INSIGNEO

Institute for *in silico* Medicine

ARTERIAL PHYSIOLOGY IN HEALTH AND DISEASE: THE FUTURE OF COMPUTATIONAL MODELLING

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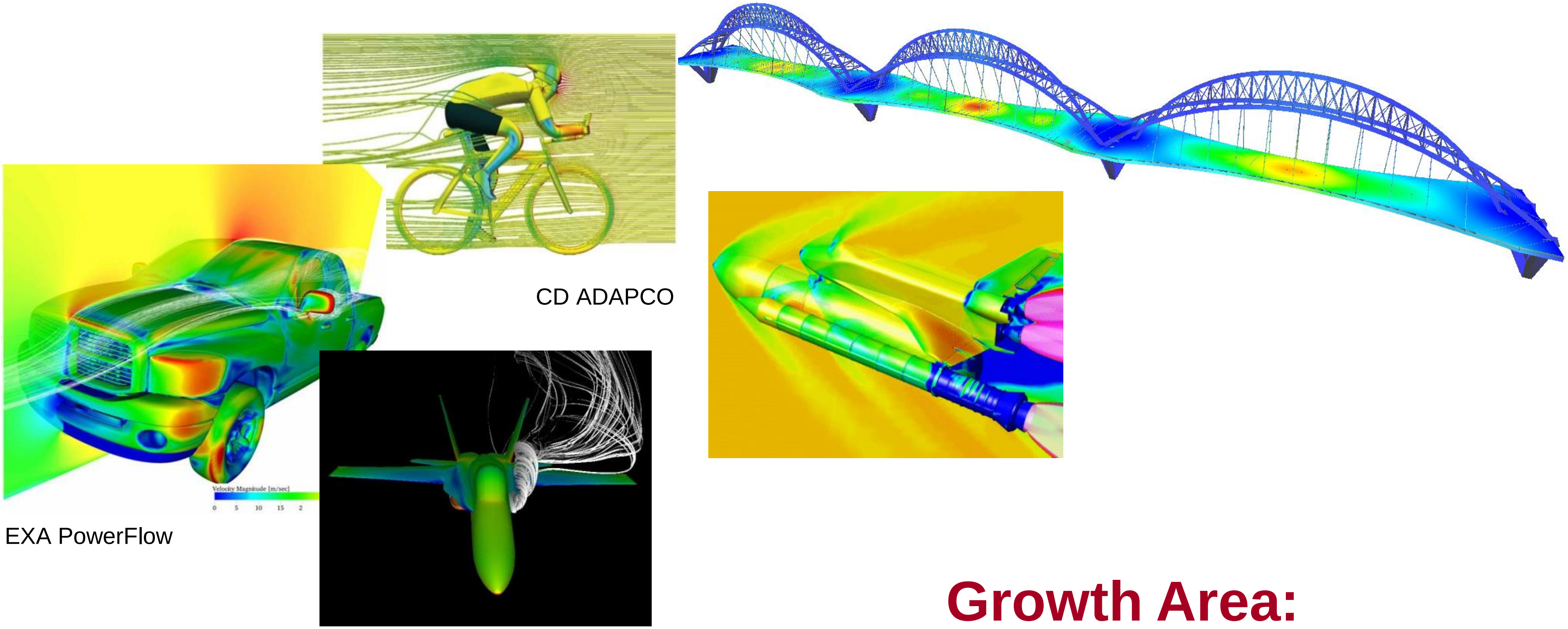
SofTMech

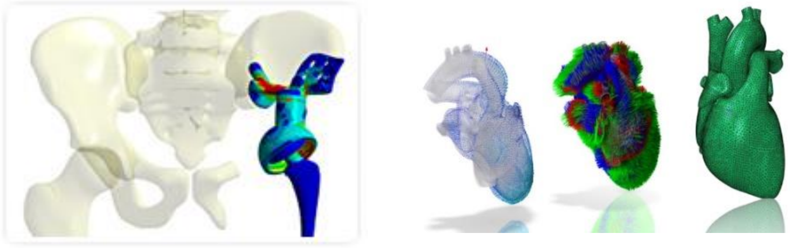
Computational Multi-physics Modelling: Highly successful in engineering industry…



CD ADAPCO

EXA PowerFlow

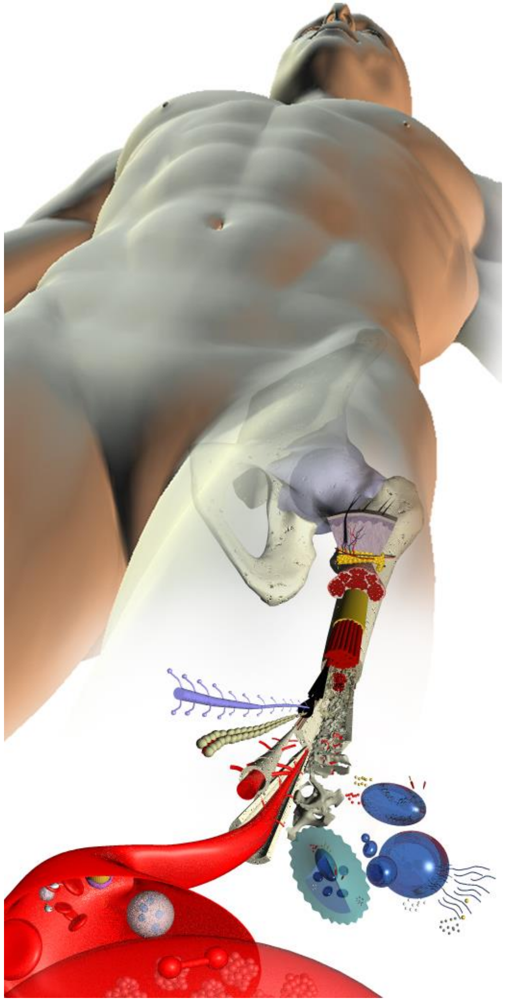
Growth Area: Health-care Technology Industries



VISION: Virtual Physiological Human

Vision : Your own **digital avatar**

A virtual replica of your anatomy and physiology



Predict disease progression

Test out clinical interventions (surgery) and your response

Test efficacy of medicines in relation to unique physiology

Optimise Health – Personalised exercise plans

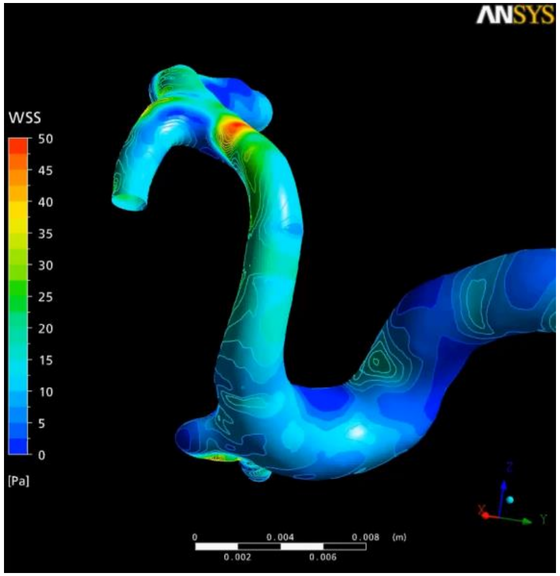
Personalised healthcare

Optimised healthcare (limited financial resources)

Overview: Modelling Examples

ECMINT 2017
Application of arterial growth and remodelling theories to modelling VASOSPASM and (Mechanical) Treatment

ECMINT 2019
Predictive Modelling of Aneurysm Evolution
Overview of state of Art
Roadmap to Clinical Impact?:



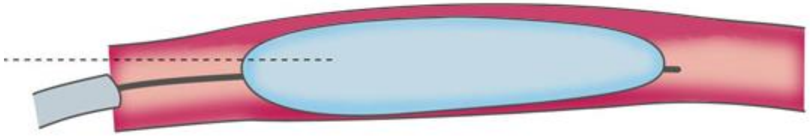
What Do You Think?

A. IA vasodilators ?
B. Balloon angioplasty?
C. Stent-retriever?

(Courtesy of Dr. P. Bhogal)

Mechanical Treatment Strategies

Possible treatment:
ballon angioplasty



Pressure: up to 300kPa

Collateral effects:
damage to the arterial tissue,
inhibition of muscle contractility

Proposed treatment:
stent-based lumen dilation

Does stent provide sufficient force to open up artery Is it sufficient?

Watton, ECMINT 2017, Oxford…

Article now online 2019

iol
g/10.1007/s00062-019-00776-2

L ARTICLE

The unexplained success of stentplasty vasospasm treatment

Insights using Mechanistic Mathematical Modeling

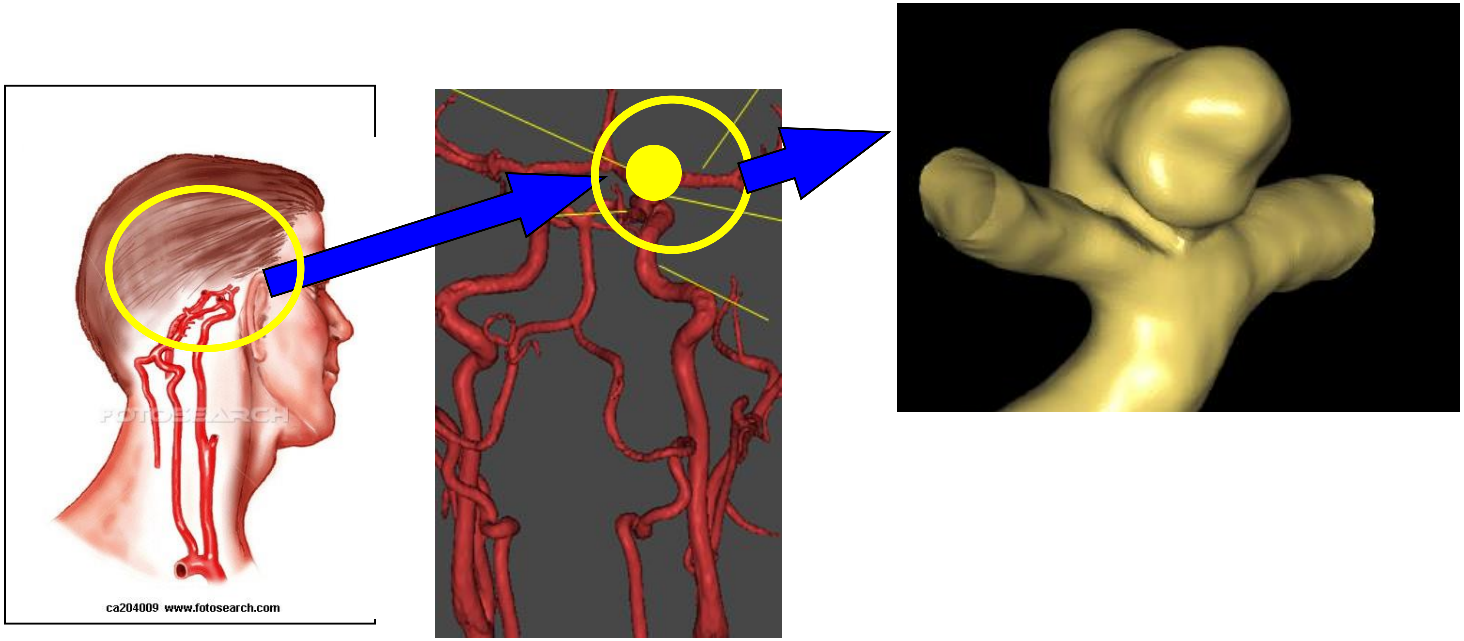
P. Bhogal[1] · G. Pederzani[2,3] · A. Grytsan[3] · Y. Loh[4,5] · P. A. Brouwer[6] · T. Andersson[6,7] · Namrata Gundiah[8] · Anne M. Robertson[9] · Paul N. Watton[2,3,9] · Michael Söderman[6]

Received: 9 July 2018 / Accepted: 8 March 2019

- Mathematics theories of arterial growth and remodelling and damage (from aneurysm approaches) to predict design requirements for a stent to treat vasospasm. (relatively low forces compared to balloon angioplasty)

- Introduces many of the ‘concepts/approaches’ covered this presentation.

