SILICOFCM

2nd Conference on Nonlinearity

How far we are from insilico clinical trials for cardiovascular disease?

22nd October, 2021

Prof. Nenad Filipovic
University of Kragujevac, Serbia

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

SILICOFCM

SILICOFCM aims to develop a computational platform for *in silico* clinical trials of Familial cardiomyopathies (FCMs) that would take into consideration comprehensive list of patient specific features (genetic, biological, pharmacologic, clinical, imaging and patient specific cellular aspects) capable of **optimizing and testing medical treatment strategy** with the purpose of **maximizing positive therapeutic outcome**, avoiding adverse effects, avoiding drug interactions, preventing sudden cardiac death, shortening time between the drug treatment commencement and the desired result.

SILICOFCM is a multi-modular, innovative *in silico* clinical trials solution for **the design and functional optimization of whole heart performance and monitoring effectiveness of pharmacological treatment**, with aim to reduce the animal studies and the human clinical trials.

The SILICOFCM platform is based on the **integrated multidisciplinary and multiscale methods** for analysis of patient-specific data and development of patient-specific models for monitoring and assessment of patient condition from current through the progression of disease.

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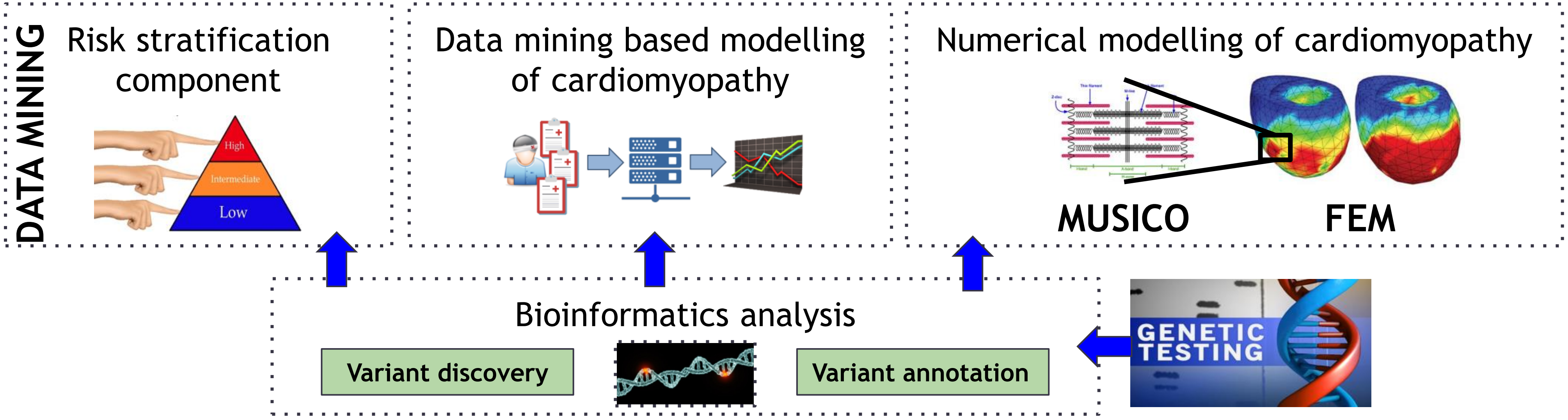
SILICOFCM

The main vision of SILICOFCM project



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Partners

- BIOIRC - Bioengineering Research and Development Center (RS)
- IIT - Illinois Institute of Technology (US)
- UNIKENT - University of Kent (UK)
- UNEW - University of Newcastle Upon Tyne (UK)
- UNIFI - University of Florence (IT)
- ICVDV - Institute of Cardiovascular Diseases Vojvodina (RS)
- UOI - University of Ioannina (EL)
- BSC - Barcelona Supercomputing Center (ES)
- UL - University of Ljubljana (SL)
- R-TECH - Steinbeis Advanced Risk Technologies (DE)
- UW - University of Washington (US)
- SBG - Seven Bridges Genomics INC (US)
- FMBG - Faculty of Medicine, University Of Belgrade (RS)

