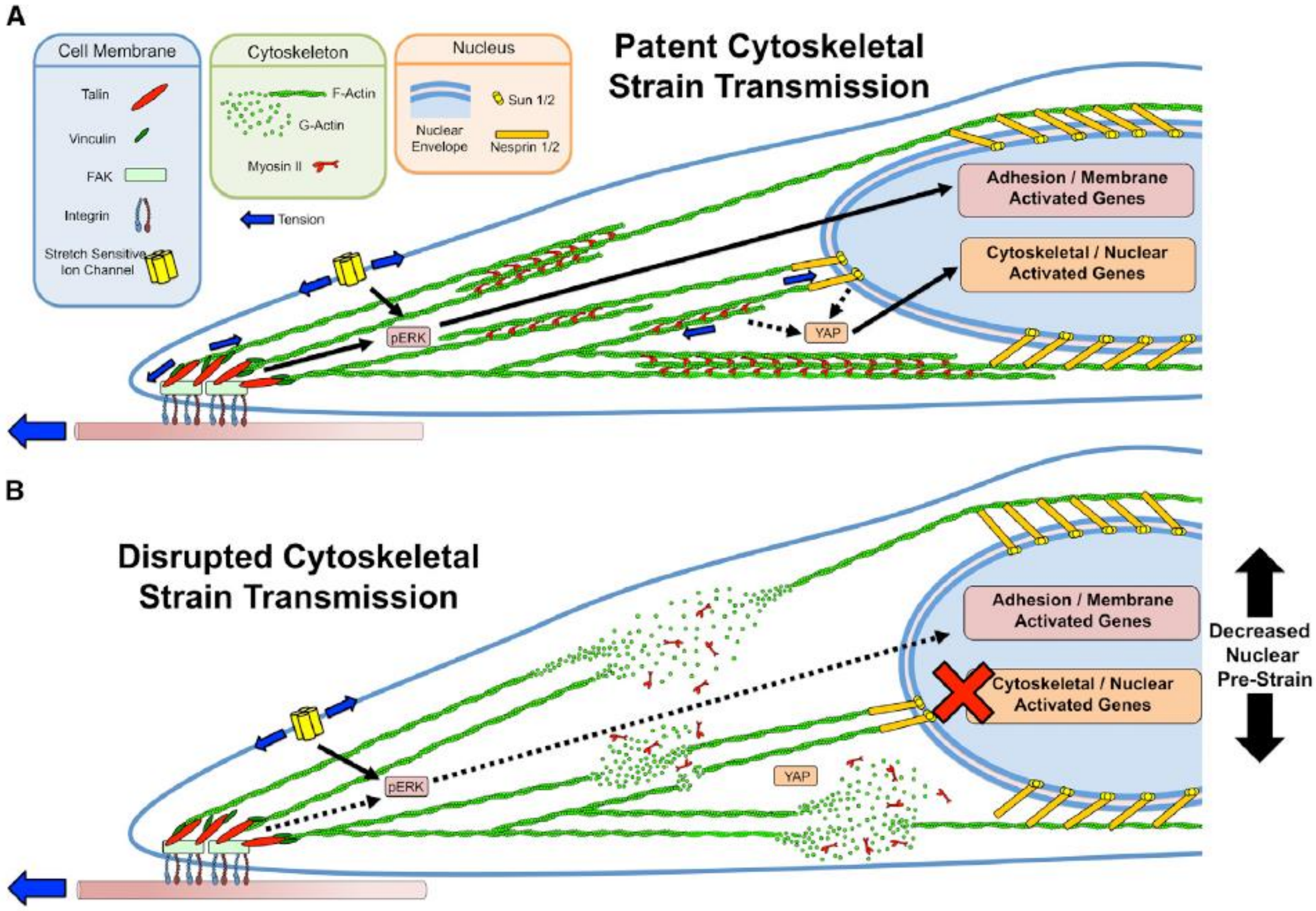




HEALTHY ANEURYSM



Linking cytoskeletal tension and tissue properties



SUMMARY AND FUTURE WORK

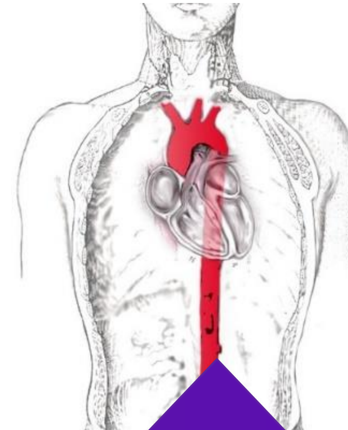
- There is a variety of smooth muscle cells with stronger ones responsible for tissue maintenance

- Cytoskeletal forces are linked to the tension of the extracellular matrix and to its stiffness

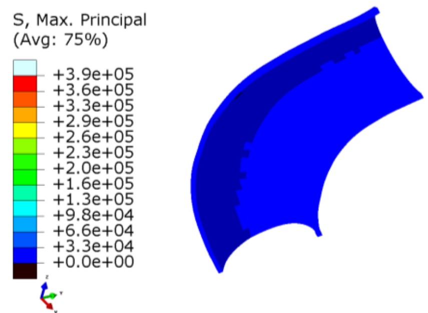
- Need to understand the internal mechanoregulation of the cell.

