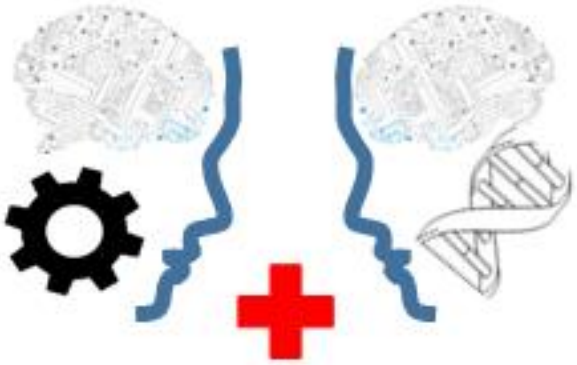
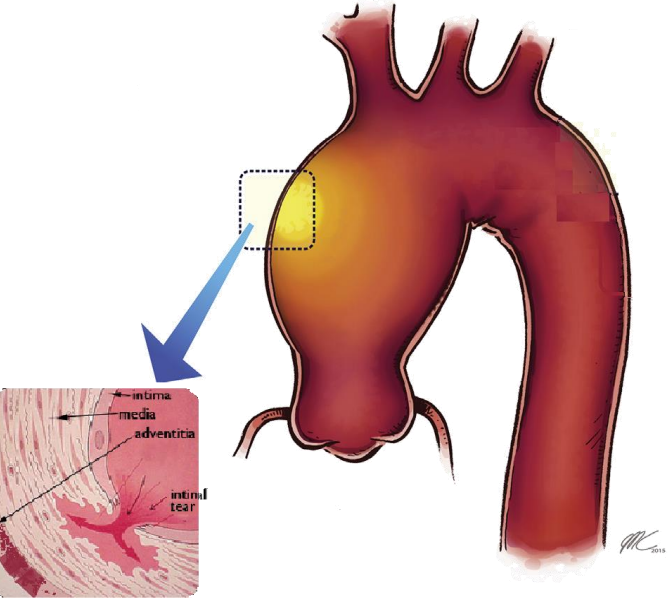


MINES Saint-Étienne
Une école de l'IMT



Digital twin: the journey towards better healthcare - Applications in cardiovascular medicine

SAINBIOSE
SAnté INgéniérie 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

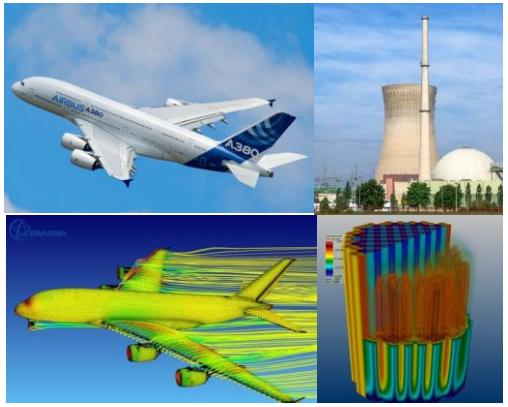
- PART I: Can computer models predict human health?
- PART II: The need of combining data driven and mechanistic models in cardiovascular mechanobiology
- PART III: From computer models to digital twins enabling precision medicine

OUTLINE

- **PART I: Can computer models predict human health**
- PART II: The need of combining data driven and mechanistic models in cardiovascular mechanobiology
- PART III: From computer models to digital twins enabling precision medicine

Numerical simulation was commonplace in automotive and aeronautics industry

In any other industrial sector



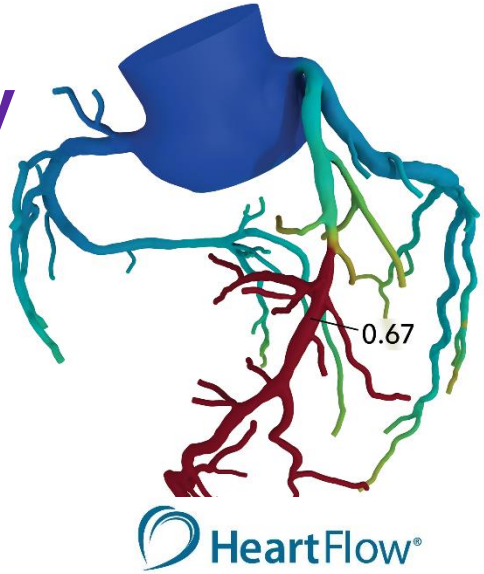
Testing is now done mostly with computer simulation

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

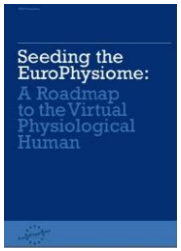
Since 1989: a 30+ years journey



Physiome Project

1993: Physiome

2005: VPH



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

2016: Avicenna

Computational models can predict health!! They even enable decisions everyday in healthcare thanks to 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.

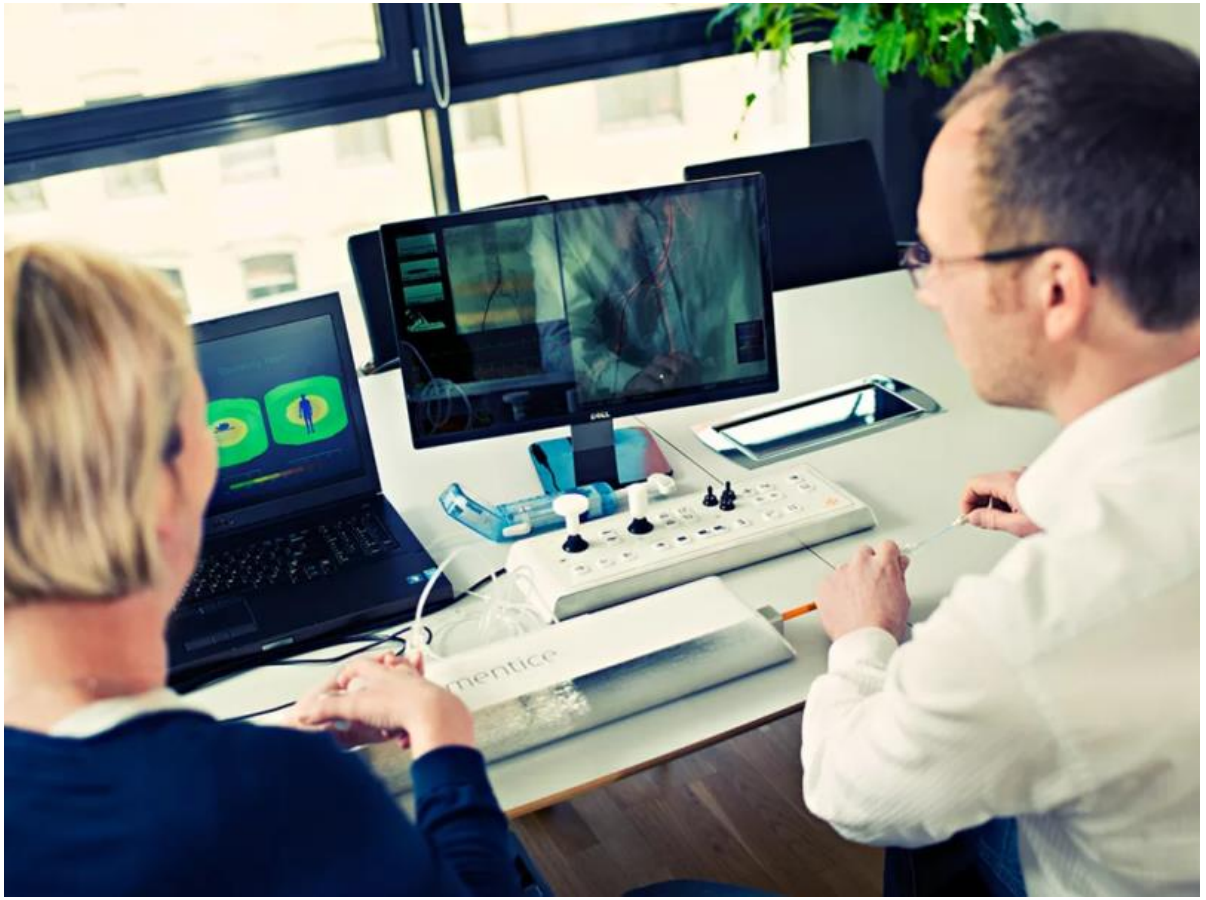
2019: FEops HEARTguide in silico tool for planning transcatheter aortic valve implantation is CE-marked