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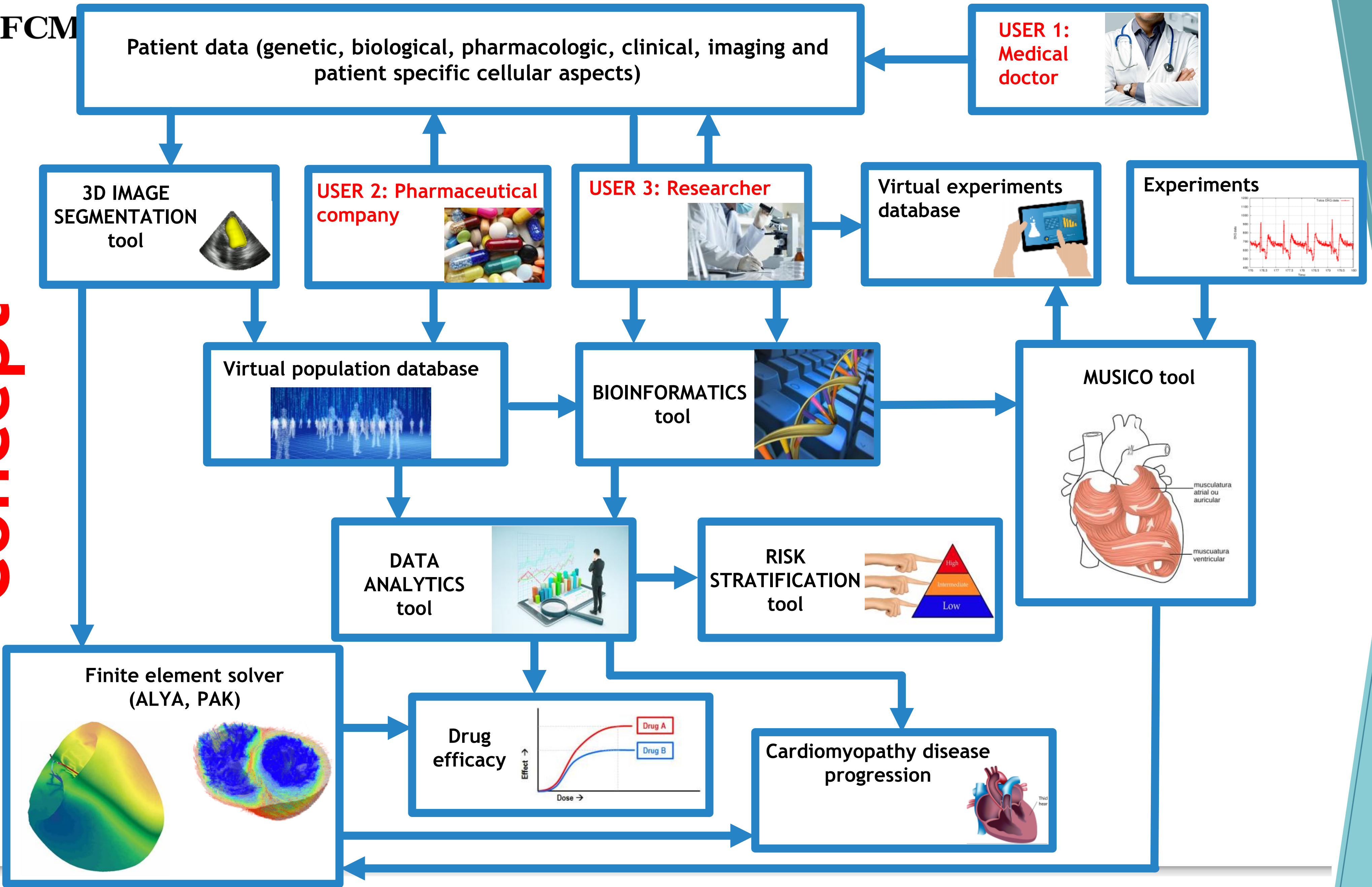
IMPACT