Example: Mechanobiology of Cerebral Aneurysms

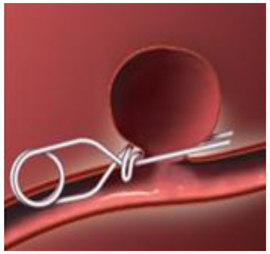


ca204009 www.fotosearch.com

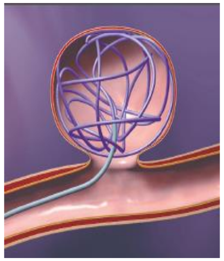
OCCURRENCE: 3-5% of population.
DETECTION: increasingly diagnosed (improved imaging).
RUPTURE: LOW risk <1% per year.
RUPTURE OUTCOME: 30%-40% fatality.

What is the best treatment ?

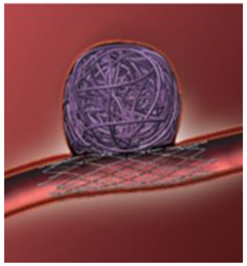
1. Clip



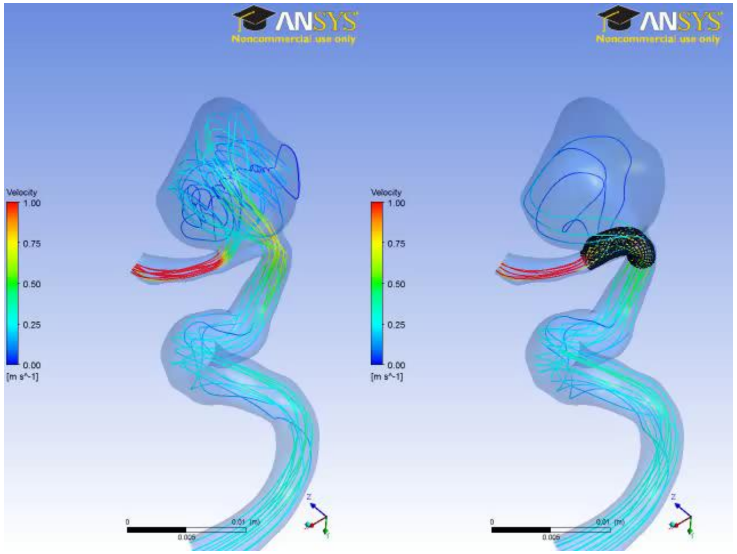
2. Coil



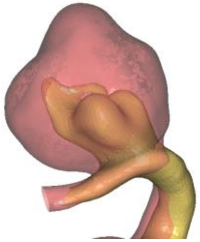
3. Coil & Stent



4. Blood Flow divertors

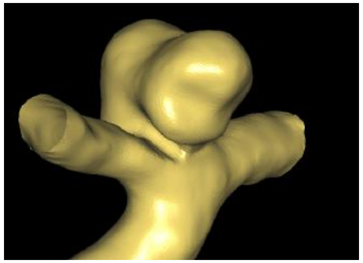


6 months



5. Do nothing

- Intervention: risky (5-7% morbidity) and expensive (£30 000)
- Low rupture risk (0.1-1%).

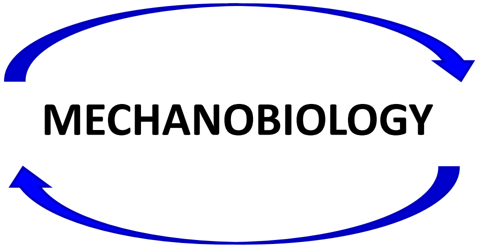


Intracranial aneurysm:
To treat, or not to treat,
that is the question:

- 0.1-1% of detected IAs rupture per year.
- Identifying when we can use conservative management would be the optimal treatment strategy (economically & patient welfare)
- Can we differentiate stable aneurysms from unstable ones?

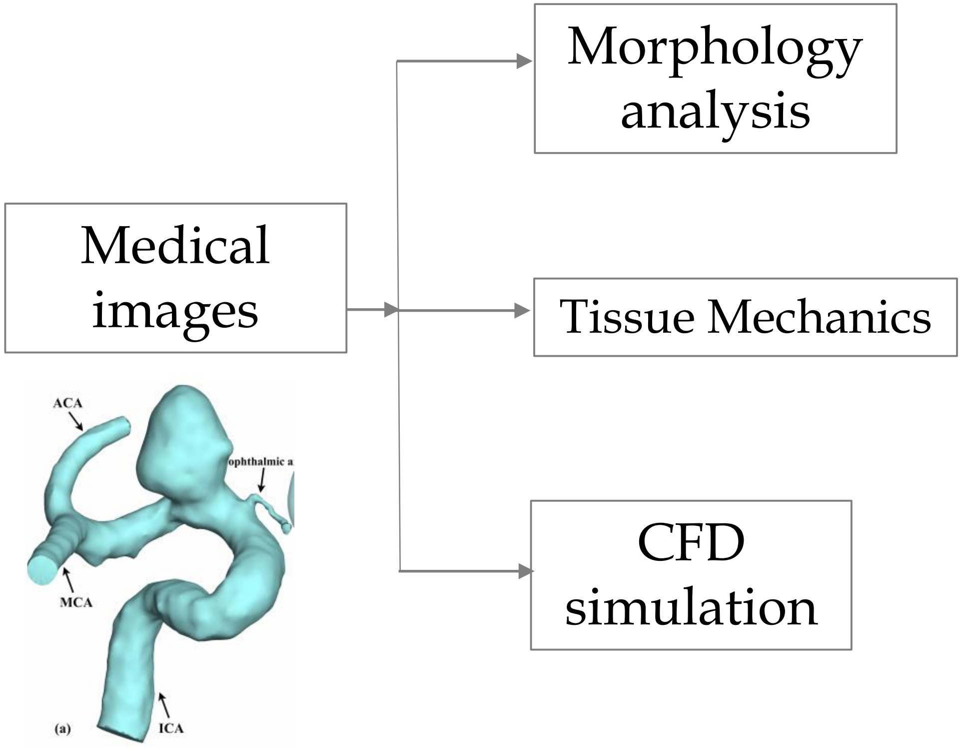
Predicting Aneurysm Stability

Quantify geometrical/ mechanical state



MECHANOBIOLOGY

Understand/ Model biology

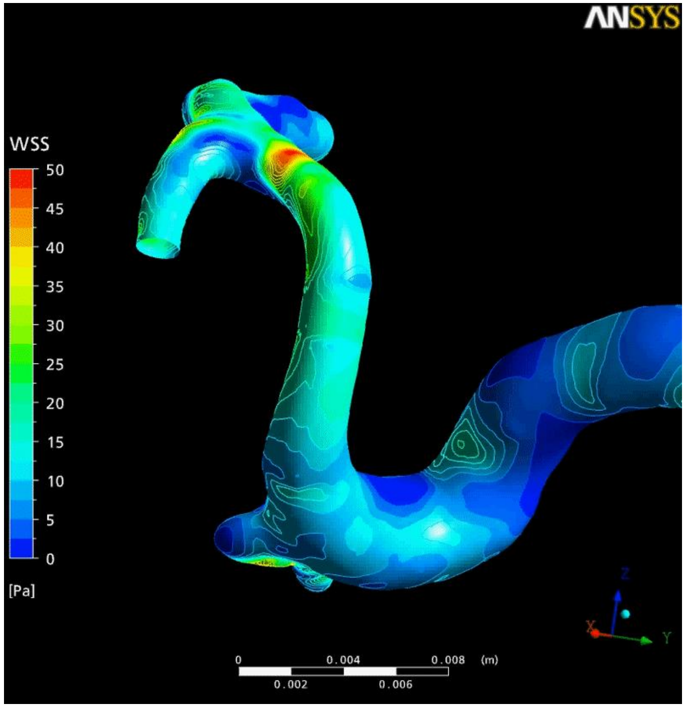


Medical images

Morphology analysis

Tissue Mechanics

CFD simulation

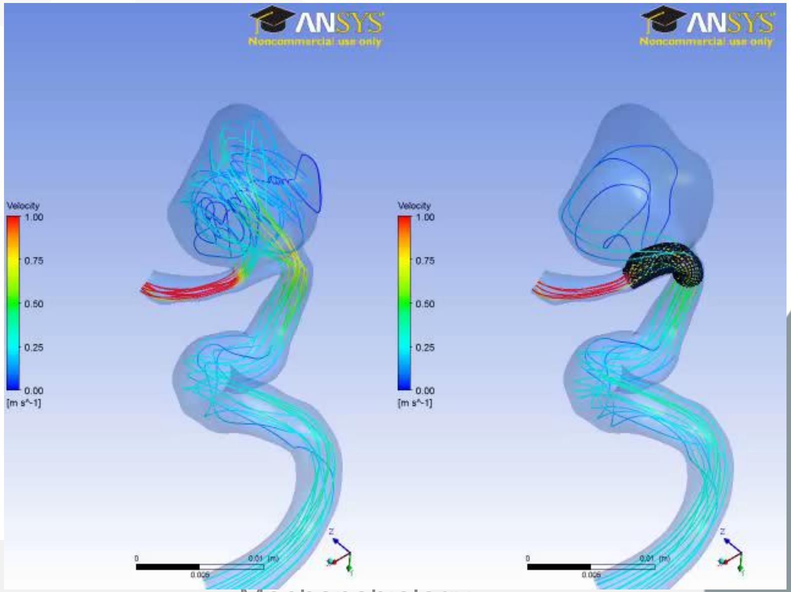


Quantification of mechanobiological state

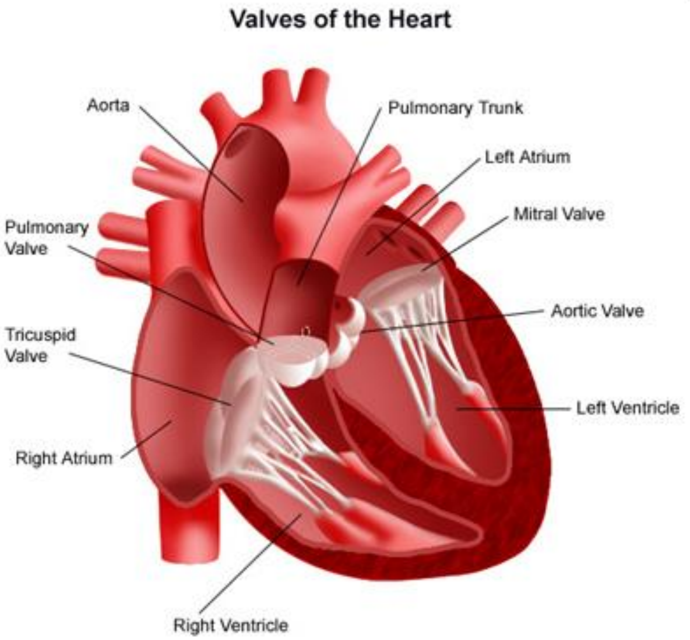
Interpretation of mechanobiology state: stability

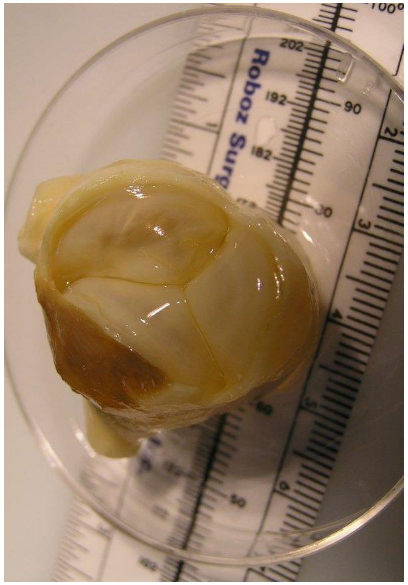
Mechanobiology

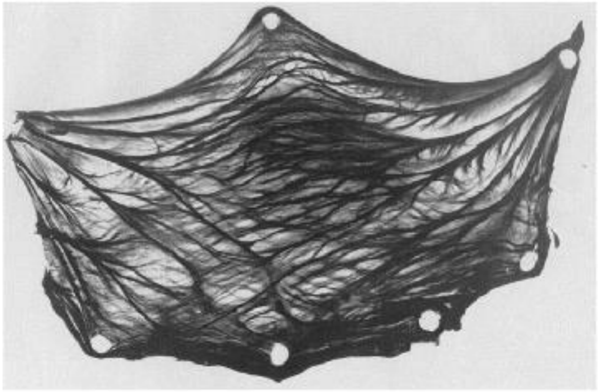
dynamic interaction of mechanics with biology



Mechanobiology and Design





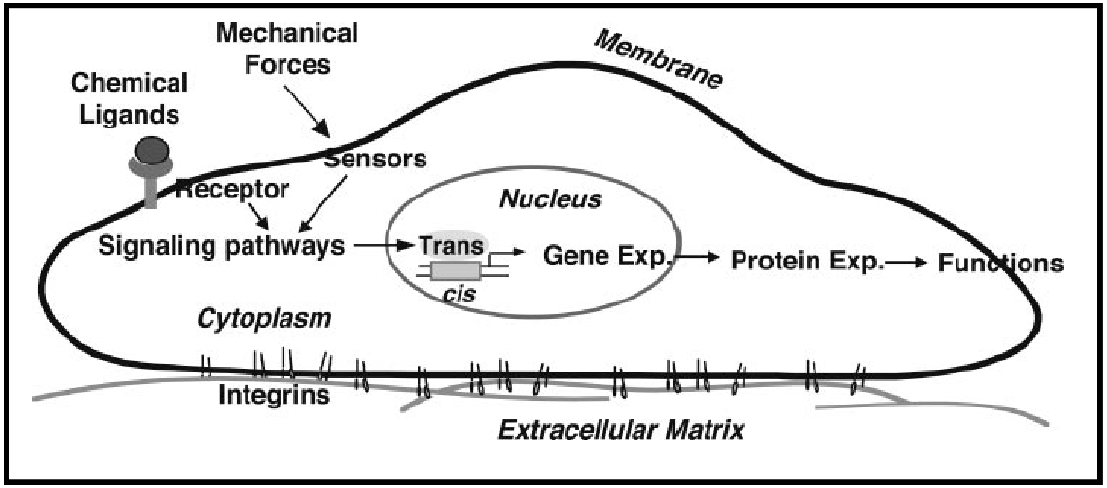


Soft tissues are fibre reinforced structures
Mechanical design to optomise mechanical function for a specific mechanical ‘job’.