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

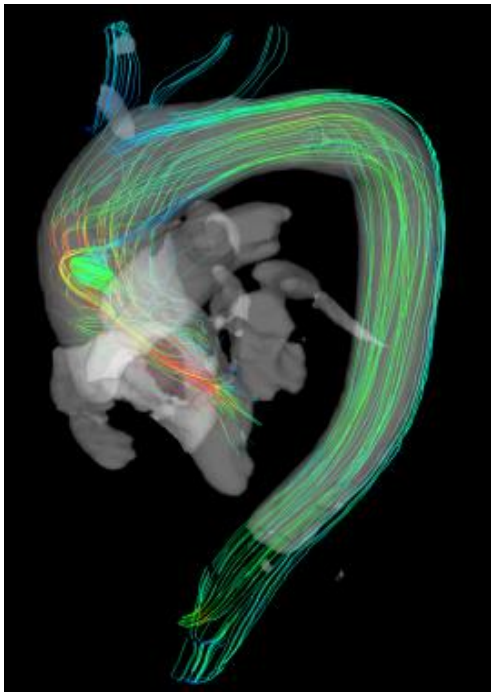
2014: Sim&Cure

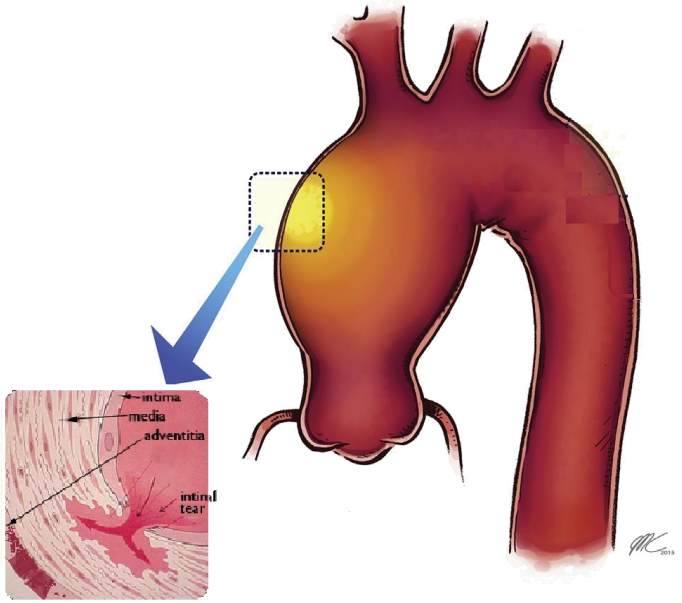
2017: Predisurge

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



Aneurysms and Dissections of the aorta

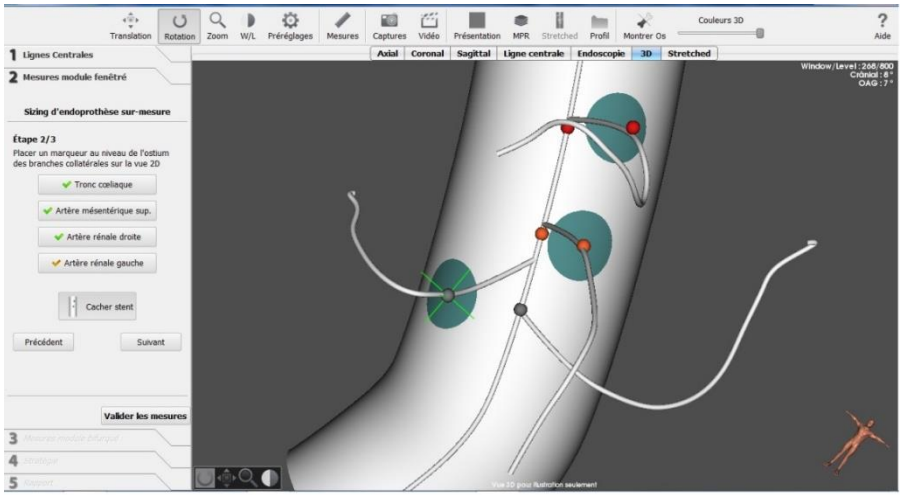


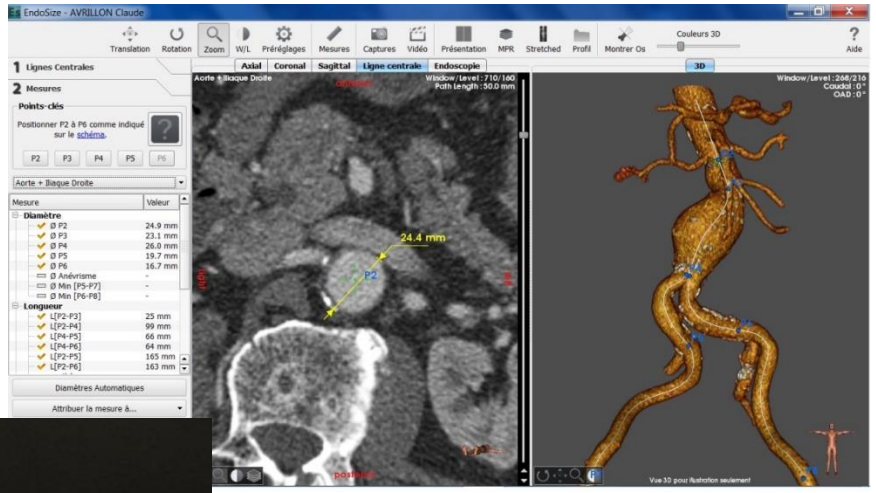


== Devastating complications!

avril@emse.fr

Planification / sizing of fenestrated stent grafts in EVAR procedures





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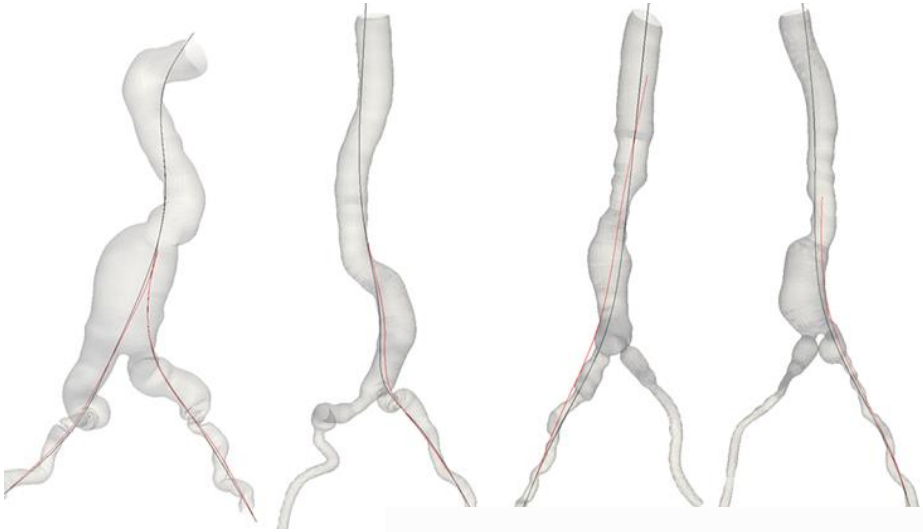
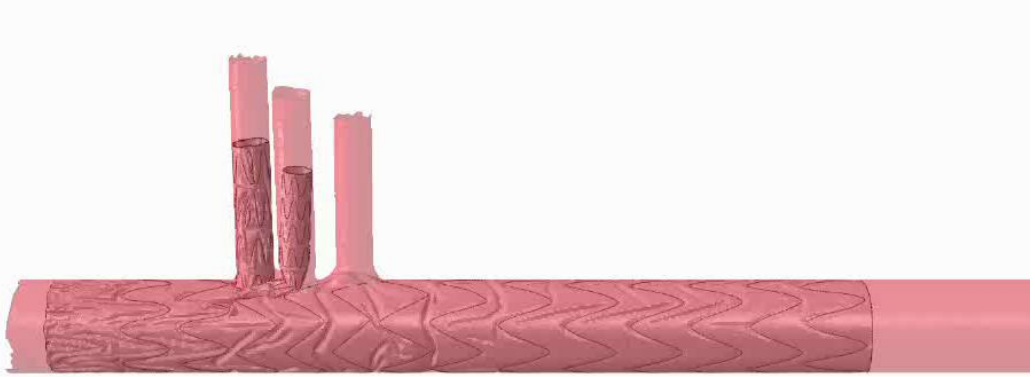
Une école de l'IMT