- Reducing the size and the duration of the human clinical trials
- A more effective human clinical trials design
- Leading to a significant reduction in animal testing
- Innovative medical products on the market with lower development costs and/or shorter time-to-market
- Improving prediction of human risks for new biomedical products
- Setting standards for *in silico* trials
- Providing libraries of virtual patients for re-use in pre- and post-competitive testing of biomedical products

SILICOFCM Concept



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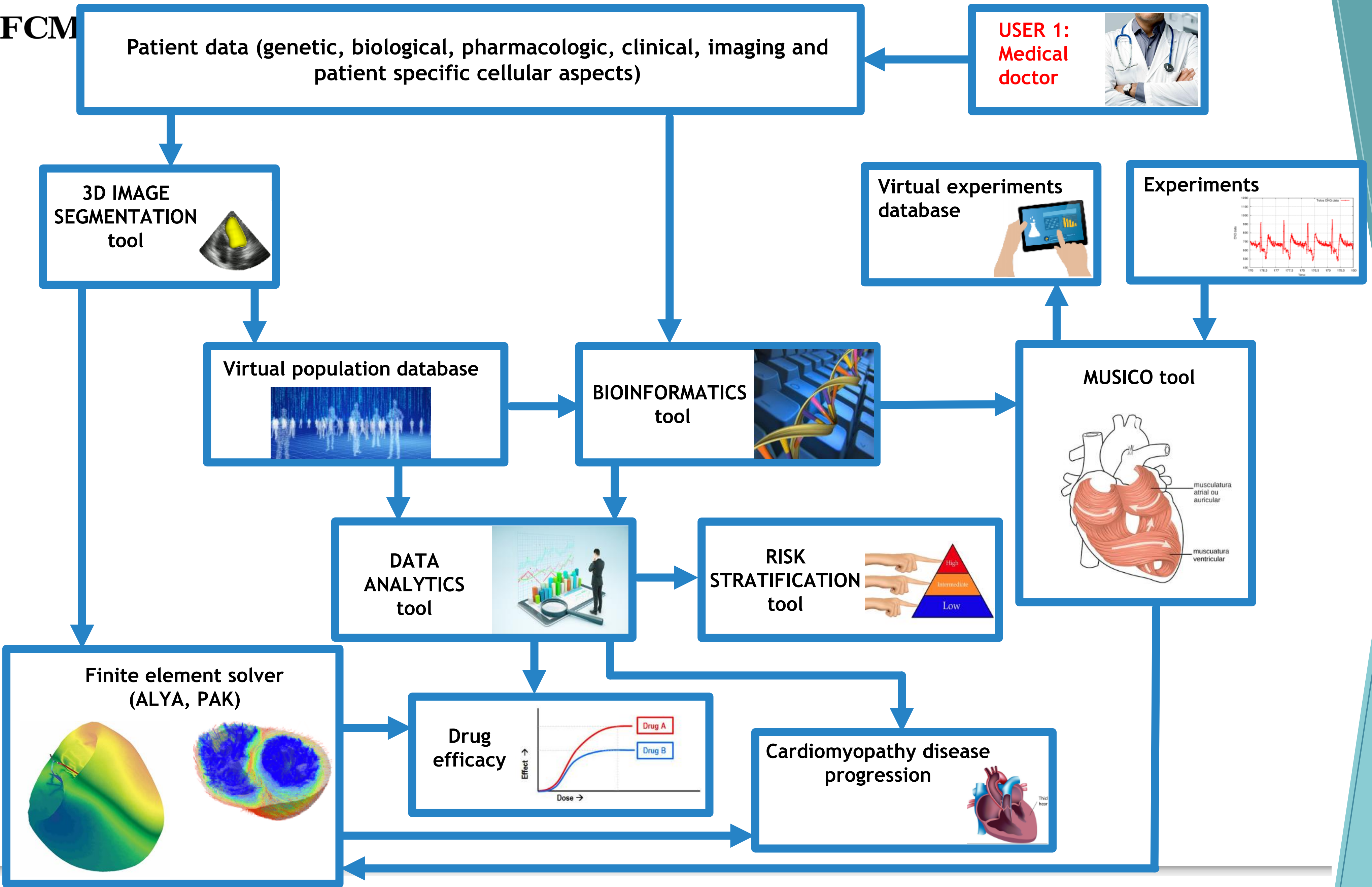
USE CASE 1