Need to monitor the biological counterpart

Monitoring mechanical regulation and epigenetics



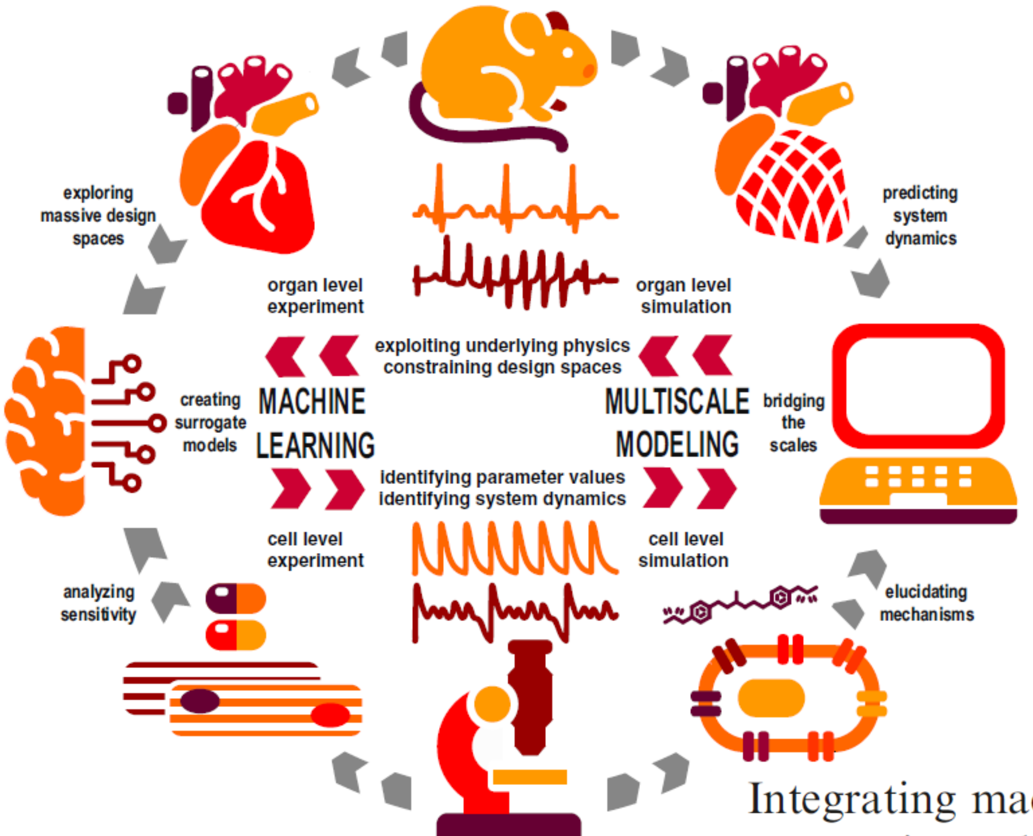
DIGITAL



TWIN

Predicting patient-specific pathophysiology and drug effects

Collaborative initiatives



MEDITATE

https://meditate-project.eu/

ESC European Society of Cardiology
European Heart Journal (2020) 0, 1–11
doi:10.1093/eurheartj/ehaa159
CLINICAL REVIEW
Frontiers in cardiovascular medicine

The 'Digital Twin' to enable the vision of precision cardiology

Jorge Corral-Acero[1], Francesca Margara [2], Maciej Marciniak [3], Cristobal Rodero [3], Filip Loncaric [4], Yingjing Feng [5,6], Andrew Gilbert [7], Joao F. Fernandes [3], Hassaan A. Bukhari[6,8], Ali Wajdan[9], Manuel Villegas Martinez[9], Mariana Sousa Santos[10], Mehrdad Shamohammdi[11], Hongxing Luo [11], Philip Westphal[12], Paul Leeson [13], Paolo DiAchille [14], Viatcheslav Gurev [14], Manuel Mayr [15], Liesbet Geris [16], Pras Pathmanathan[17], Tina Morrison[17], Richard Cornelussen[12], Frits Prinzen[11], Tammo Delhaas [11], Ada Doltra [4], Marta Sitges [4,18], Edward J. Vigmond [5,6], Ernesto Zacur [1], Vicente Grau [1], Blanca Rodriguez [2], Espen W. Remme[9], Steven Niederer [3], Peter Mortier[10], Kristin McLeod [7], Mark Potse [5,6,19], Esther Pueyo [8,20], Alfonso Bueno-Orovio [2], and Pablo Lamata [3*]