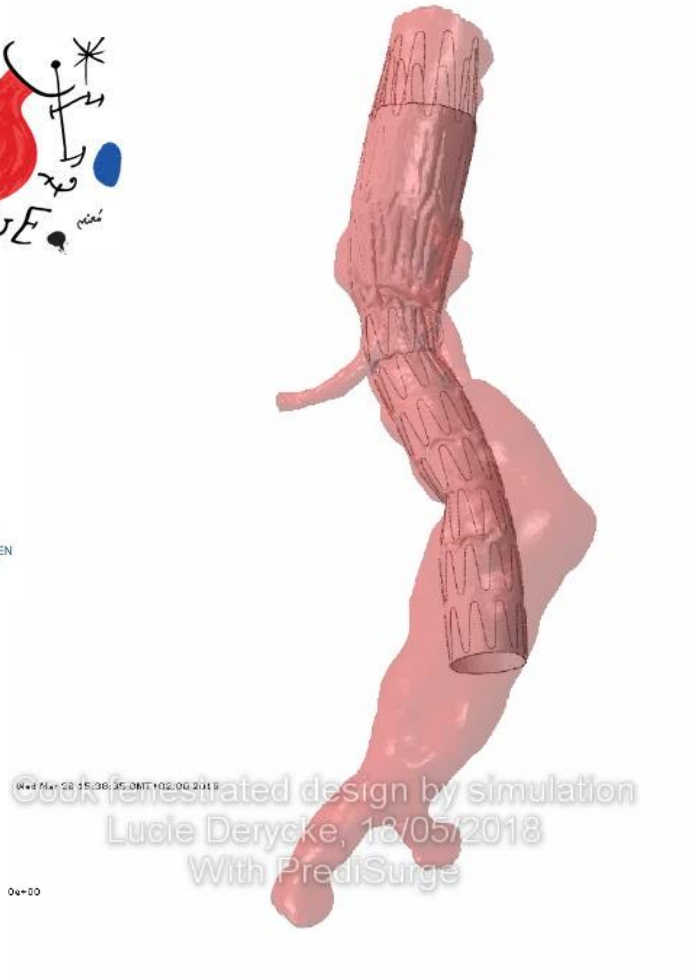
Simulation of stent-graft deployment

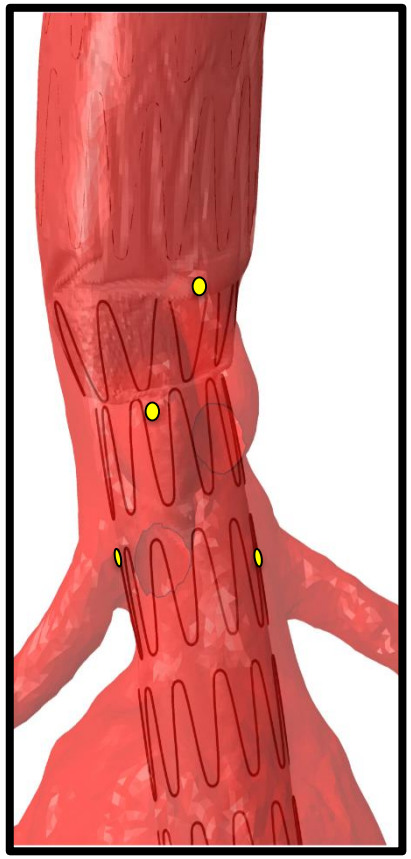


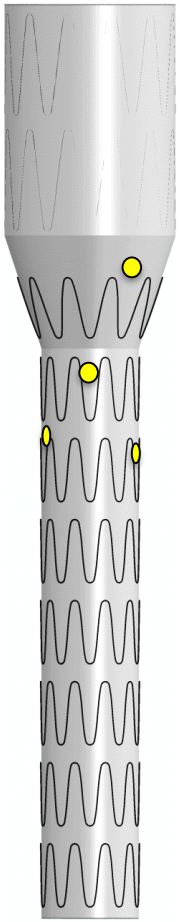


avril@emse.fr

Clinically validated for FEVAR Zenith® Cook Medical







OUTLINE

- PART I: Can computer models predict human health
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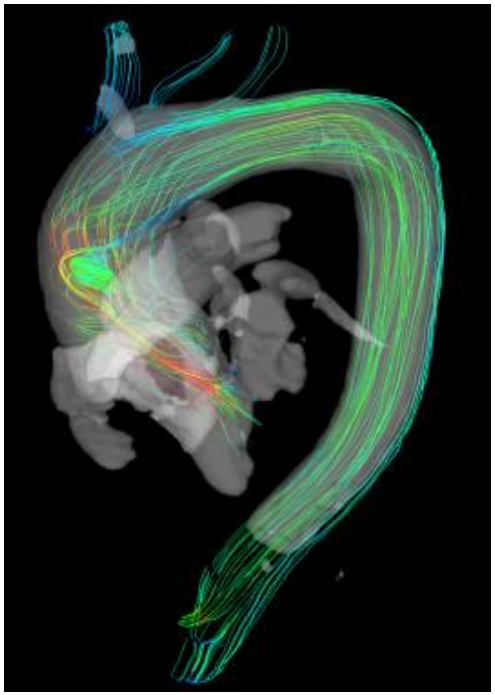
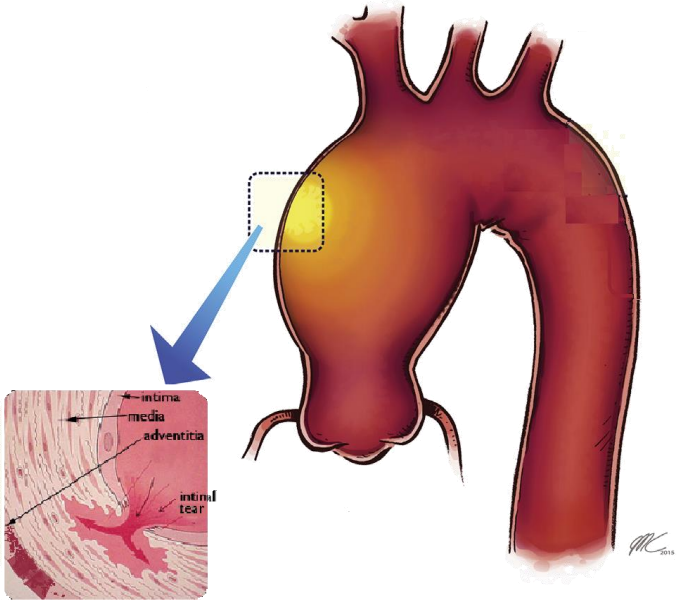
Aneurysms and Dissections of the aorta

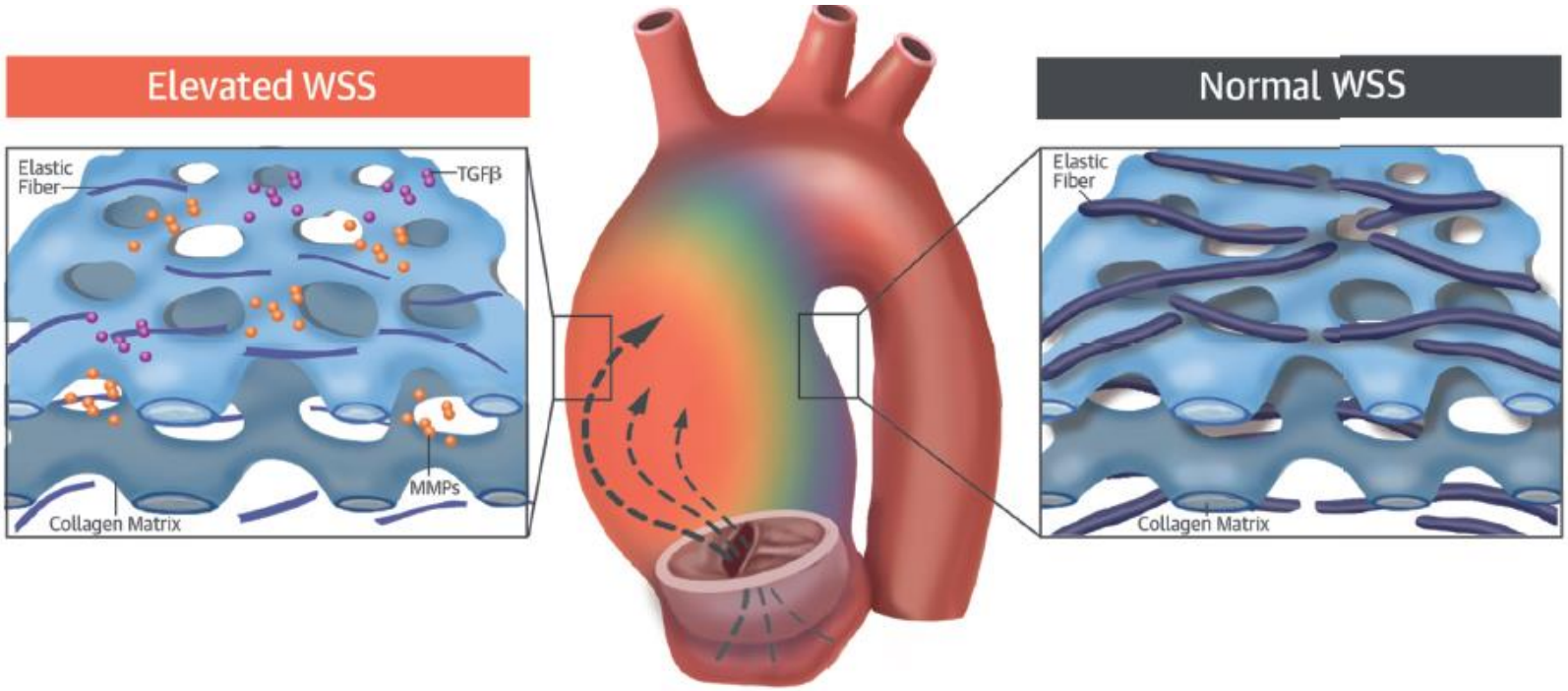




Challenge: decision making to avoid aortic dissections!