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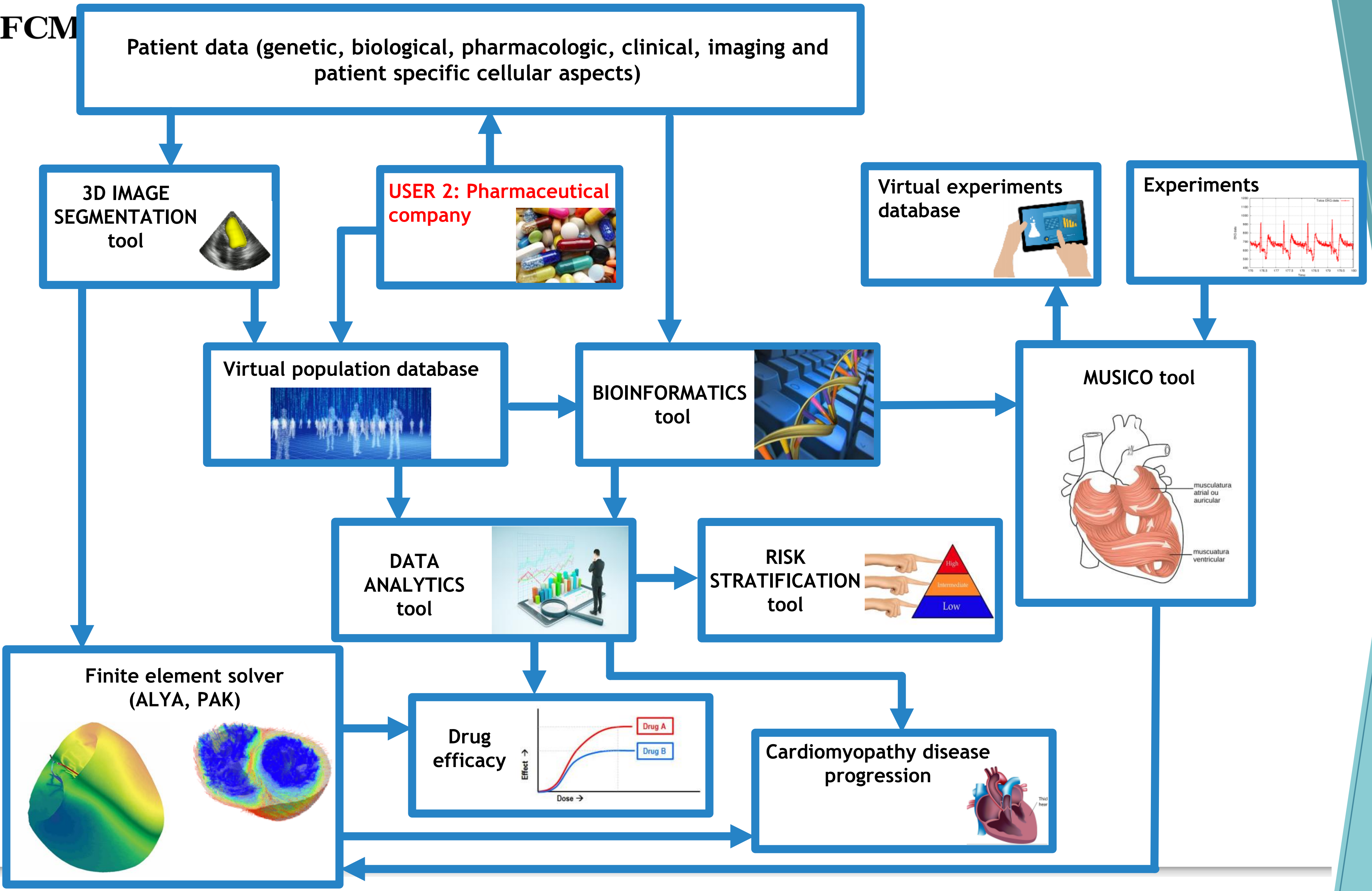
USE CASE 2