How do the cells know how to build these structures?
What can go wrong with repair mechanisms or if mechanical job changes?
Mathematical modelling of **soft-tissue mechanobiology** can investigate these questions: provide understanding and predictive models of disease/intervention

Chemical stimuli and mechanical forces stimulate vascular cells…

- leading to modulations gene/protein expression and cellular functions
- influencing growth and remodelling (G&R) of tissue.



Shu Chien (2007)

Modelling Evolution of Soft-Tissue Disease:

- Quantify chemical and mechanical environment of cells.
- Understand/Model the influence of the stimuli on cell functionality.

Context: Evolution of

Modelling Aneurysm Evolution

Then…1999

No: gmail, facebook, twitter, smartphones

Coolpix 950
2MP digital camera

No computational/mathematical models of aneurysm evolution

***Watton PN, Mathematical Modelling of Abdominal Aortic Aneurysm*, PhD Thesis, Department of Mathematics, University of Leeds, UK 1999-2002.**

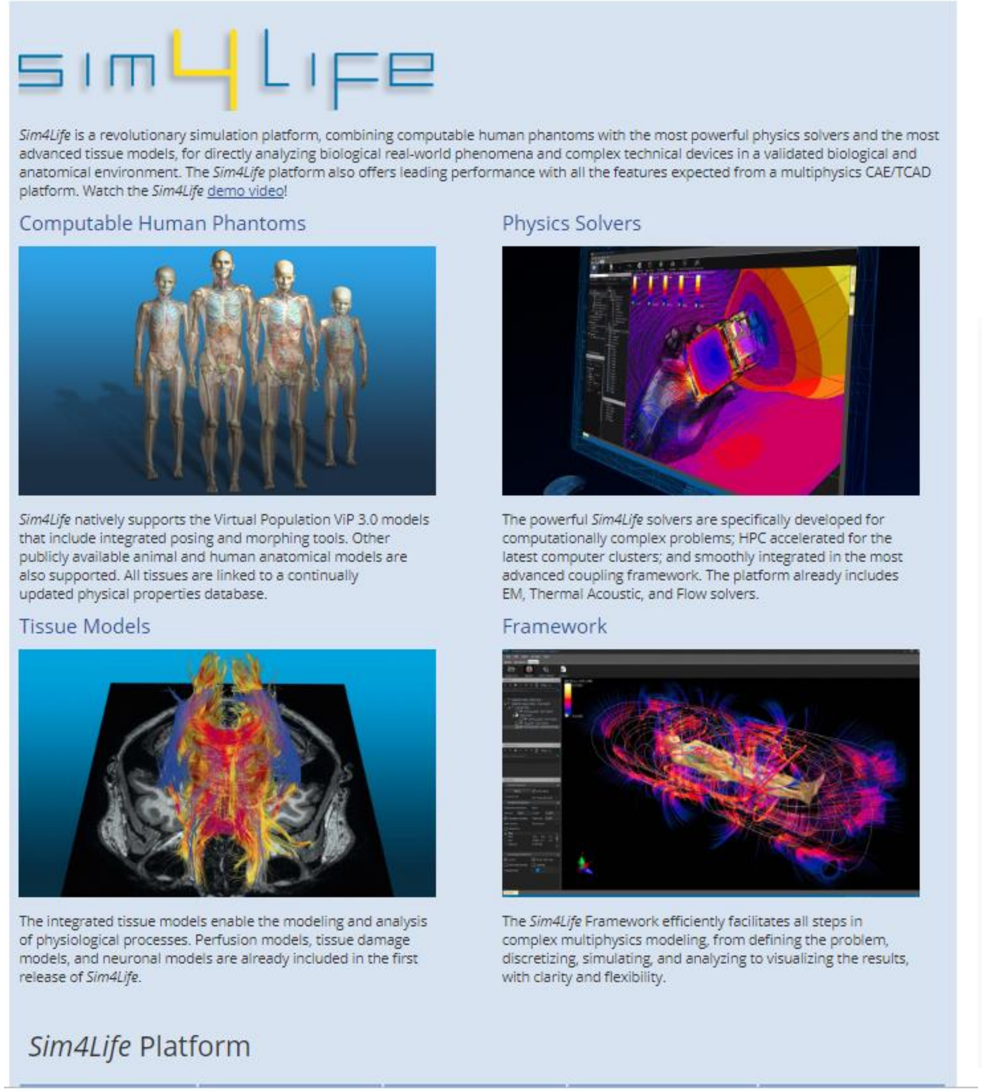
1st published computational model of aneurysm evolution
Watton PN, Hill NA, Heil M, (2004) A Mathematical Model for the Growth of the Abdominal Aortic Aneurysm, *Biomechanics and Modeling in Mechanobiology*, 3:98-113.

Now…2019

Aneurysm evolution model integrated into Sim4Life Framework

Workflow: Segmentation Meshing to Simulation (Fluid, Solid, Growth)

https://zmt.swiss/



sim4life

Sim4Life is a revolutionary simulation platform, combining computable human phantoms with the most powerful physics solvers and the most advanced tissue models, for directly analyzing biological real-world phenomena and complex technical devices in a validated biological and anatomical environment. The *Sim4Life* platform also offers leading performance with all the features expected from a multiphysics CAE/TCAD platform. Watch the *Sim4Life* demo video!

Computable Human Phantoms

Sim4Life natively supports the Virtual Population ViP 3.0 models that include integrated posing and morphing tools. Other publicly available animal and human anatomical models are also supported. All tissues are linked to a continually updated physical properties database.

Physics Solvers

The powerful *Sim4Life* solvers are specifically developed for computationally complex problems; HPC accelerated for the latest computer clusters; and smoothly integrated in the most advanced coupling framework. The platform already includes EM, Thermal Acoustic, and Flow solvers.

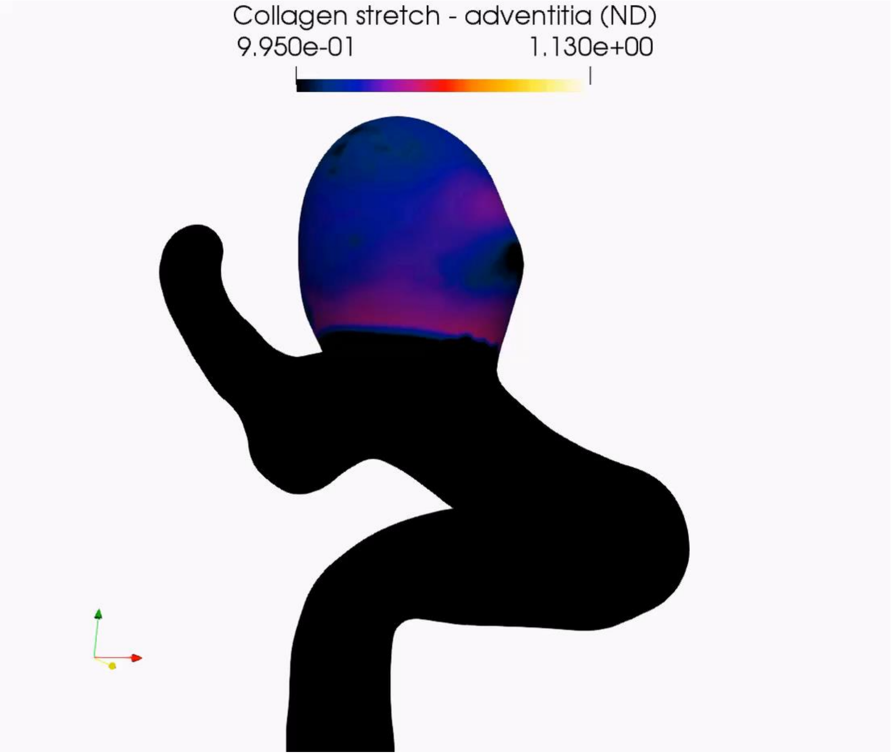
Tissue Models

The integrated tissue models enable the modeling and analysis of physiological processes. Perfusion models, tissue damage models, and neuronal models are already included in the first release of *Sim4Life*.

Framework

The *Sim4Life* Framework efficiently facilitates all steps in complex multiphysics modeling, from defining the problem, discretizing, simulating, and analyzing to visualizing the results, with clarity and flexibility.

Sim4Life Platform



20 years of computational modelling aneurysm evolution!

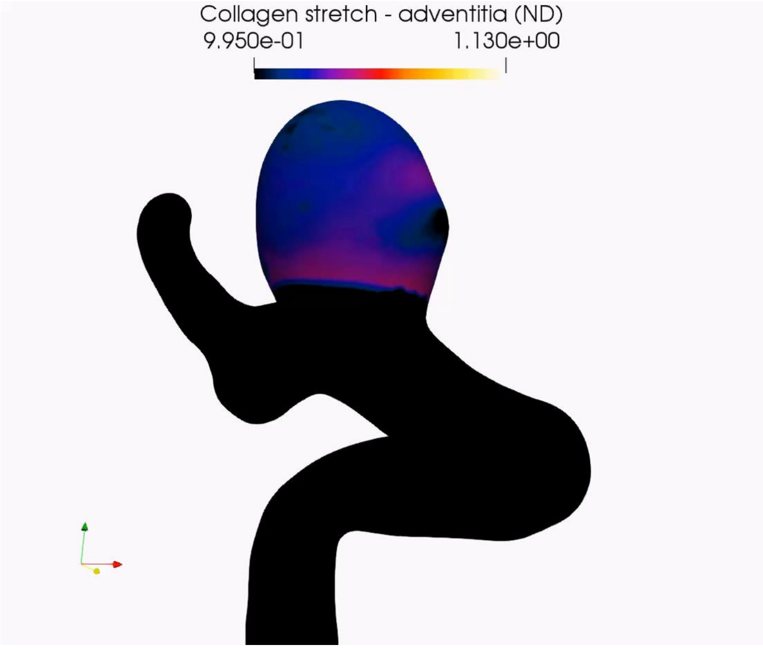
Where is the clinical Impact?

When is the clinical Impact?