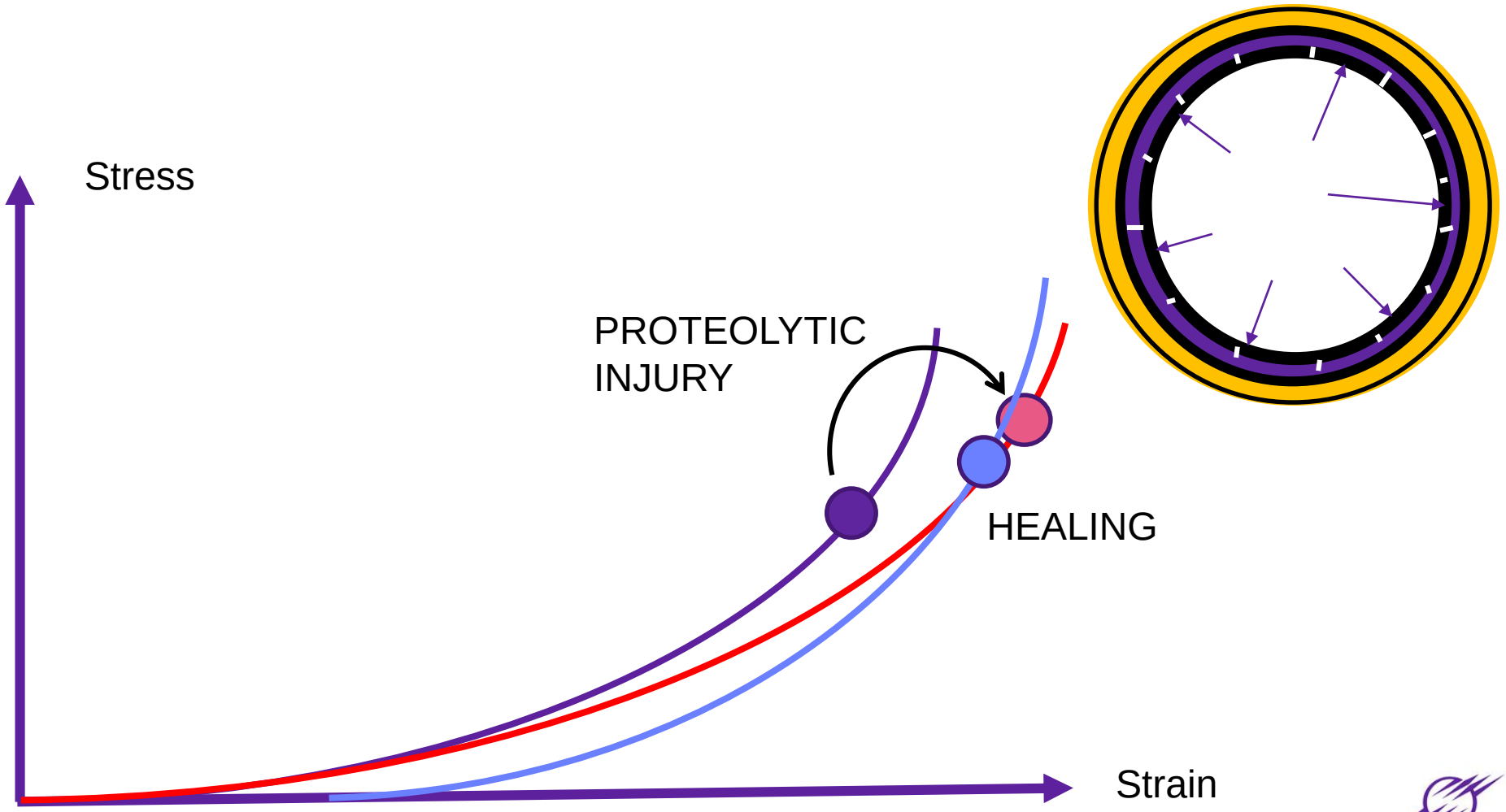
Mechanistic approach

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



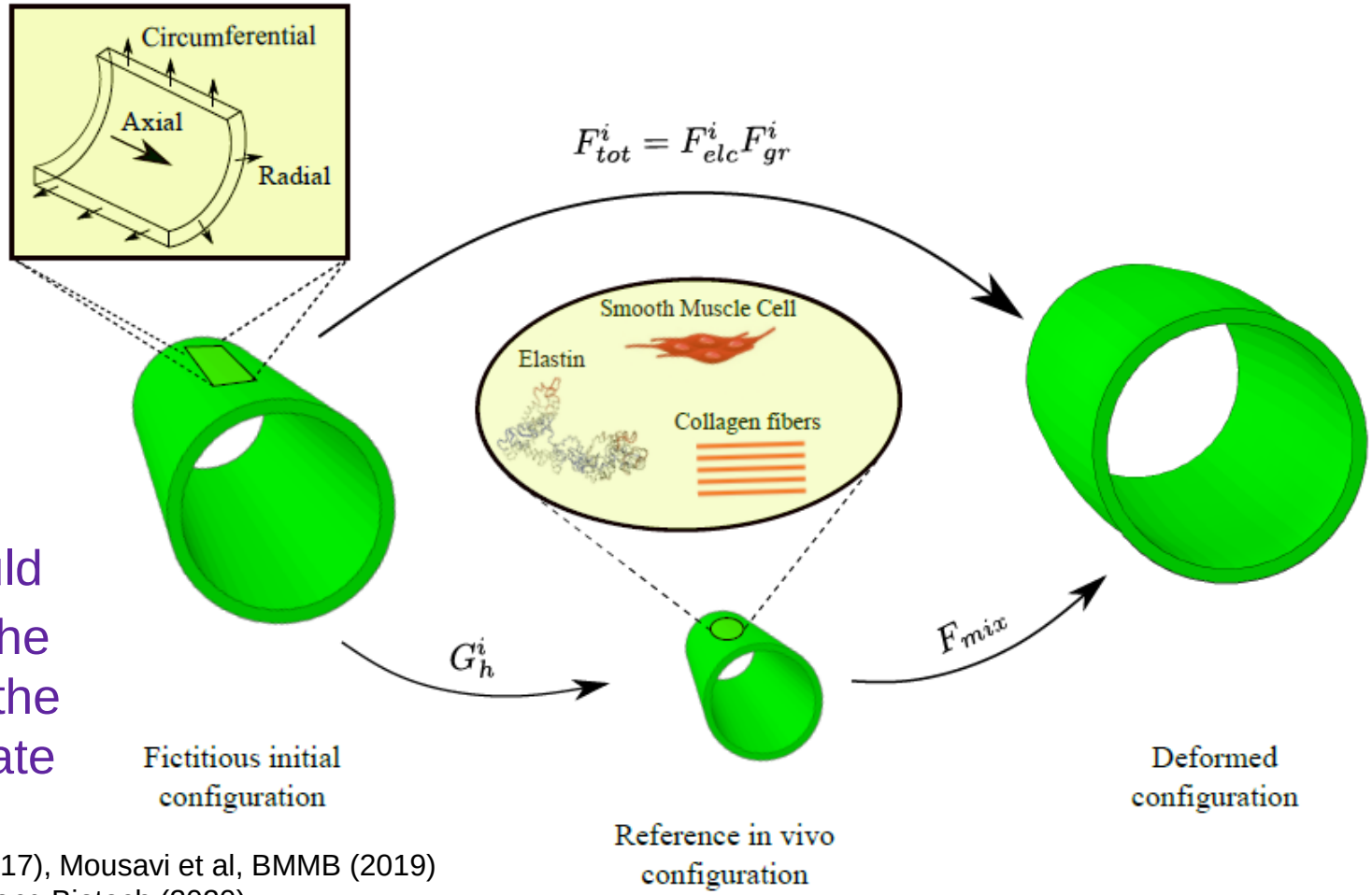
Mechanistic approach

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)

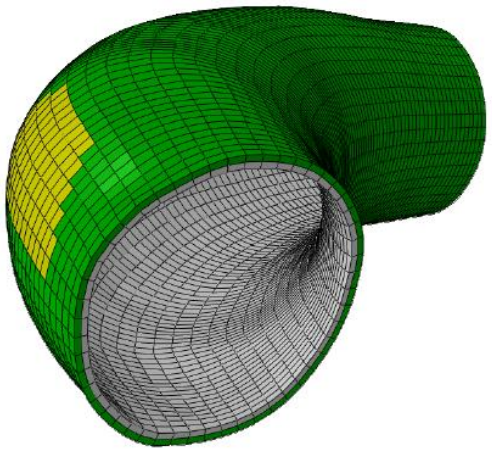
Mechanistic approach

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

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

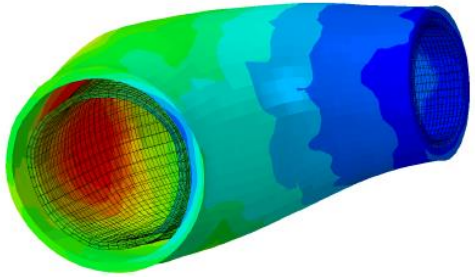
$$\dot{\varrho}^{\mathrm{e}} = -\frac{\varrho^{\mathrm{e}}(\mathbf{X},t)}{T^{\mathrm{e}}} - \frac{D_{\max}}{t_{\mathrm{dam}}}\varrho^{\mathrm{e}}(\mathbf{X},0)e^{-0.5\left(\frac{X_3}{L_{\mathrm{dam}}}\right)^2 - \frac{t}{t_{\mathrm{dam}}}}$$

Localization function around the point of TAWSS max



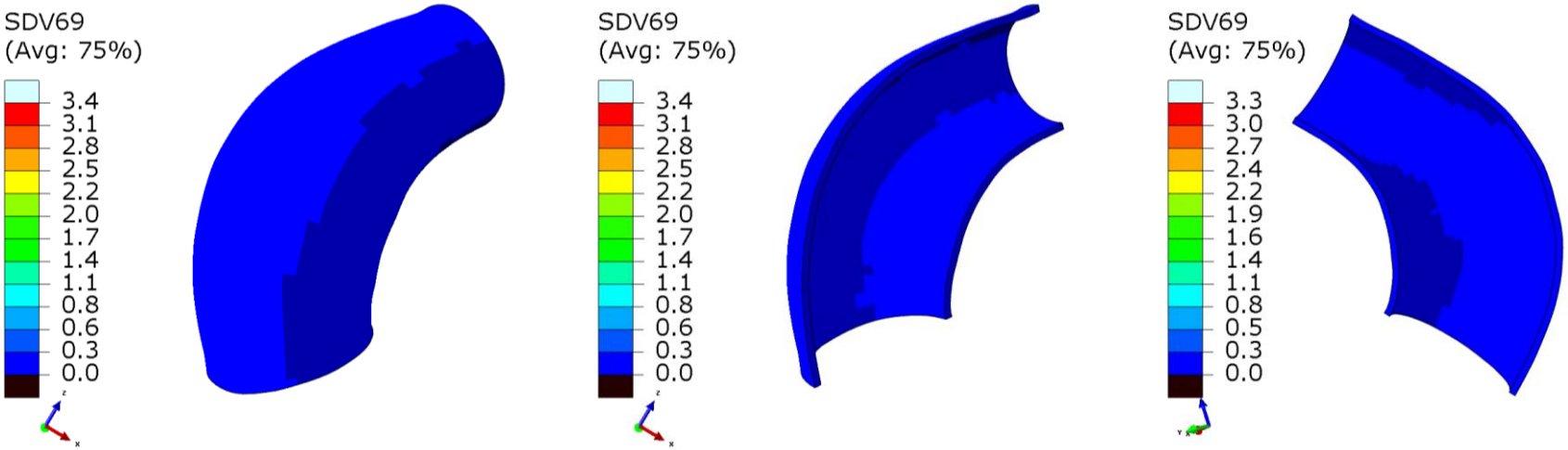
Mousavi et al, BMMB (2019)

Patient-specific predictions



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

Small growth parameter

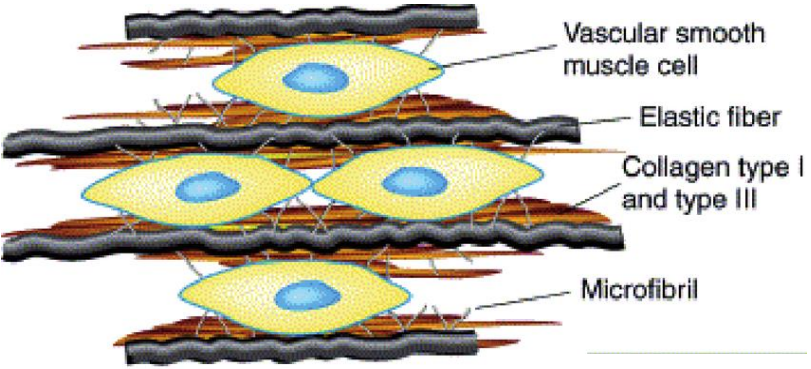


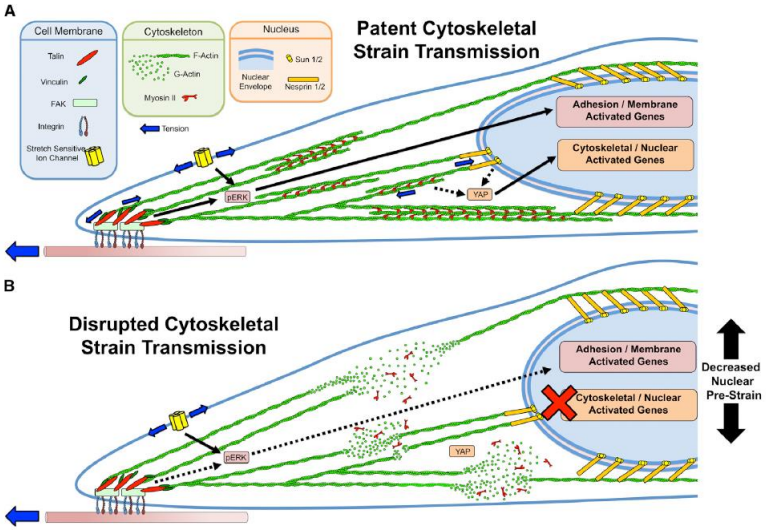
Normalized Thickness

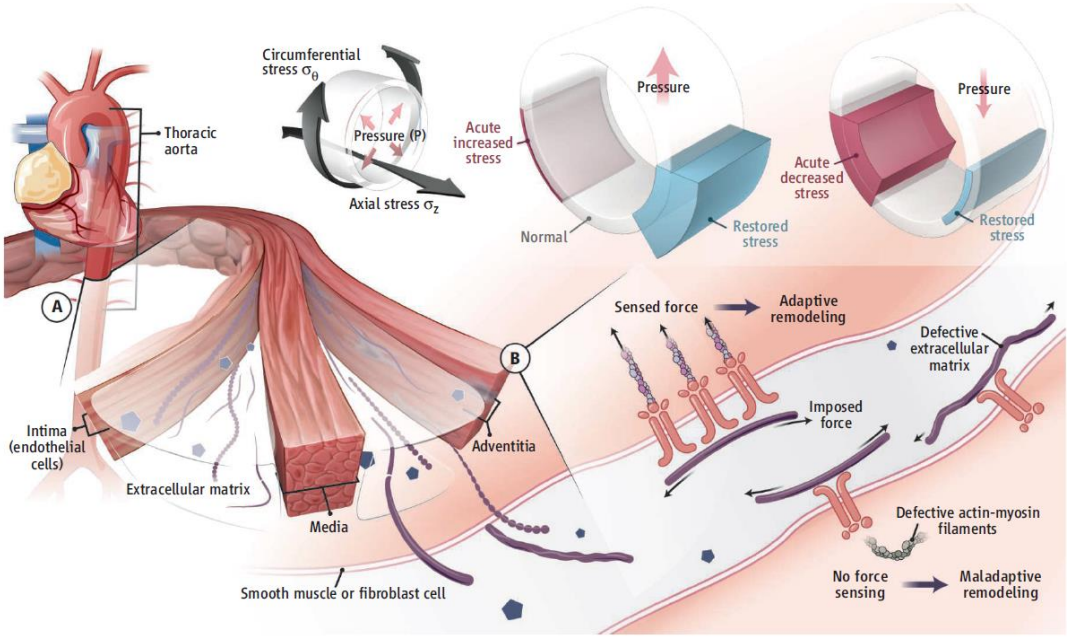
Mousavi et al, BMMB (2019)