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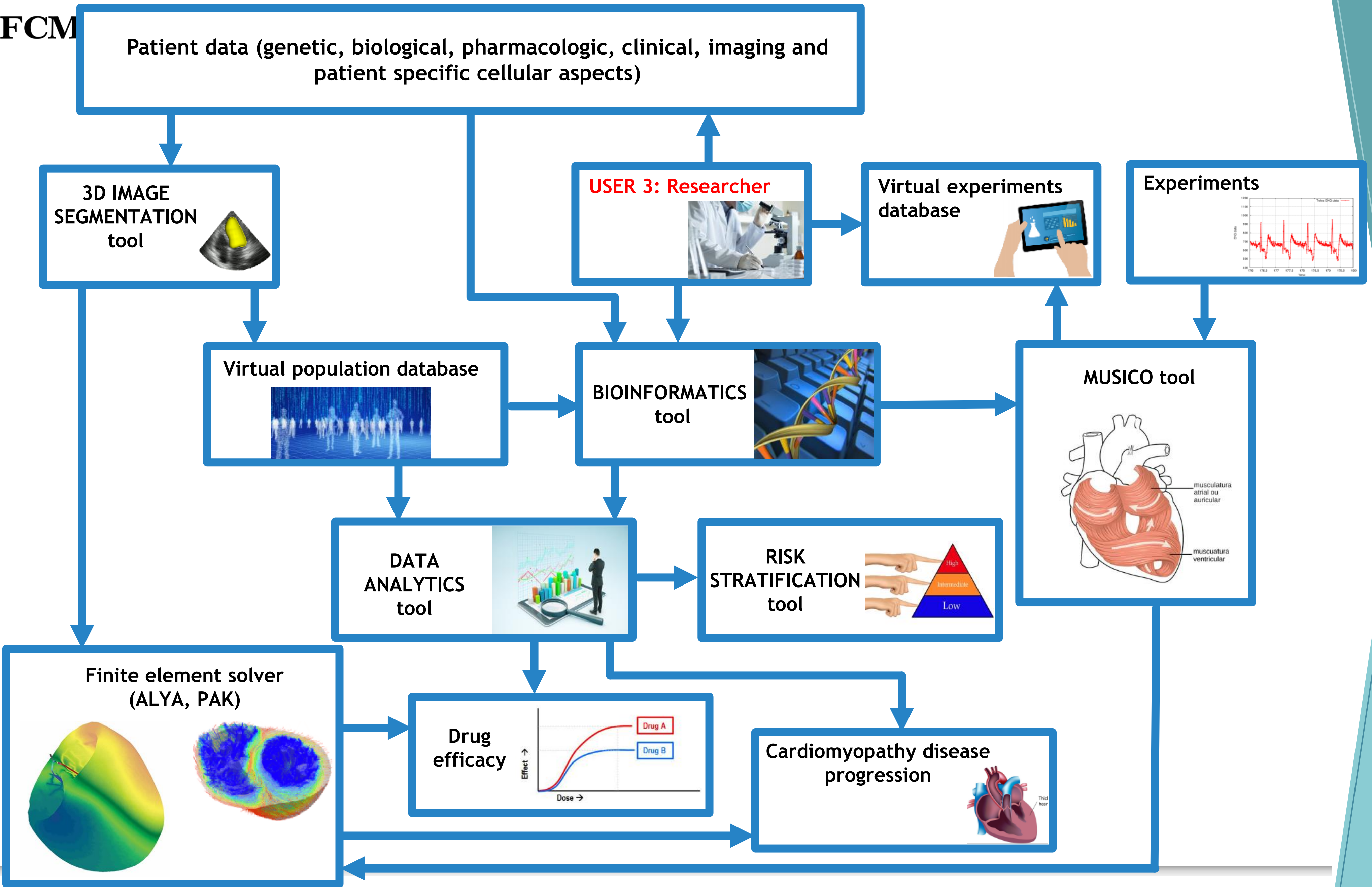
USE CASE 3