Enhanced contrast MRI
(quantify permability)

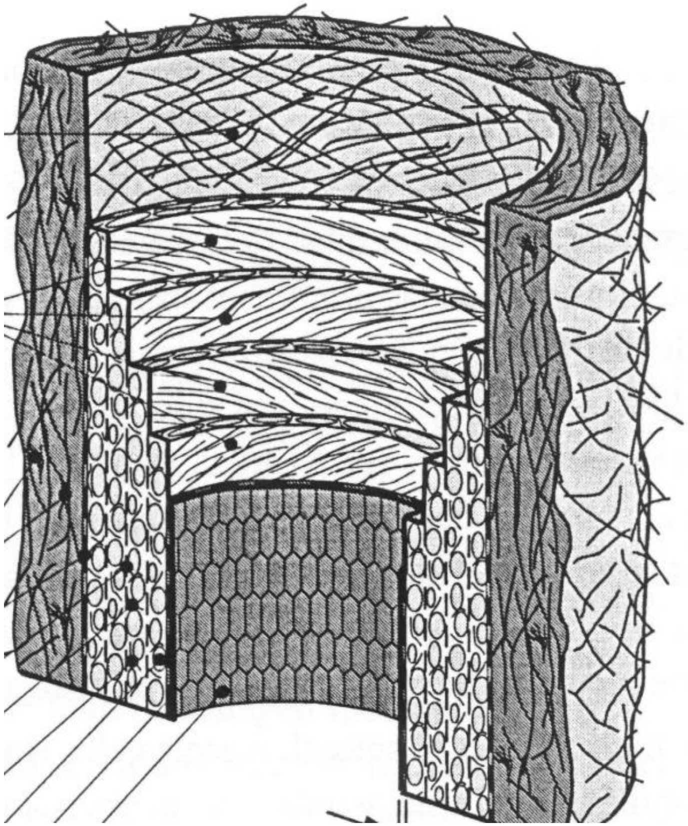
Improved prediction of
mechanobiological state &
assessment of aneurysm stability
Research Tool
Clinical Tool?

Computational
mechanobiology

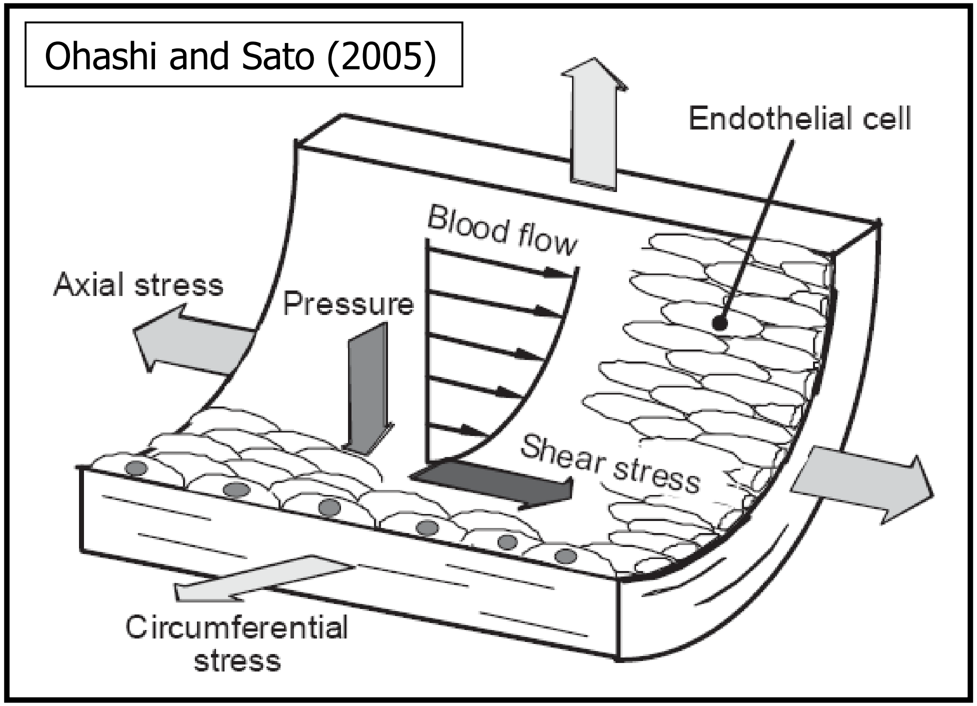


Key Modelling Assumptions: Healthy Artery

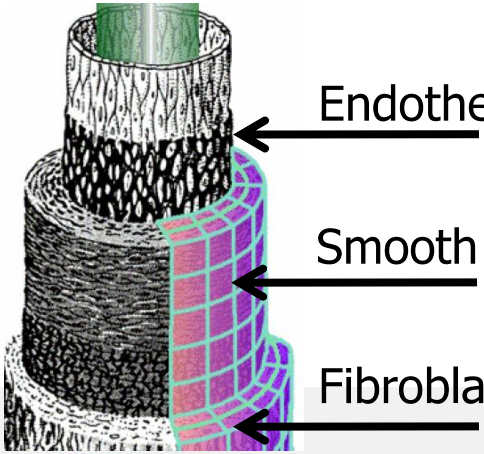
- Artery is modelled as an fibre reinforced elastic tube
- Load bearing constituents: **collagen**, **elastin** and **smooth muscle cells** (SMCs)
- SMCs have both a **passive and active response**
- **Elastin** is the **main load-bearer**, followed by smooth muscle
- **Collagen (adventitia)** acts as a **protective sheath**
- **Model stretches of individual components of wall**



The mechanical environment of the arterial wall



- **blood flow:**
  friction forces acting on ECs
  magnitude/gradients/direction
  WSS,WSS spatial gradients, OSI
- **normal stress:**
  perpendicular to the EC surface
- **cyclic circumferential stretch/stress:**
  due to pulsatile blood pressure
- **axial stress**



Endothelial cells: sense WSS, regulate function of arterial wall

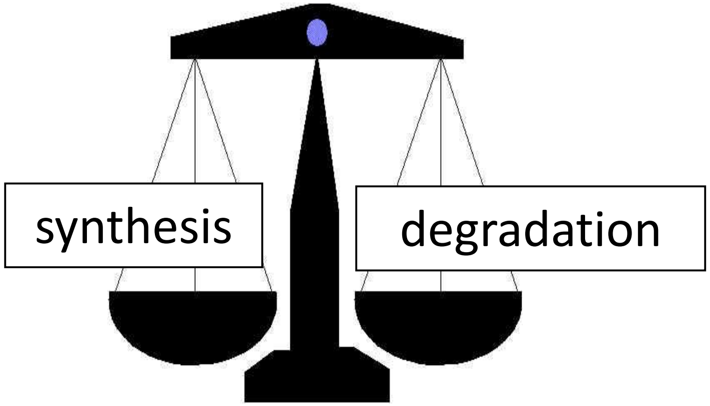
Smooth muscle cells: regulate diameter

Fibroblast cells: produce/degrade ECM

Key Concept: Homeostasis; Growth; Remodelling.

Cells continuously produce ECM and enzymes to degrade the ECM.

Homeostasis

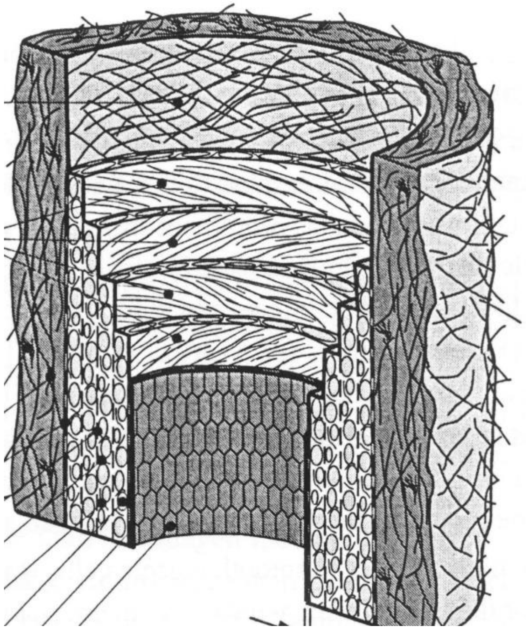


Growth/Atrophy Changes in mass of the constituents

Remodelling Reorganization of the constituents
(no change in mass),
e.g. Constituent reference configurations, orientations.

Aneurysm evolution: Modelling

Healthy artery



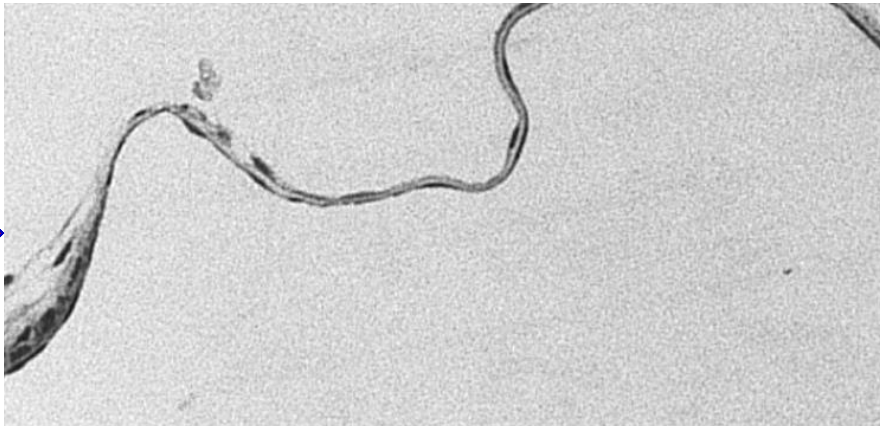
Layers of the Arterial Wall

intima (endothelial cells)

media (elastin, collagen, smooth muscle cells)

adventitia (collagen, fibroblasts)

Aneurysmal artery(cerebral)



Abrupt destruction of medial layer:

fragmentation/loss of elastin fibres

adaption of collagen fabric

MODELLING ANEURYSM EVOLUTION (& more generally vascular disease):

Model healthy arterial wall (Holzapfel et al 2000)

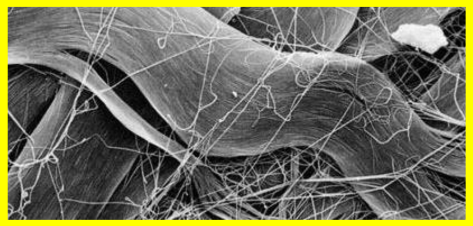
theoretical framework to describe growth and remodelling of tissue.

Natural reference configurations for constituents

CHALLENGES:

For Biological tissues, the unloaded configurations of constituents/cells:

may be distinct



wavy collagen fibres

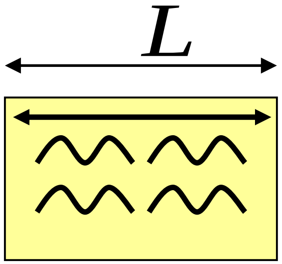
may evolve

Our skin grows with us!

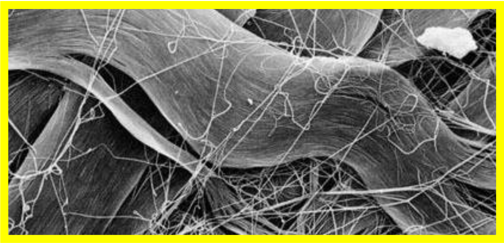
How does the aneurysm skin grow?

General modelling hypothesis (research community):New material is deposited in current geometry in small state of stretch

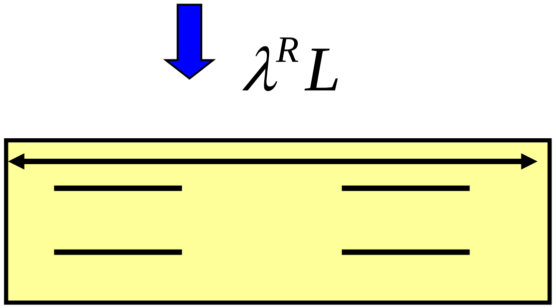
Concepts: Recruitment and Attachment Stretches



Collagen fibers: - crimped in unloaded artery

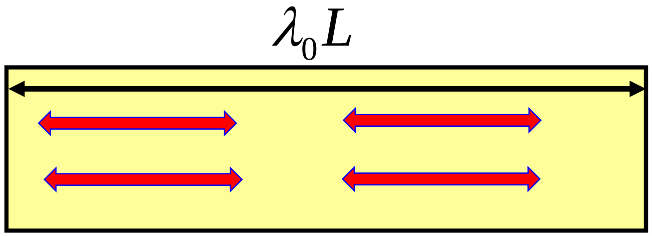


Unloaded configuration



recruitment stretch:

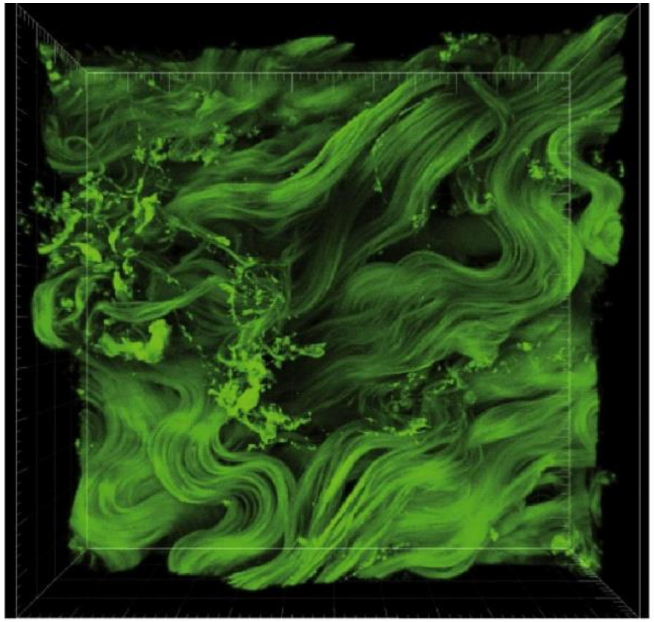
onset of load bearing of collagen fibre $\lambda^C = 1$

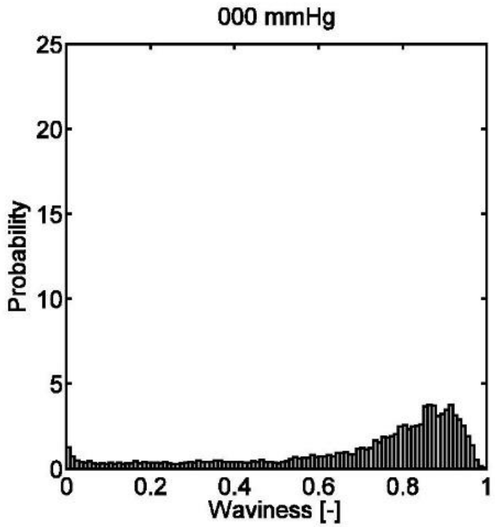


attachment stretch: $\lambda^C = \lambda^C_{AT}$

Fibre configured in loaded configuration in state of stretch

Distributions of attachment and recruitment stretches





Schrauwen et al (2012). A method for the quantification of the pressure dependent 3D collagen configuration in the arterial adventitia. *Journal of Structural Biology.*

Observation of collagen waviness distribution in the unloaded configuration

⇩

Distribution of collagen recruitment stretches

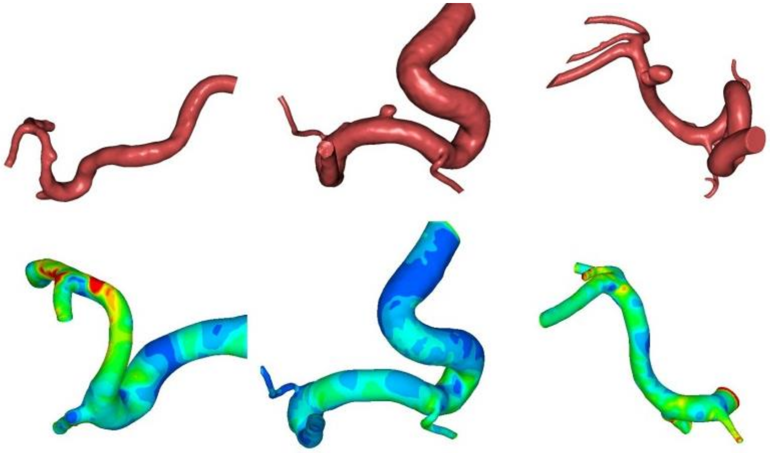
⇩

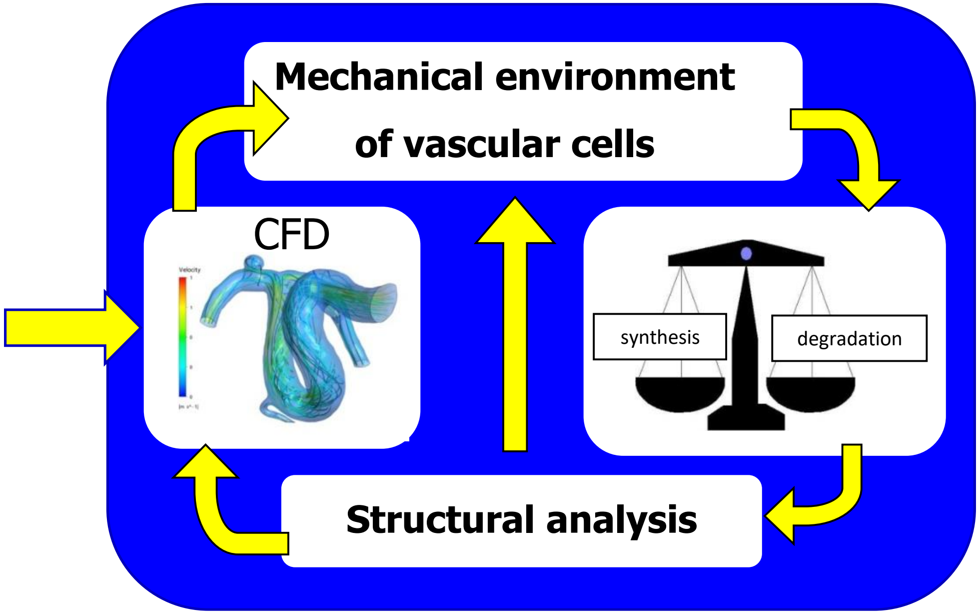
Distribution of collagen attachment stretches (loaded configuration)

⇩

Strain energy of fibre ensemble (Hill et al, J Biomech 2015)

Framework for Modelling Aneurysm Evolution

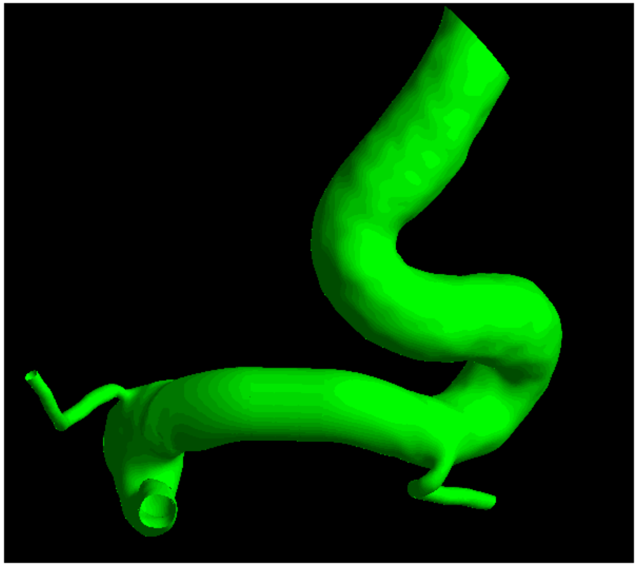




Mechanical environment of vascular cells

CFD

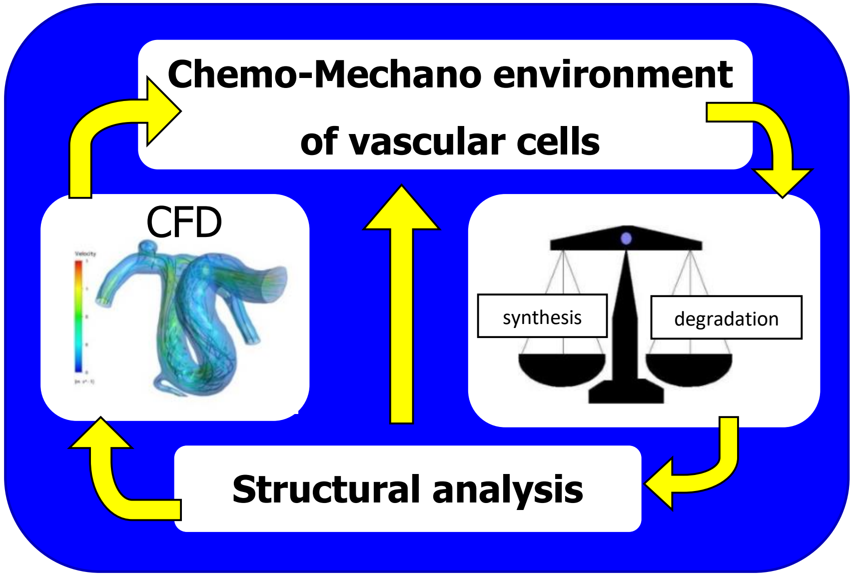
Structural analysis



- **CLINICAL CASE**
- **GROW ANEURYSM**
- **TEST HYPOTHESES FOR G&R and Stabilisation**

Publications

http://www.themebio.org/publications/



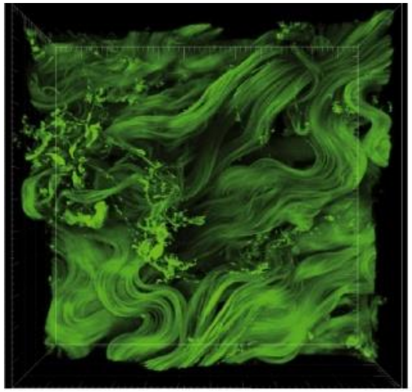
Chemo-Mechano environment of vascular cells