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

Difficulties related to the uncertainty of molecular and cellular biology



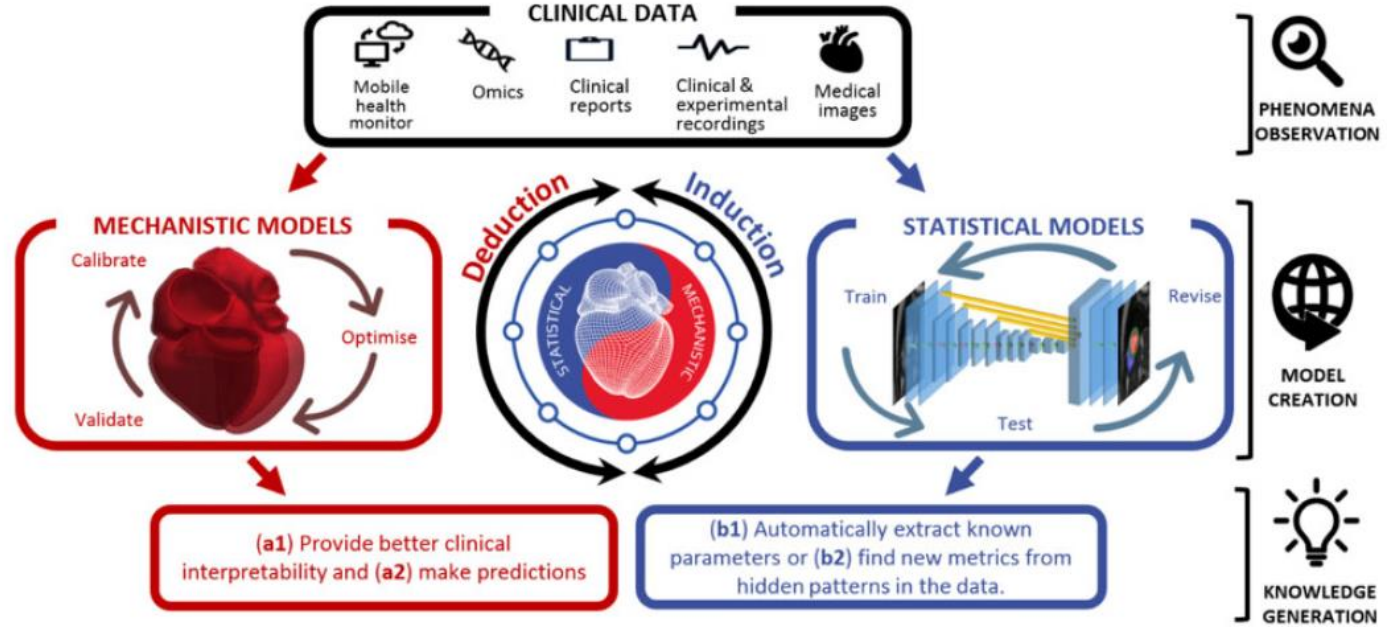


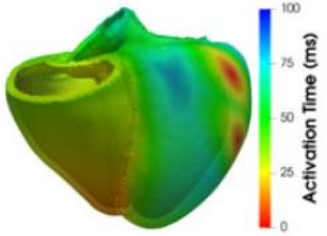


Humphrey et al, Science 2014

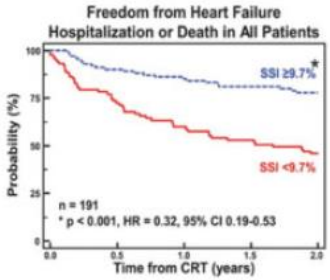
Solution: combining statistical models and the mechanistic approach

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

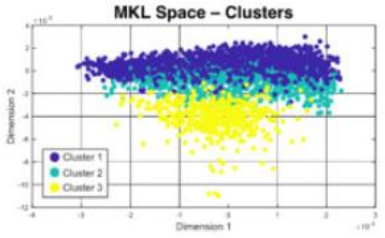




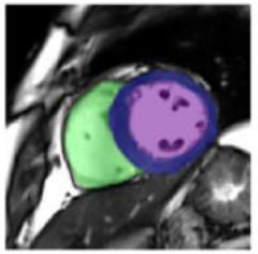
a1) Patient-specific electromechanical computer simulations



a2) A strain-based parameter based on myofiber mechanics simulations can help to predict CRT therapy response

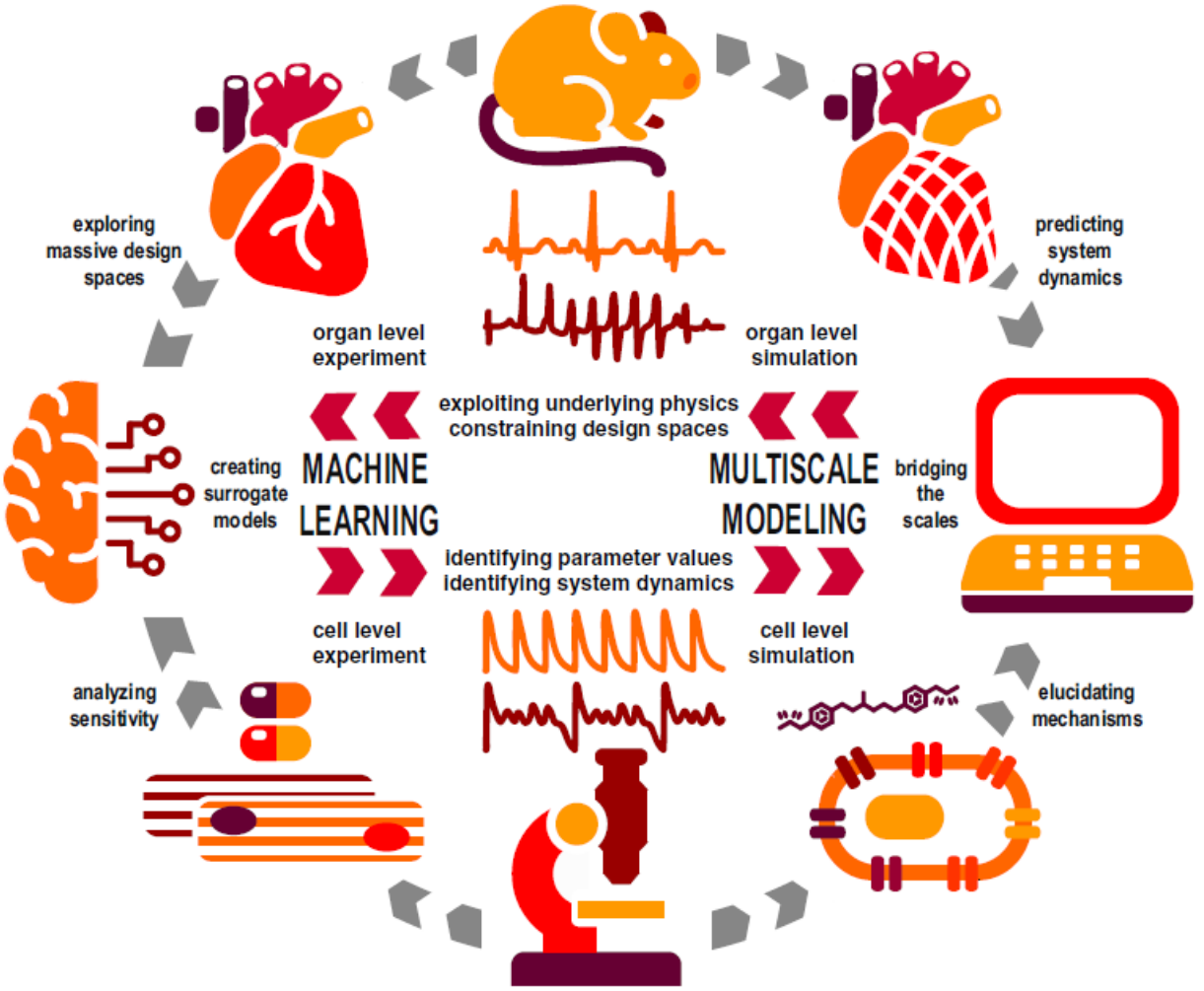


b2) Unsupervised machine learning can integrate clinical data to predict outcomes and categorize patients based on similarity