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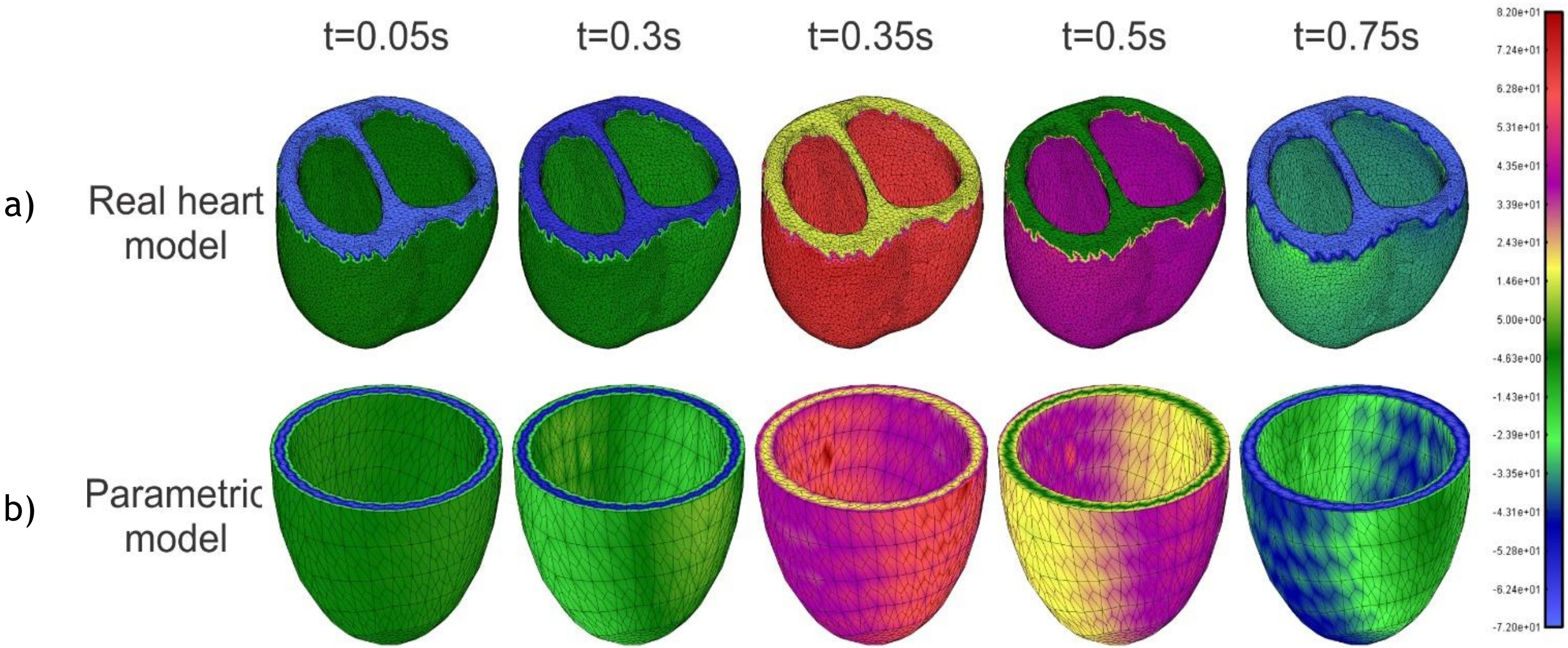
PAK module