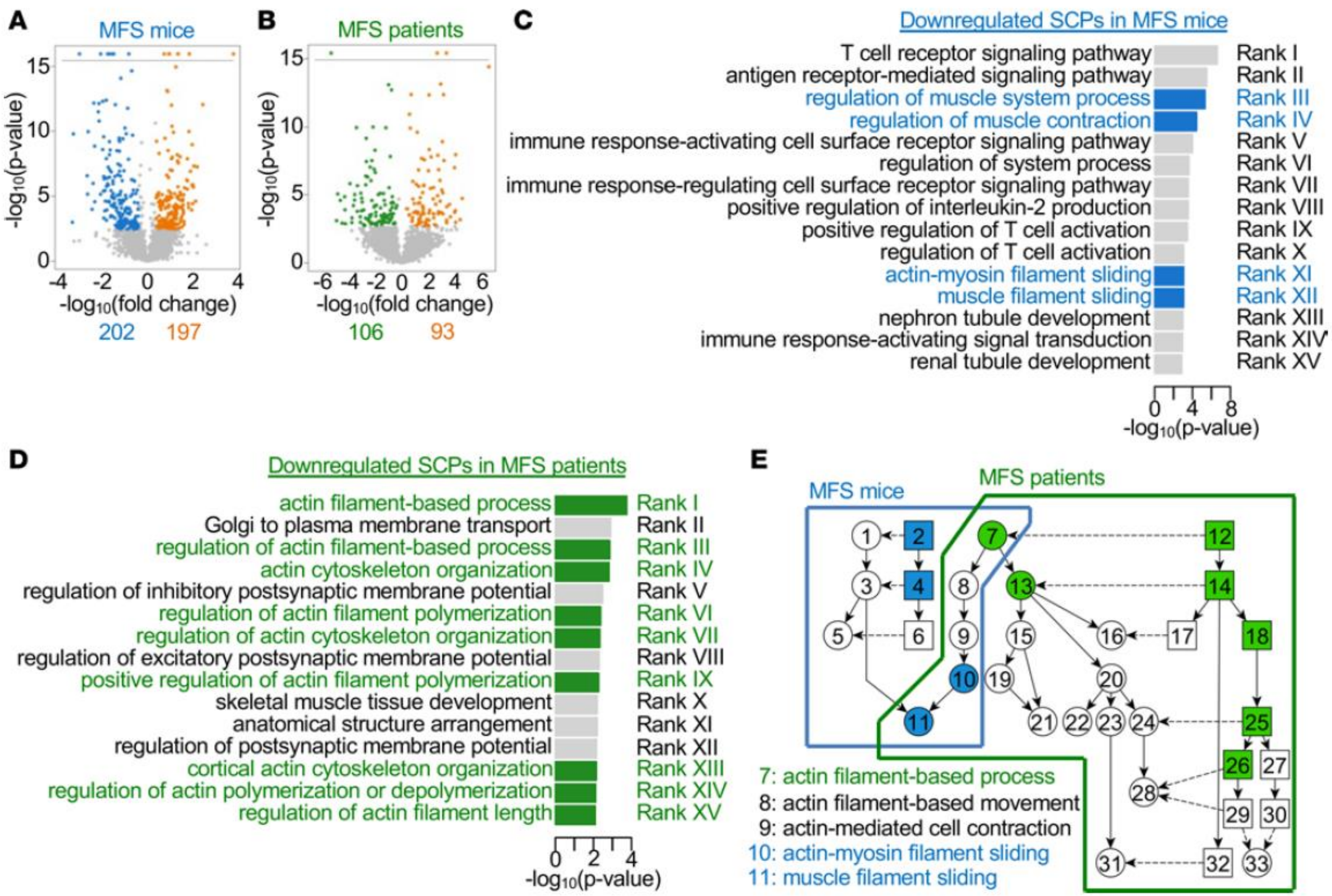
npj | Digital Medicine

Integrating machine learning and multiscale modeling—perspectives, challenges, and opportunities in the biological, biomedical, and behavioral sciences

Mark Alber[1], Adrian Buganza Tepole[2], William R. Cannon [3], Suvranu De[4], Salvador Dura-Bernal[5], Krishna Garikipati[6], George Karniadakis[7], William W. Lytton[5], Paris Perdikaris[8], Linda Petzold[9] and Ellen Kuhl [10*]

JCI insight

Systems pharmacology–based integration of human and mouse data for drug repurposing to treat thoracic aneurysms



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