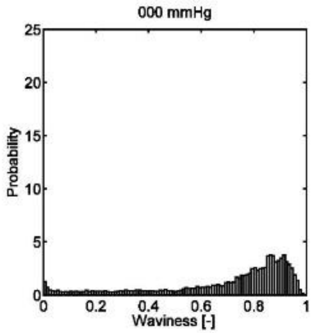
CFD

synthesis

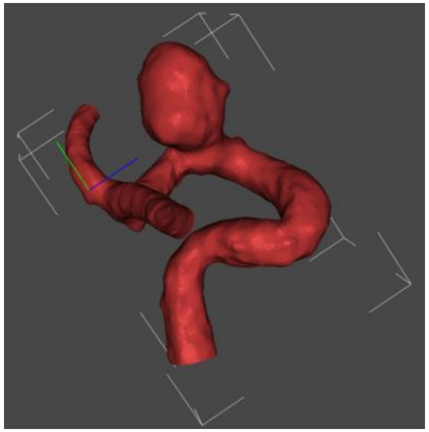
degradation

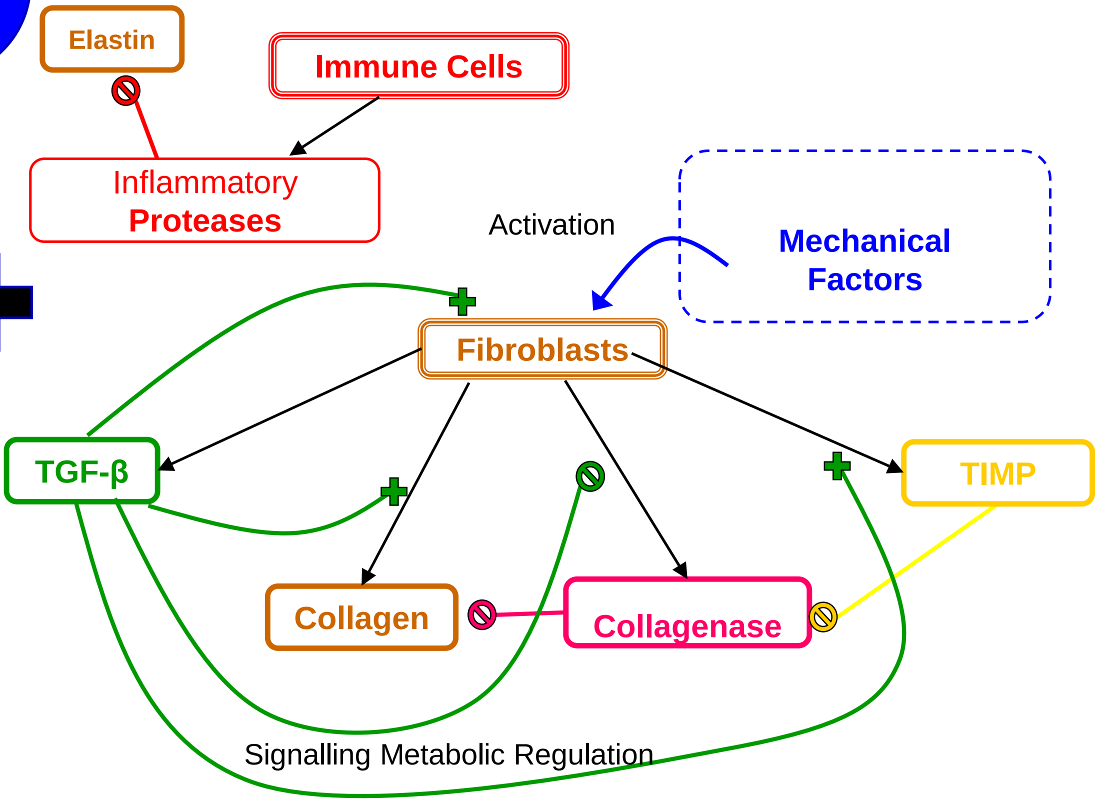
Structural analysis





CA-09





Elastin

Immune Cells

Inflammatory Proteases

Activation

Mechanical Factors

Fibroblasts

TGF-β

TIMP

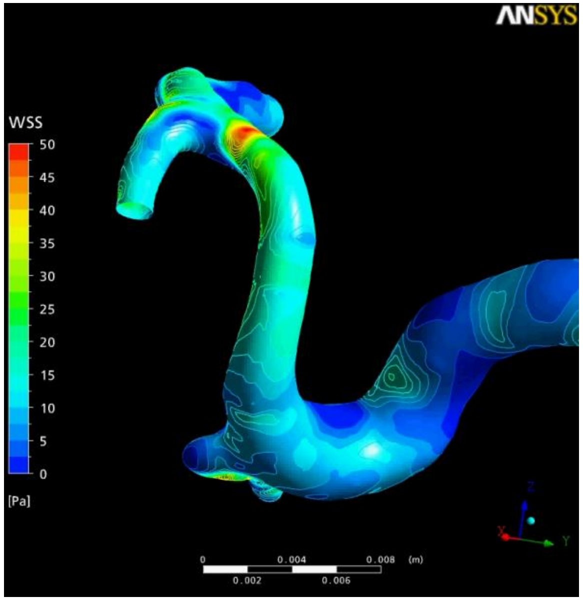
Collagen

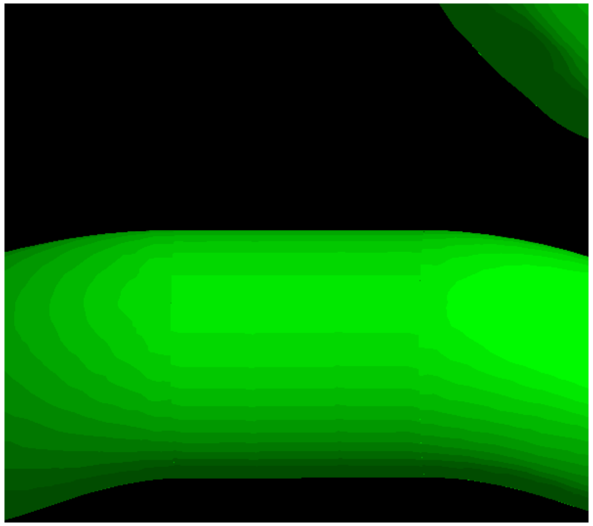
Collagenase

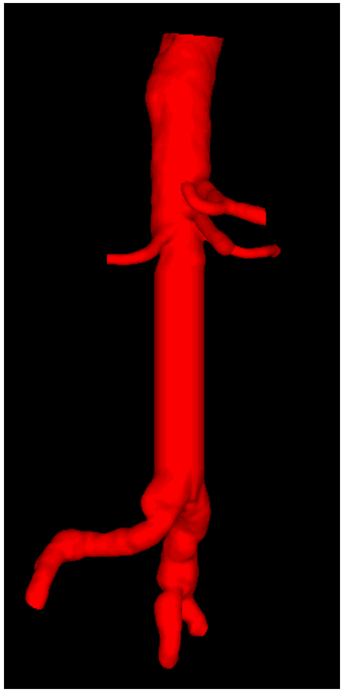
Signalling Metabolic Regulation

Aparicio P, Thompson M, Watton PN (2016) A novel chemo-mechano-biological model of arterial tissue growth and remodelling, *Journal of Biomechanics.*

Modelling Evolution from the healthy artery







Aparicio et al (2014), International Journal for Numerical Methods in Biomedical Engineering' 30(5):563-586.
Selimovic et al (2014), Proceedings of the The 23rd International Congress of Theoretical and Applied Mechanics, 10:396-409.
Watton et al (2011) Biomechanics and Mechanobiology of Aneurysms. Springer-Verlag, Heidelberg, 373-399.
Watton et al (2011) Modelling Evolution and the Evolving Mechanical Environment of Saccular Cerebral Aneurysms, Biomechanics and Modeling in Mechanobiology, 11:109-13
Watton et al (2009) ASME Journal of Biomechanical Engineering, 131:101003.
Watton & Ventikos Y (2009) Modelling Evolution of Saccular Cerebral Aneurysms, Journal of Strain Analysis, 44:375-389.

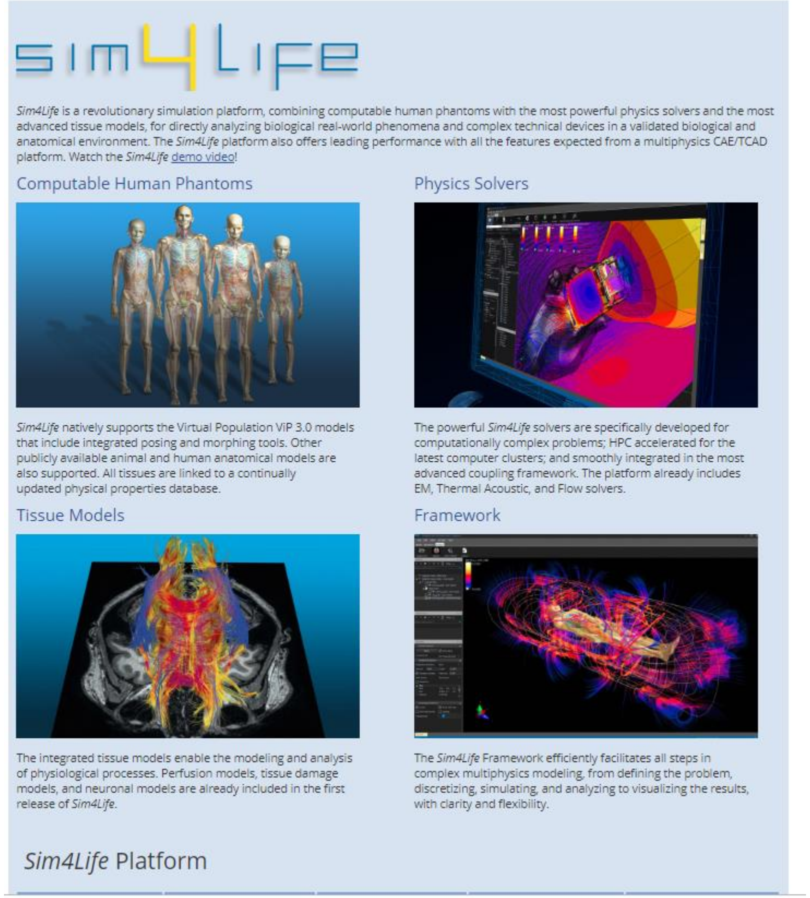
2019…

Frederico Teixeira (ITIS)

https://zmt.swiss/

Aneurysm evolution model integrated into ***Sim4Life*** Framework

Workflow: Segmentation Meshing to Simulation (Fluid, Solid, Growth)



Sim4Life is a revolutionary simulation platform, combining computable human phantoms with the most powerful physics solvers and the most advanced tissue models, for directly analyzing biological real-world phenomena and complex technical devices in a validated biological and anatomical environment. The *Sim4Life* platform also offers leading performance with all the features expected from a multiphysics CAE/TCAD platform. Watch the *Sim4Life* demo video!

Computable Human Phantoms

Sim4Life natively supports the Virtual Population ViP 3.0 models that include integrated posing and morphing tools. Other publicly available animal and human anatomical models are also supported. All tissues are linked to a continually updated physical properties database.

Physics Solvers

The powerful *Sim4Life* solvers are specifically developed for computationally complex problems; HPC accelerated for the latest computer clusters; and smoothly integrated in the most advanced coupling framework. The platform already includes EM, Thermal Acoustic, and Flow solvers.

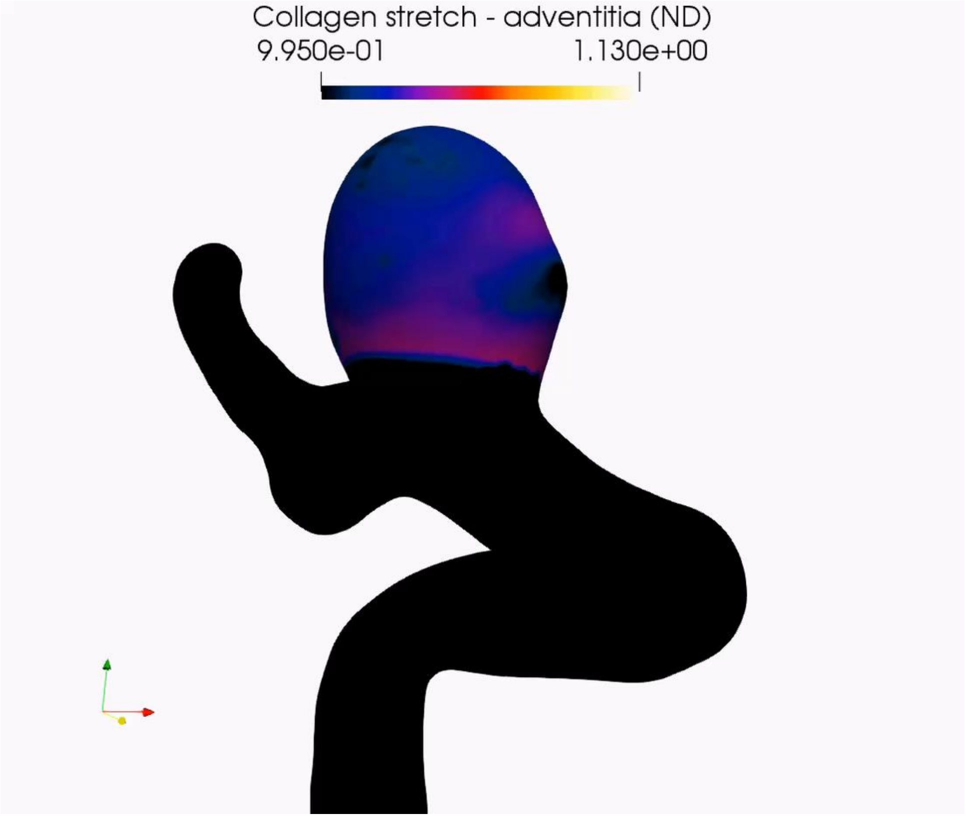
Tissue Models

The integrated tissue models enable the modeling and analysis of physiological processes. Perfusion models, tissue damage models, and neuronal models are already included in the first release of *Sim4Life*.

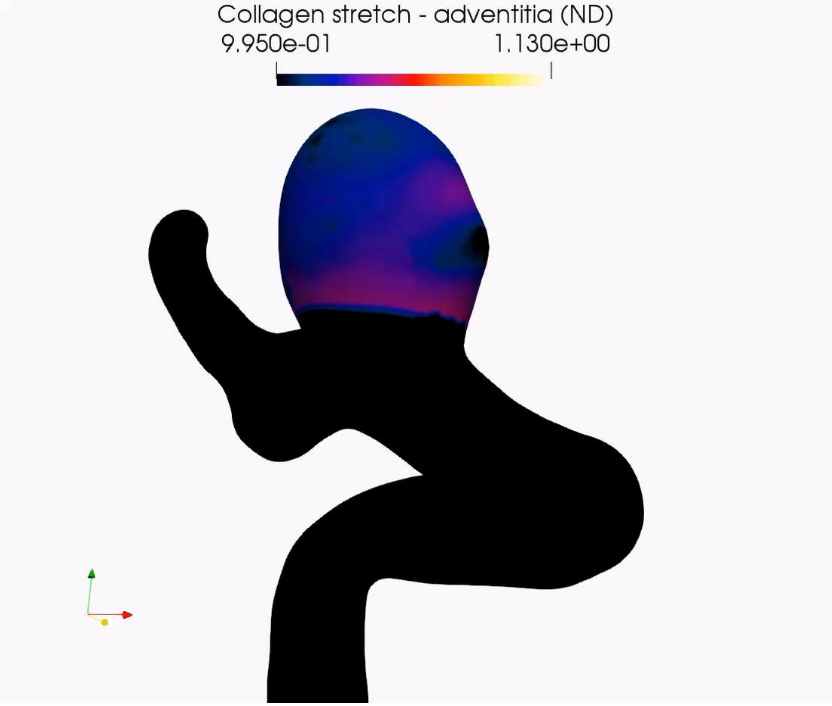
Framework

The *Sim4Life* Framework efficiently facilitates all steps in complex multiphysics modeling, from defining the problem, discretizing, simulating, and analyzing to visualizing the results, with clarity and flexibility.