b1) Automatic cardiac MR segmentation using a deep learning neural network

Combining machine learning and traditional modeling



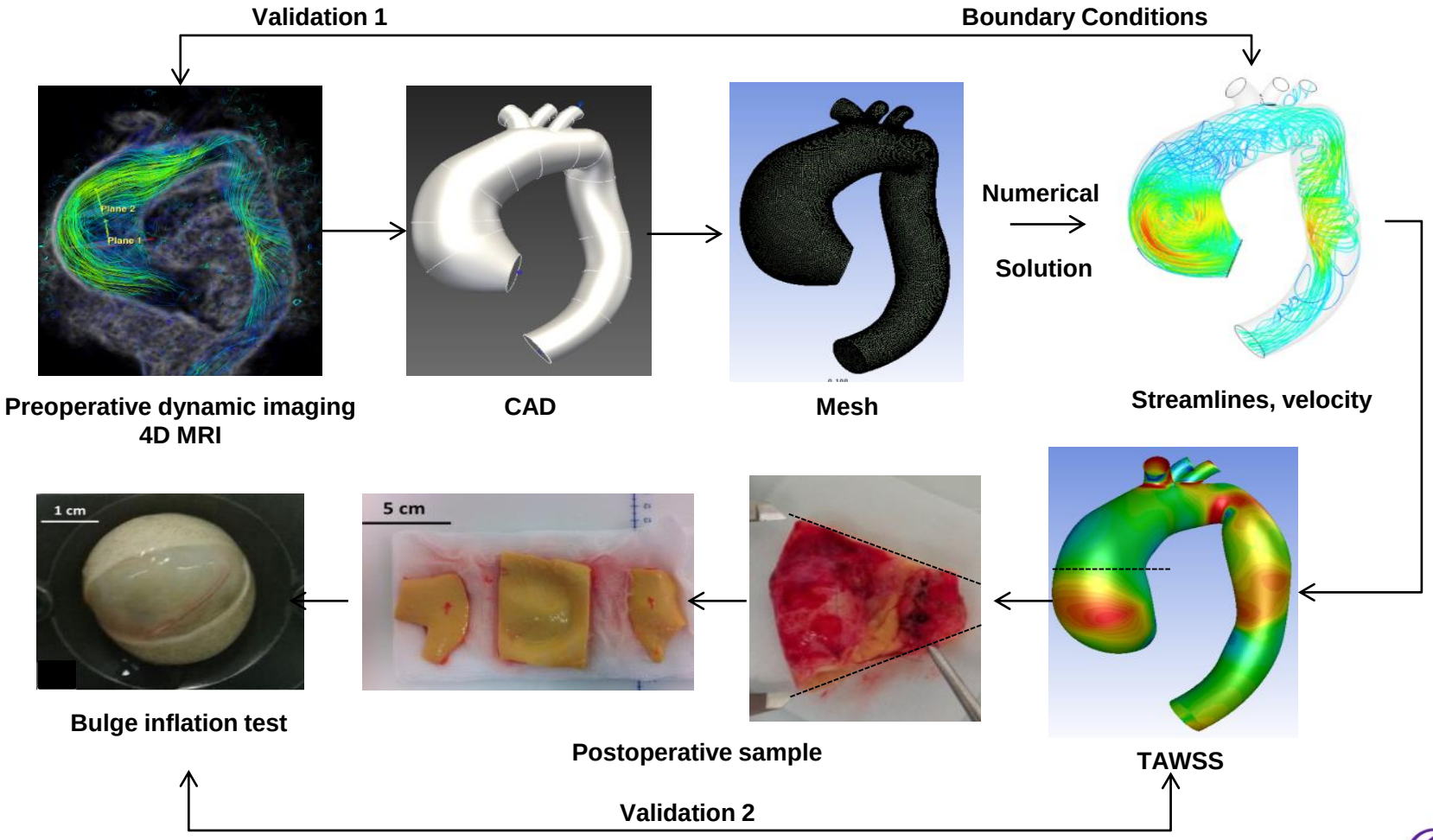
npj | Digital Medicine

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

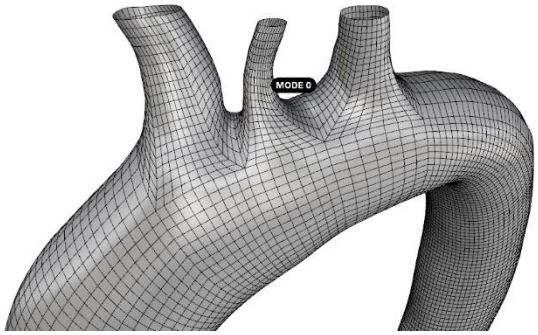
Mark Alber[1], Adrian Buganza Tepole[2], William R. Cannon[3], Suvranu De[4], Salvador Dura-Bernal[5], Krishna Garikipati[6], George Karniadakis[7], William W. Lytton[5], Paris Perdikaris[8], Linda Petzold[9] and Ellen Kuhl[10*]

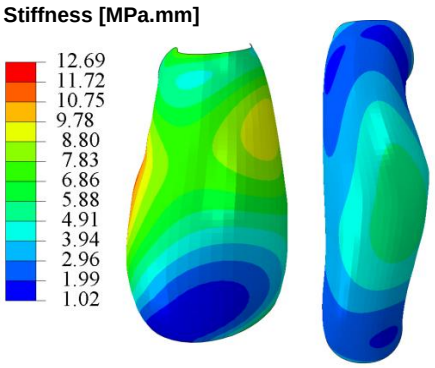
MINES Saint-Étienne

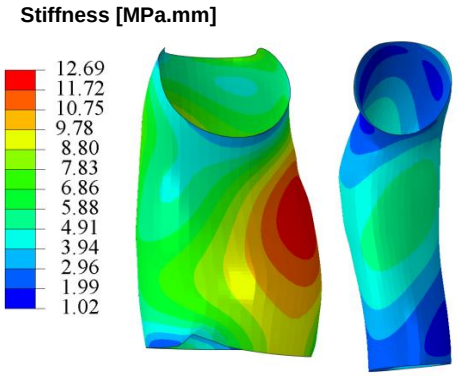
Learn boundary conditions, material properties and initial conditions from image analysis

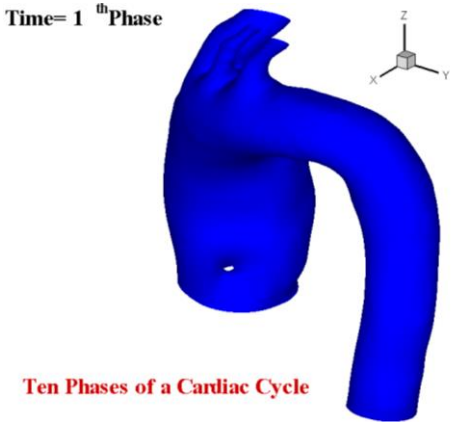


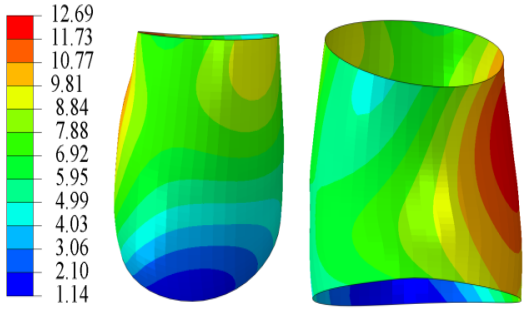
Learn boundary conditions, material properties and initial conditions from image analysis