Sim4Life Platform



- Integrative software suite – segmentation to growth simulation
- Constrained mixture model. Thick-walled FE.
- Patient-specific intracranial aneurysm
- Fluid-Solid-Growth sim4Life
- Growth and Remodelling linked to pulsatile flow and cyclic deformation metrics
- Representation of endothelial morphology
- Adaptive role of adventitia
- Formation of secondary blebs



With **Frederico Teixeira** (PhD student)

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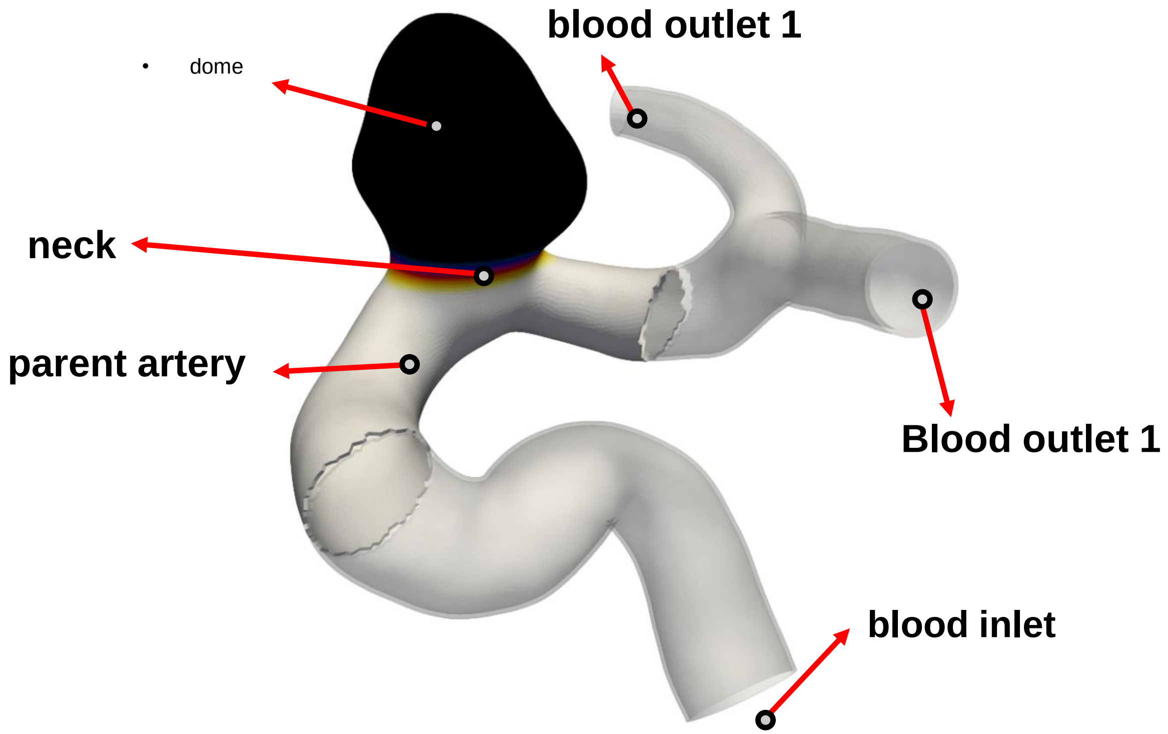
The AneuX Project (2015-19)

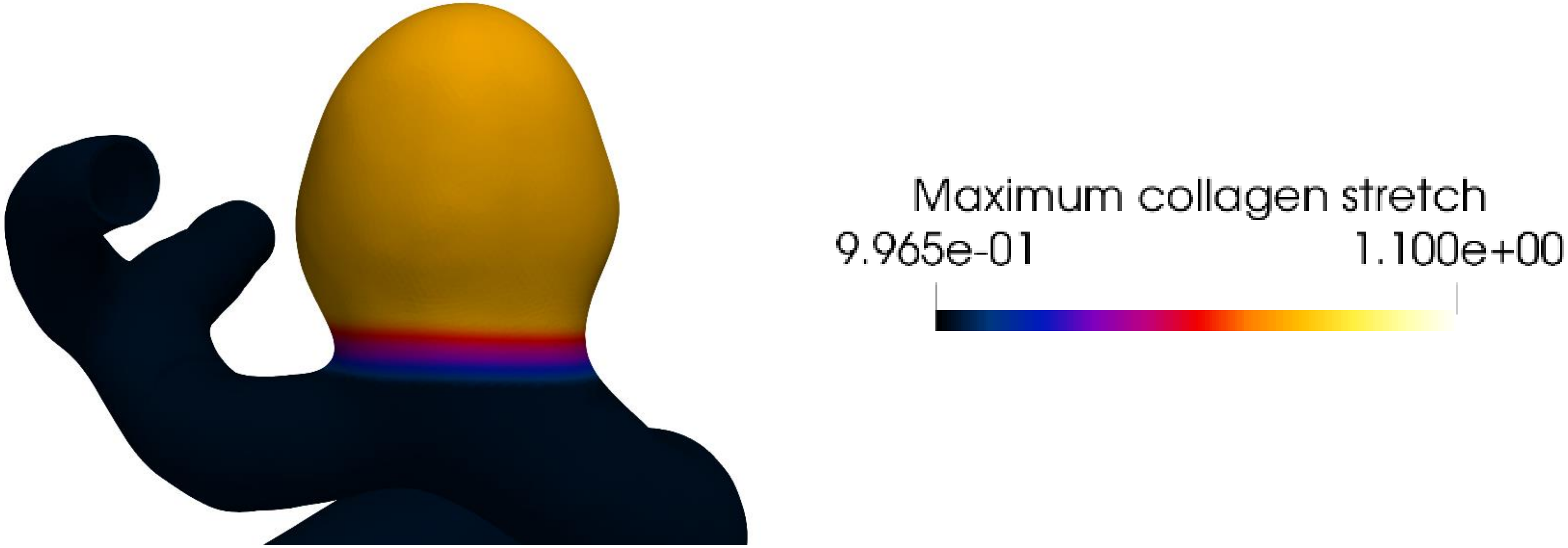
Patient-specific geometry



Anne Robertson Lab

Initial homeostatic state

- Adventitia parent artery bears no load (max collagen stretch equals 1).
- Aneurysm sac – collagen stretch distribution from 1.0 to 1.07 and spatially uniform

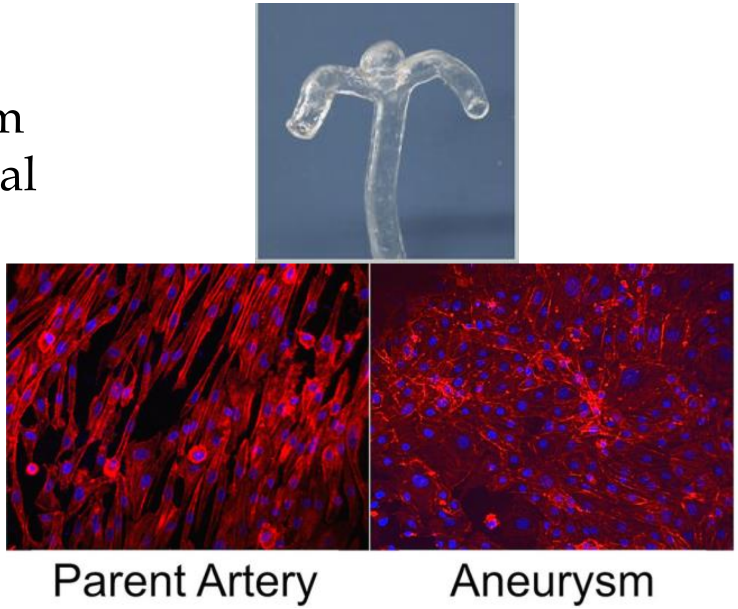


SIMULATION FOR SECONDARY BLEBS

- collagen degradation linked to low WSS, followed by stabilization

ECs Morphology

A patient-specific intracranial aneurysm model with endothelial lining



Kaneko n, et al. J NeuroIntervent Surg 2017;0:1–5.

Spindle shaped

irregular

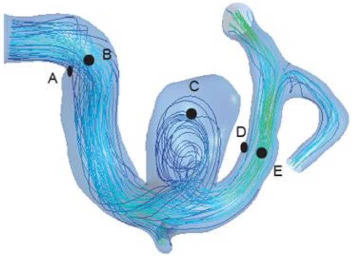
Mechanistic Modelling:

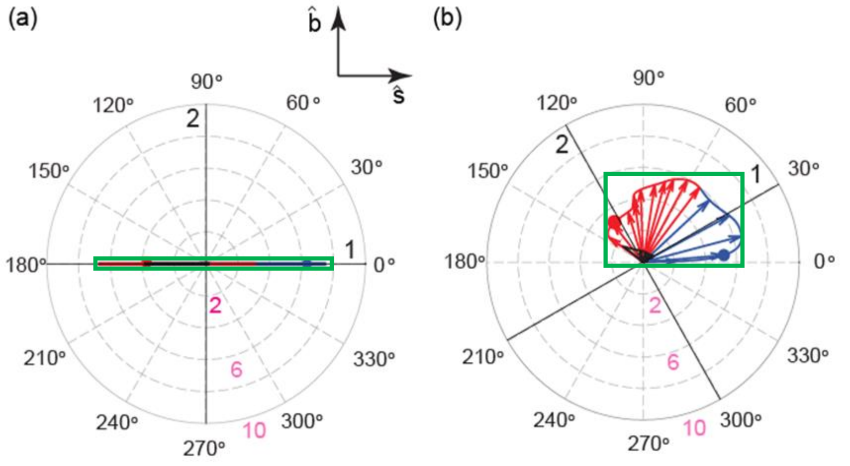
Can we predict endothelial morphology ?

Can we link endothelial morphology to tissue remodelling?

Endothelial cells (ECs) Morphology Quantification

Shear Stress Rosettes (SSR): Behaviour of WSS vector at a point over cardiac cycle



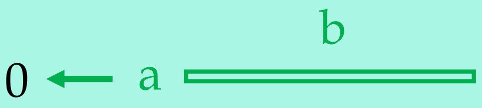


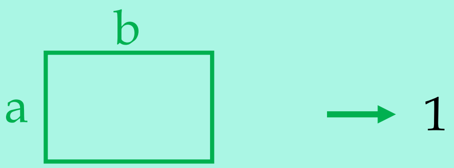
GUNDIAH LAB
Krishna, et al. Shear Stress Rosettes Capture the Complex Flow Physics in Diseased Arteries Medical Engineering and Physics (submitted)

SSR Metric: Aspect Ratio of Shear Stress Rosetter (AR, 0~1)

The minimum ratio of breadth to the length of a rectangular box bounding the shear rosette.