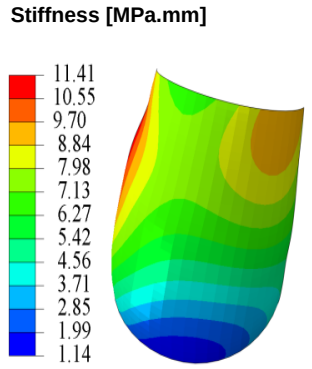




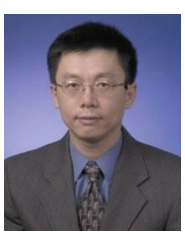




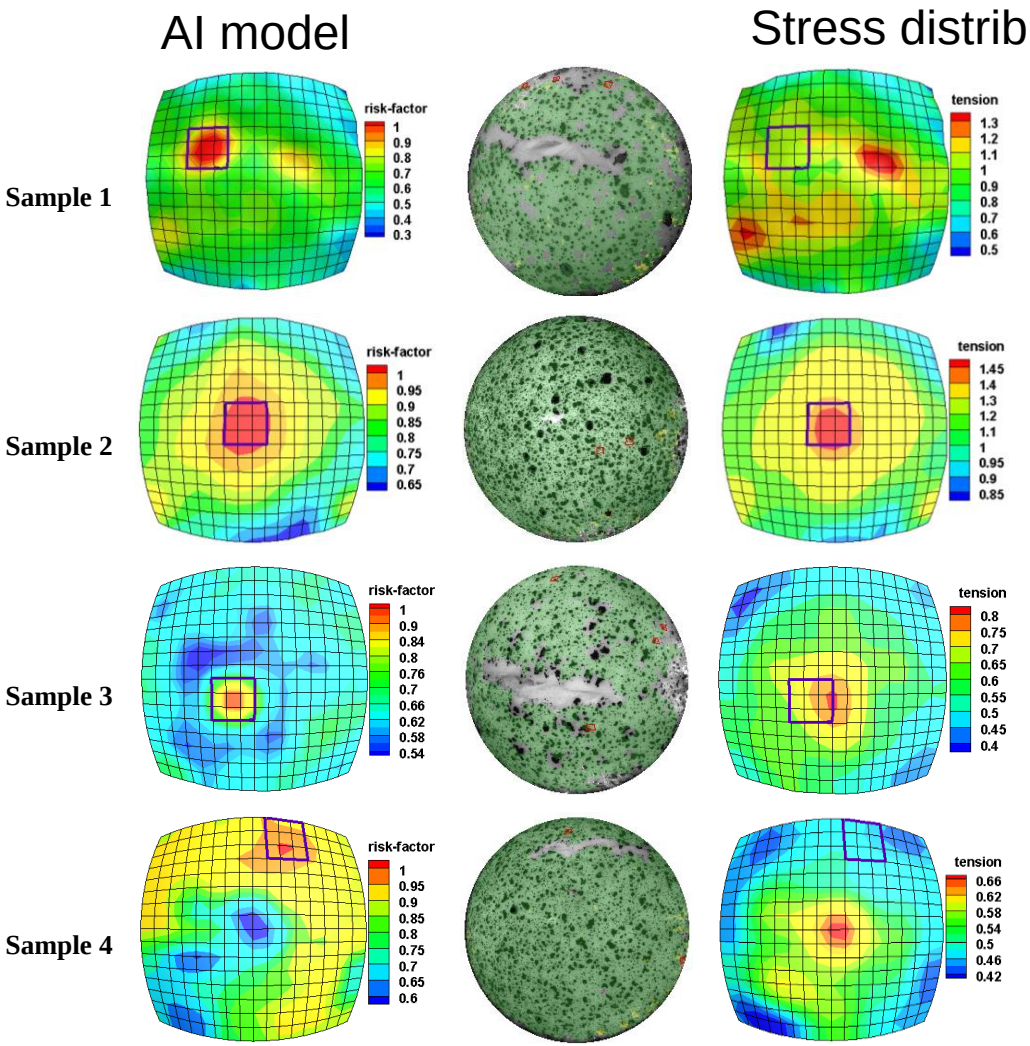




AI model of rupture criterion…



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

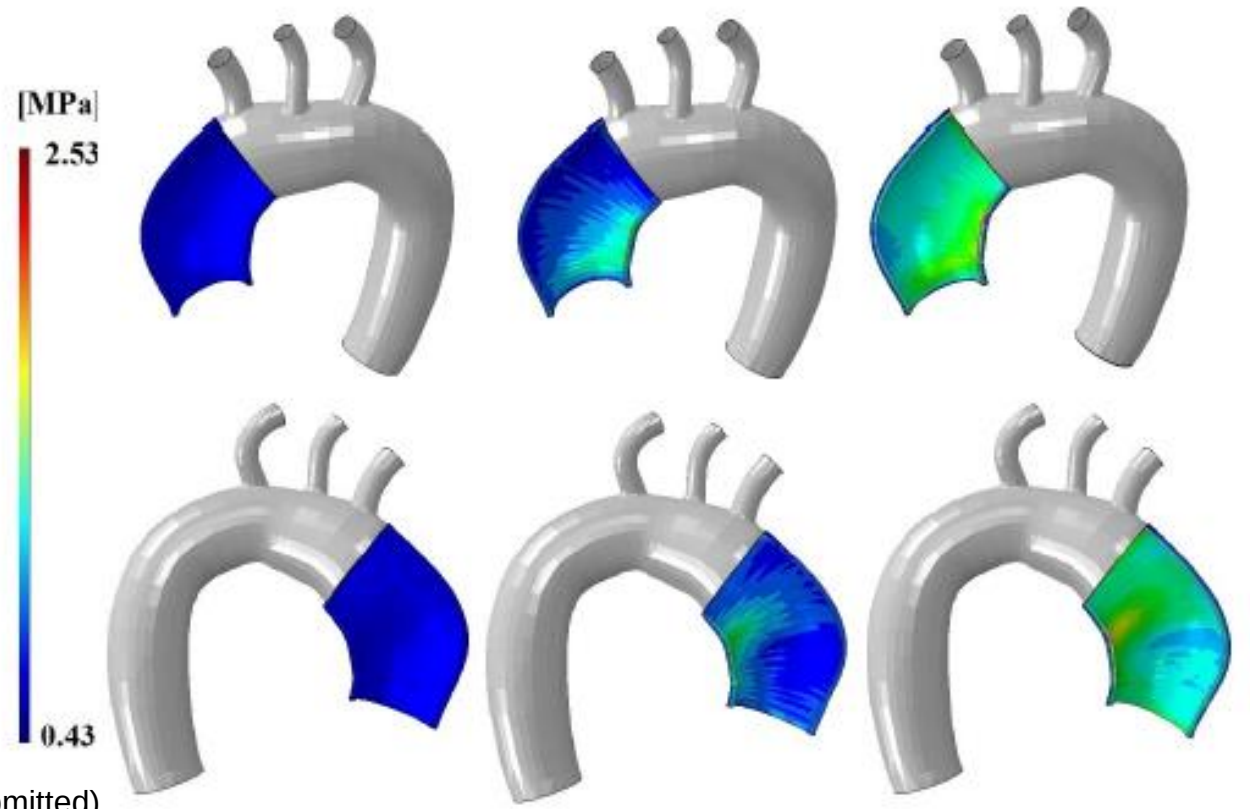


Defining patient subgroups depending on genetic factors

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

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

Tangent stiffness after 10 years



Mousavi et al, ABME (2020, submitted)

MINES Saint-Étienne
Une école de l'IMT

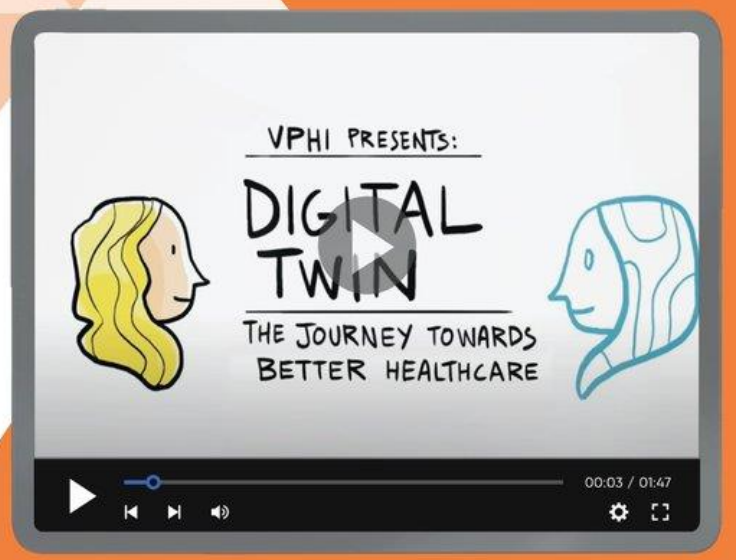
OUTLINE

- PART I: Material stiffness is a predictor for aortic rupture
- PART II: The need of combining data driven and mechanistic models in cardiovascular mechanobiology
- **PART III: From computer models to digital twins enabling precision medicine**

Collaborative initiatives

VPH Institute
Building the Virtual Physiological Human

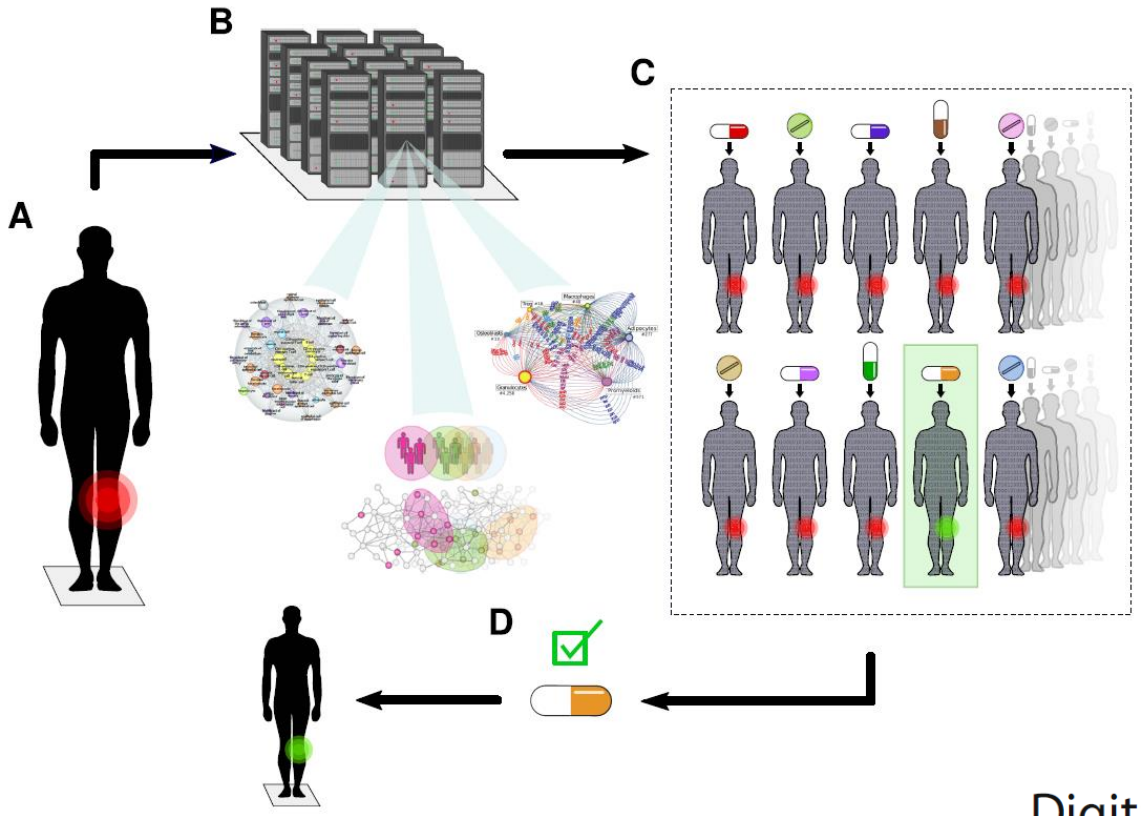
A quick video to explain the **Digital Twin** in very simple terms



Collaborative initiatives

MEDITATE

https://meditate-project.eu/



Genome Medicine

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

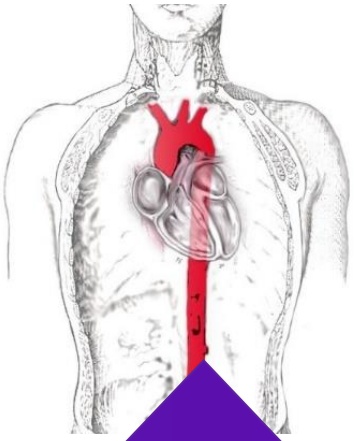
Jorge Corral-Acero[1], Francesca Margara[2], Maciej Marciniak[3], Cristobal Rodero[3], Filip Loncaric[4], Yingjing Feng[5,6], Andrew Gilbert[7], Joao F. Fernandes[3], Hassaan A. Bukhari[6,8], Ali Wajdan[9], Manuel Villegas Martinez[9], Mariana Sousa Santos[10], Mehrdad Shamohammdi[11], Hongxing Luo[11], 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]*

Digital twins to personalize medicine

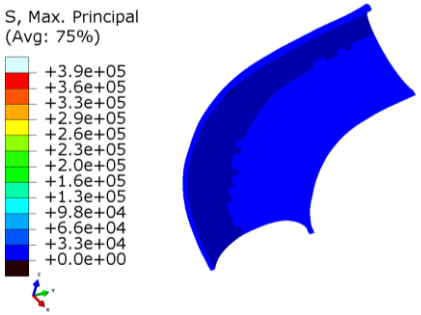
Bergthor Björnsson[1], Carl Borrebaeck[2], Nils Elander[3], Thomas Gasslander[1], Danuta R. Gawe
Rebecka Jörnsten[6], Eun Jung Lee[4,7], Xinxiu Li[4], Sandra Lilja[4], David Martínez-Enguita[5], And
Per Sandström[1], Samuel Schäfer[4], Margaretha Stenmarker[10,11], X. F. Sun[3], Oleg Sysoev[12], H
Mikael Benson[4,13,14]* and on behalf of the Swedish Digital Twin Consortium

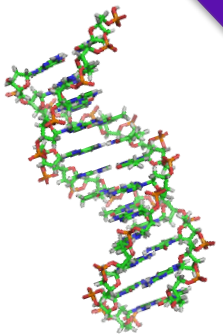
Need to monitor the biological counterpart

Monitoring mechanical regulation and epigenetics



DIGITAL





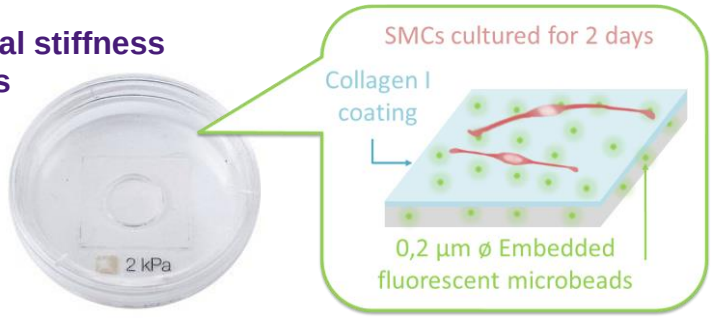
TWIN

Predicting patient-specific pathophysiology and drug effects

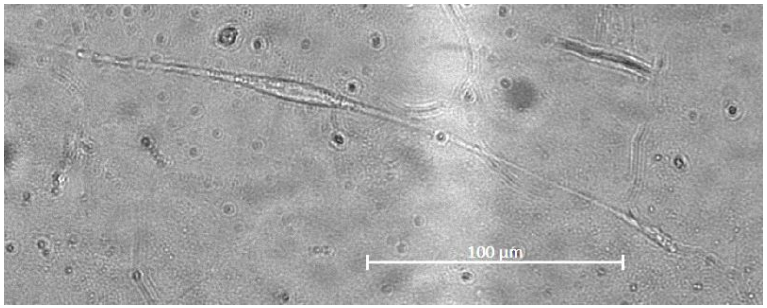
avril@emse.fr

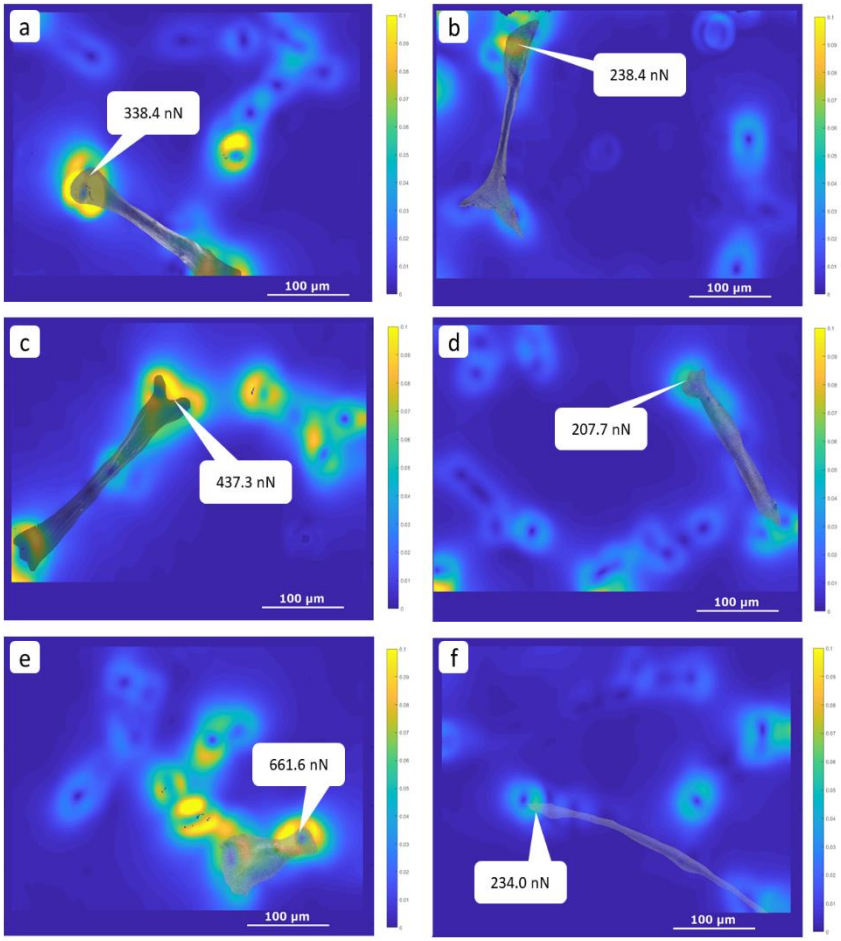
Monitoring mechanobiology *in vivo*

Several stiffness values



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

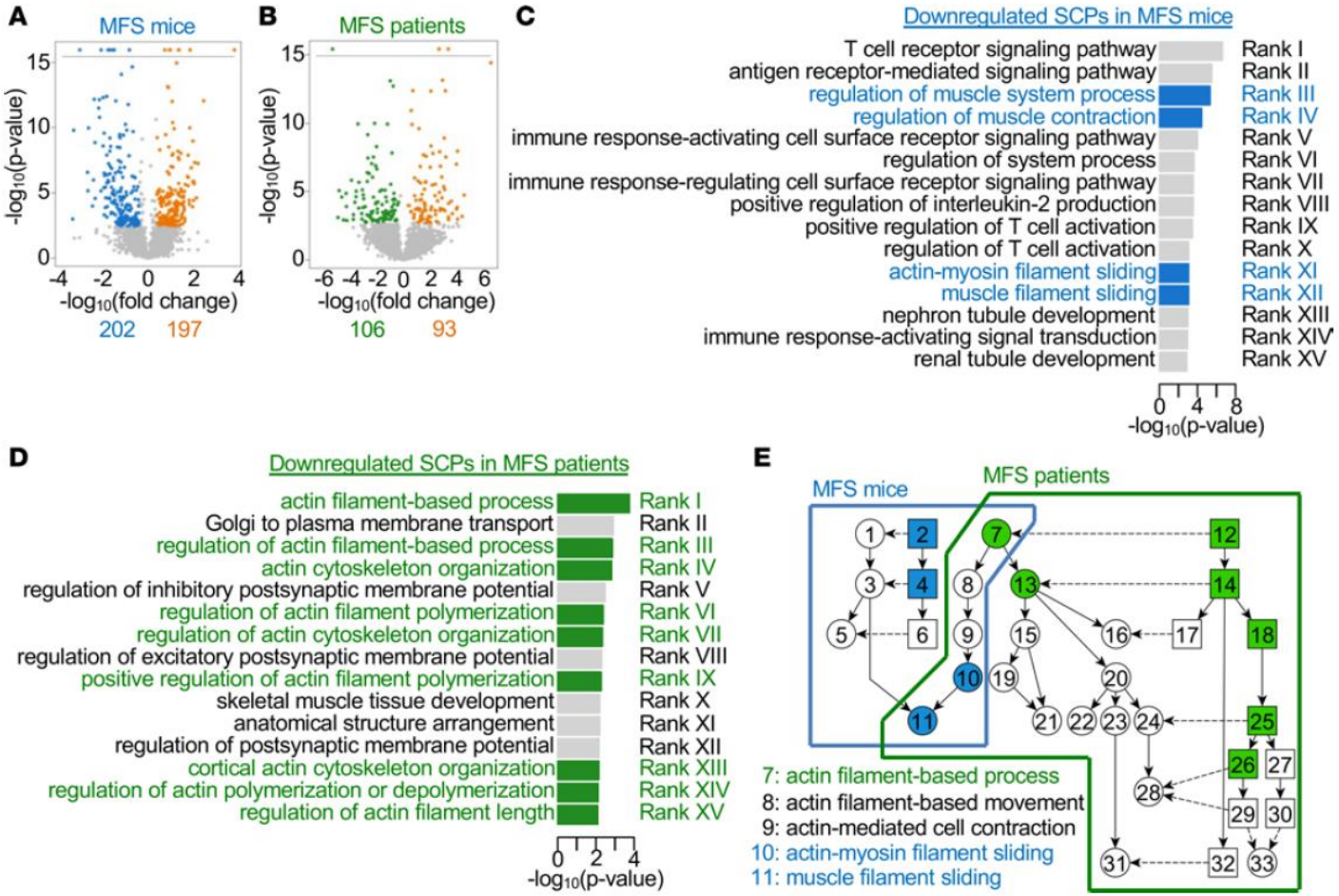




- **Fluorescent microscopy + DIC :** track the displacement of fluorescent microbeads
- **Cell unbinding method (with trypsin) :** assess the homeostatic state of single SMCs

JCI insight

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



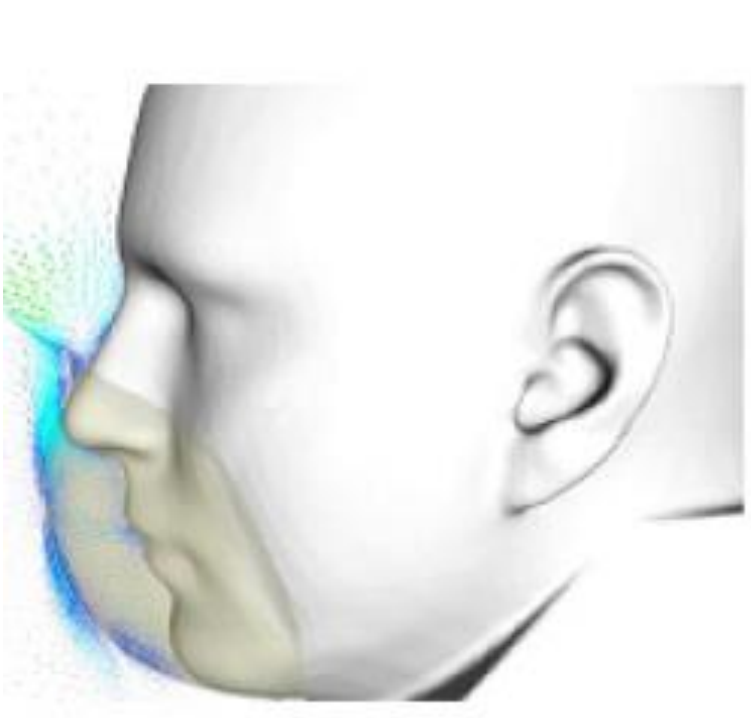
avril@emse.fr

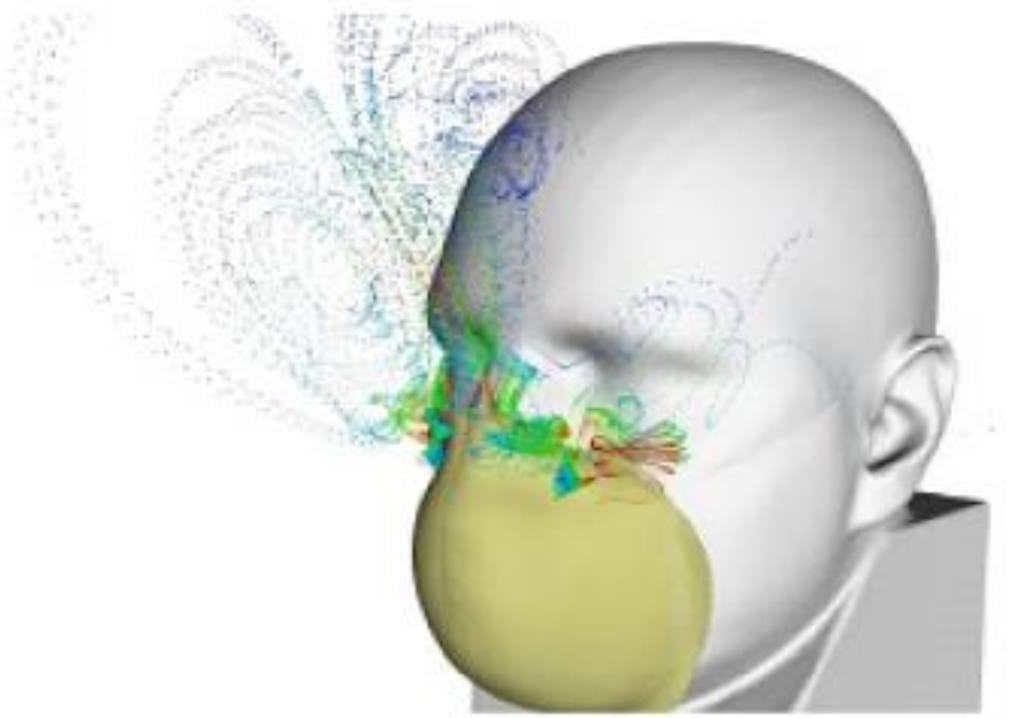
MINES Saint-Étienne
Une école de l'IMT

SUMMARY AND FUTURE WORK

- Computational models combining AI and mechanics are now used commonly in healthcare for developing medical devices and drugs
- Major challenges still need to be overcome to go beyond the virtual patient and establish digital twins of oneself
- Simple mechanistic models will always be useful!!

Wear a mask!





avril@emse.fr

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