AR= a/b

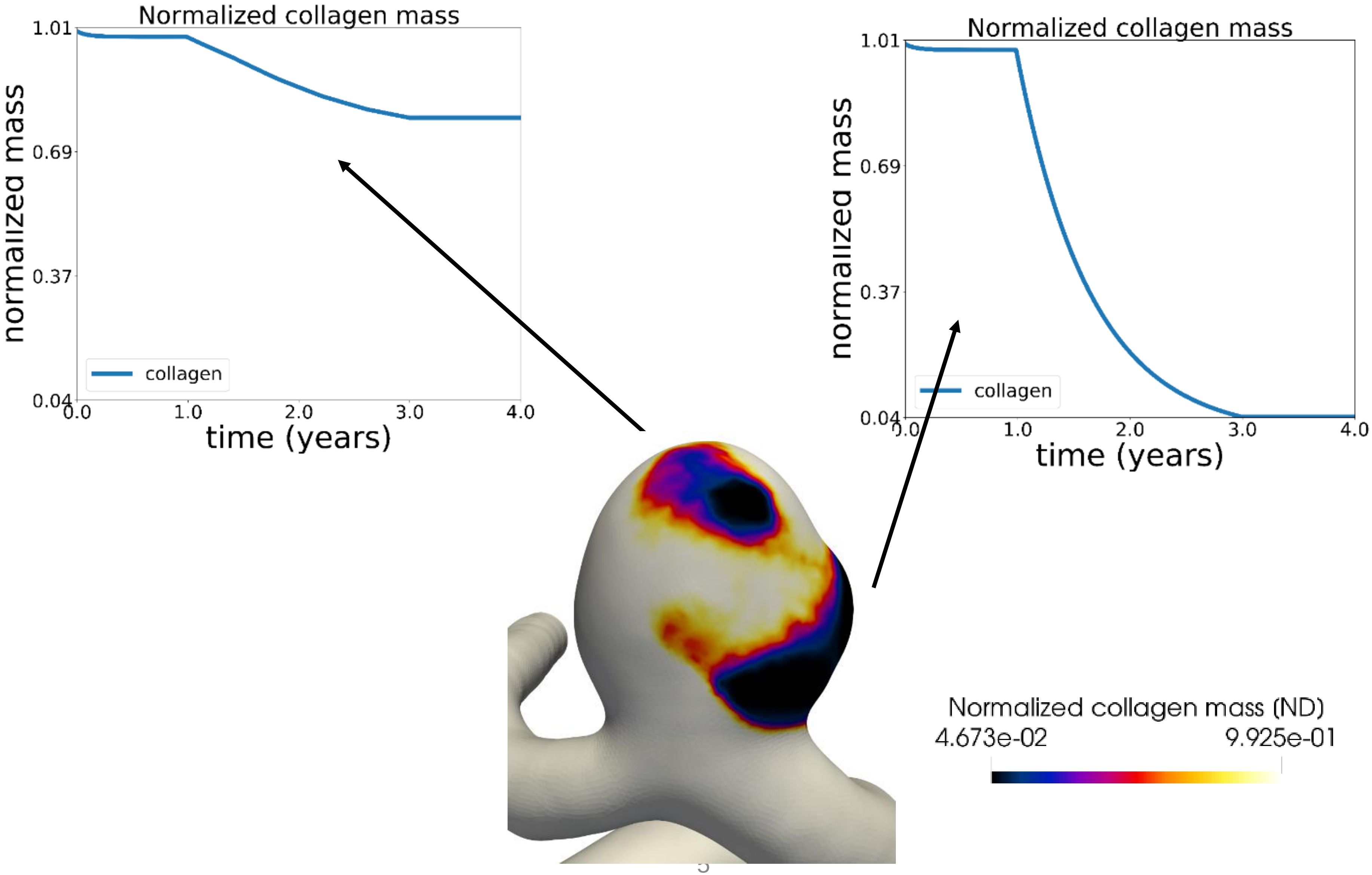




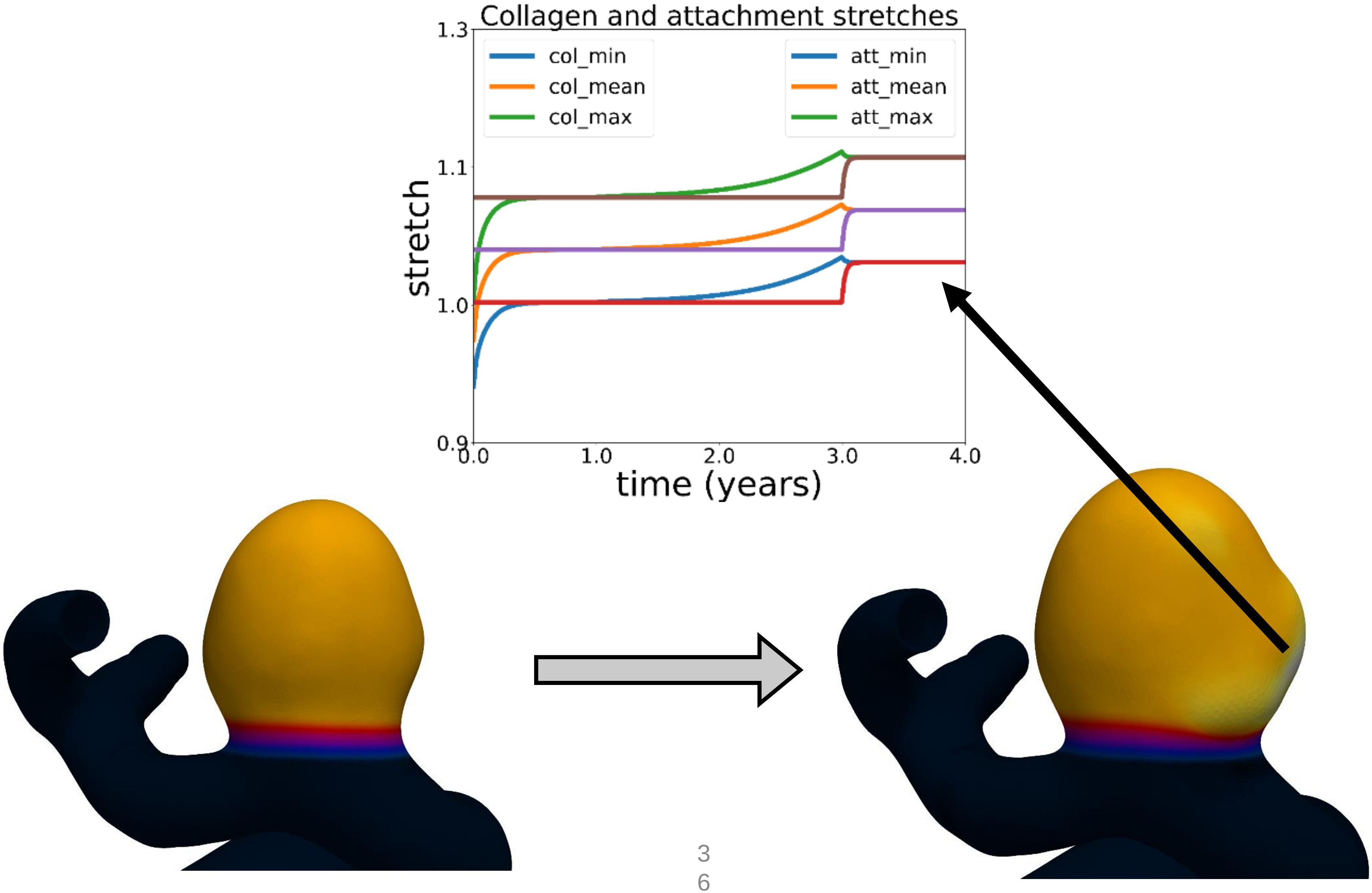
CURRENT WORK:

Oscillatory flow metrics → EC Morphology (Spindle/Irregular) → Localised Permeability Growth & Remodelling → Aneurysm Growth/ Stabilty

collagen degradation linked to low WSS, followed by stabilization

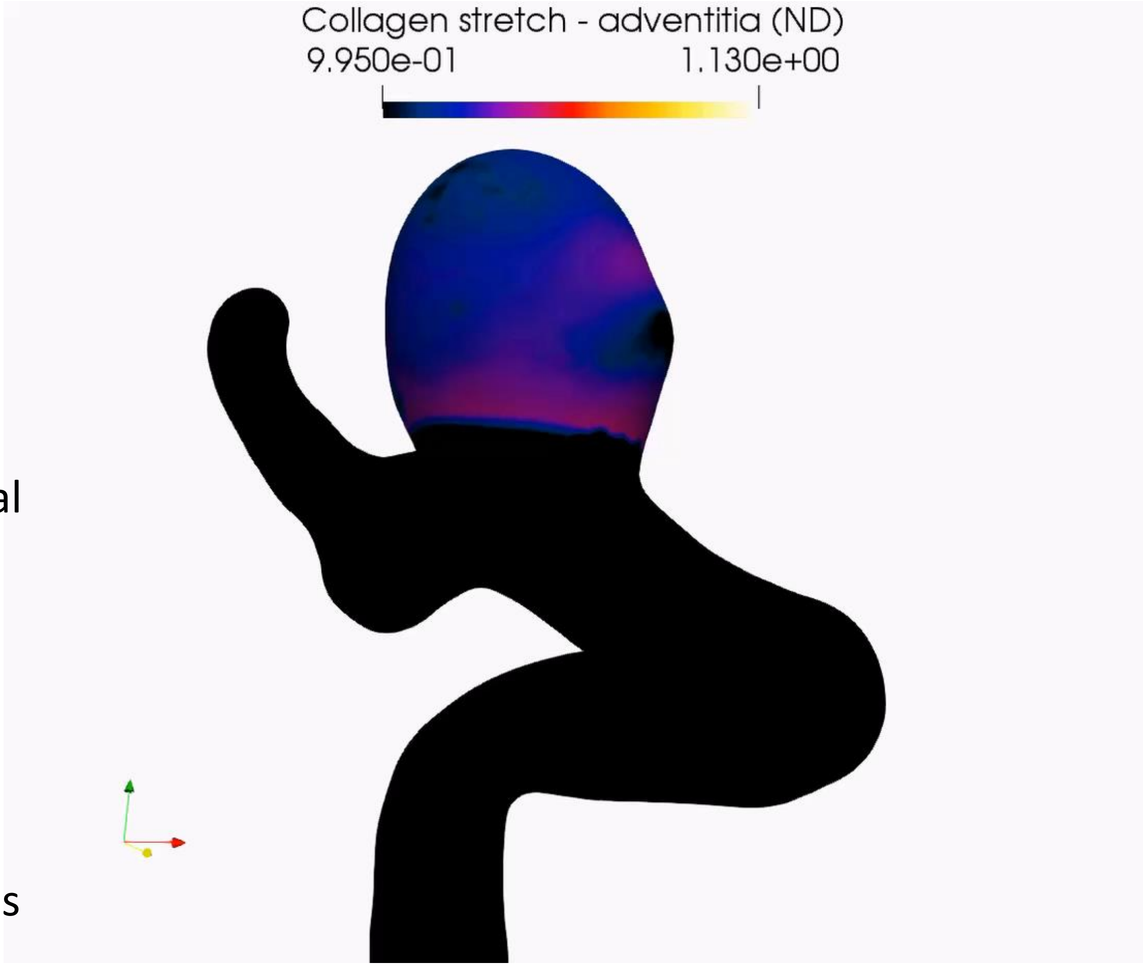


Collagen stretches increase in region of secondary bleb as it grows.
For bleb stabilisation, the attachment stretches in this region increase



Now…

- Patient-specific intracranial aneurysm growth model
- Fluid-Solid-Growth
- Representation of endothelial morphology
- Structural loss of media
- Adaptive role of adventitia
- Formation of secondary blebs



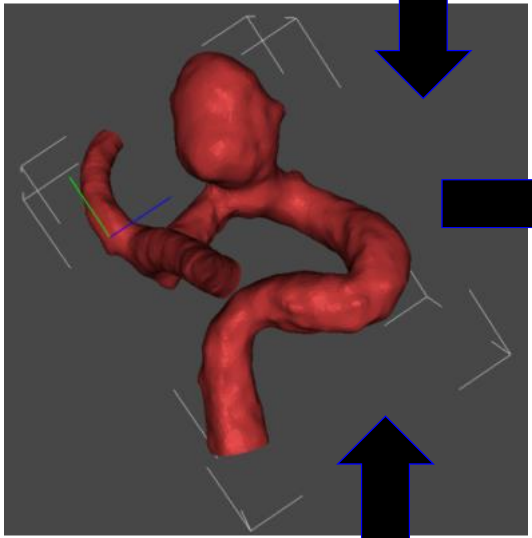
The AneuX Project (2015-19)

IT'IS FOUNDATION (Philppe Bilenga)

With **Frederico Teixeira**, Esra Neufeld, Sven Hirsch

Outlook…

LAB
Improve representation of collagen mechanobiology



CLINIC
Vessel Wall Imaging enhancement (MRI): geometry, permeability

MULTI-PHYSICS
Fluid-Solid-Growth-Transport Modelling Frameworks

NOVEL MATHEMATICAL MODELLING OF VASCULAR BIOLOGY
Linking EC Permeability and Dysfunction to Molecular Transport and Tissue Maintenance

RESEARCH TOOL
Aneurysm pathobiology
Understand/interpret enhanced contrast

CLINICAL TOOL: PREDICTION/STRATIFICATION ?
Enhanced contrast, Enhanced interpretation
Predictions of (in) stability

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wellcome

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aneurIST
Integrated biomedical informatics for the management of cerebral aneurysms

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Sven Hirsch

Esra Neufeld

Frederico Teixeira

AneuX

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Eidgenössische Technische Hochschule Zürich
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Pedro Aparicio (Ox)
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Yuqian Mei (Sheff)
Frederico Teixeira (ETH)

SofTMech

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