- Example: Realistic models for electrical field and electromechanical coupling



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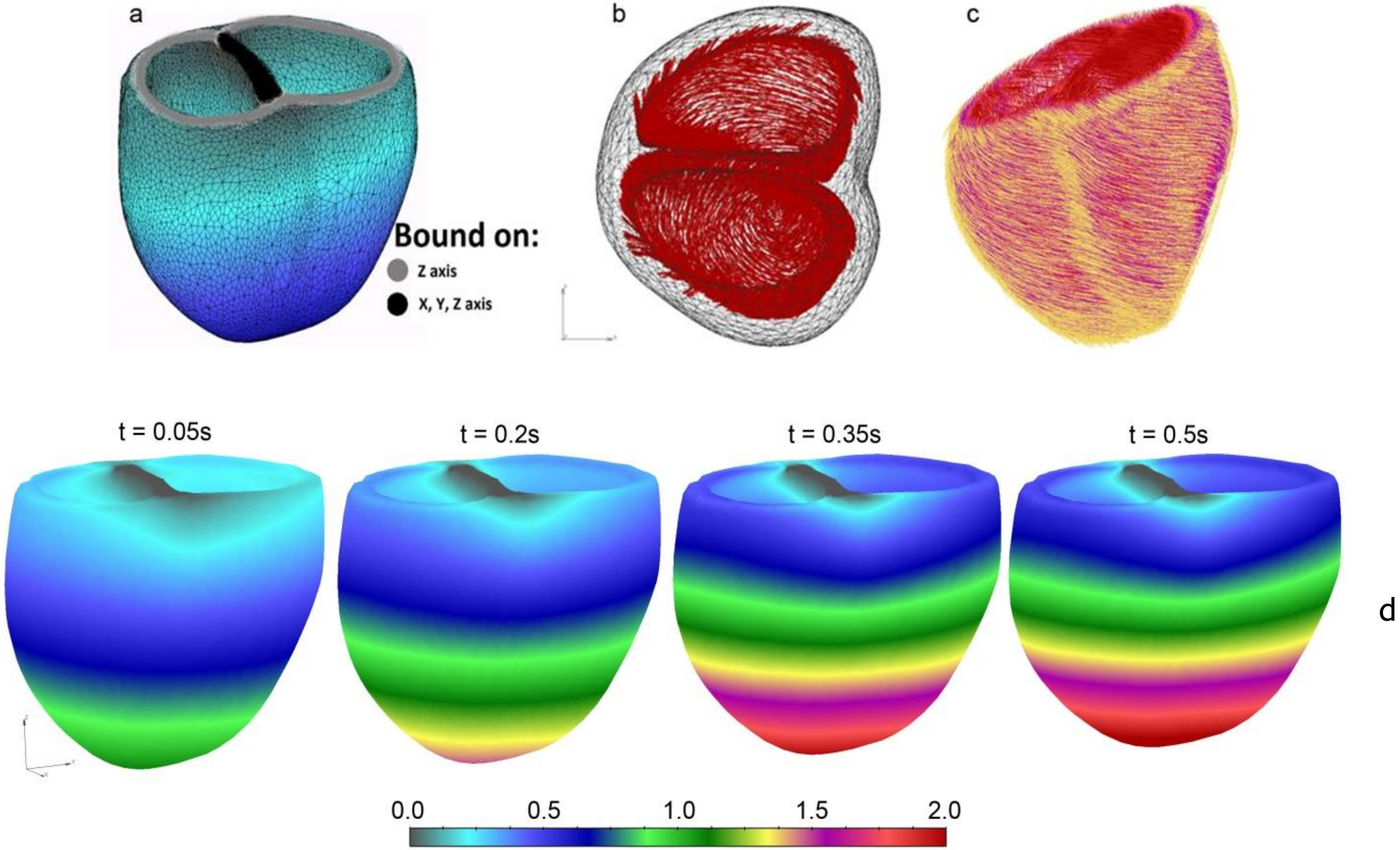
SILICOFCM

PAK module

- Example: Realistic models for electrical field and electromechanical coupling



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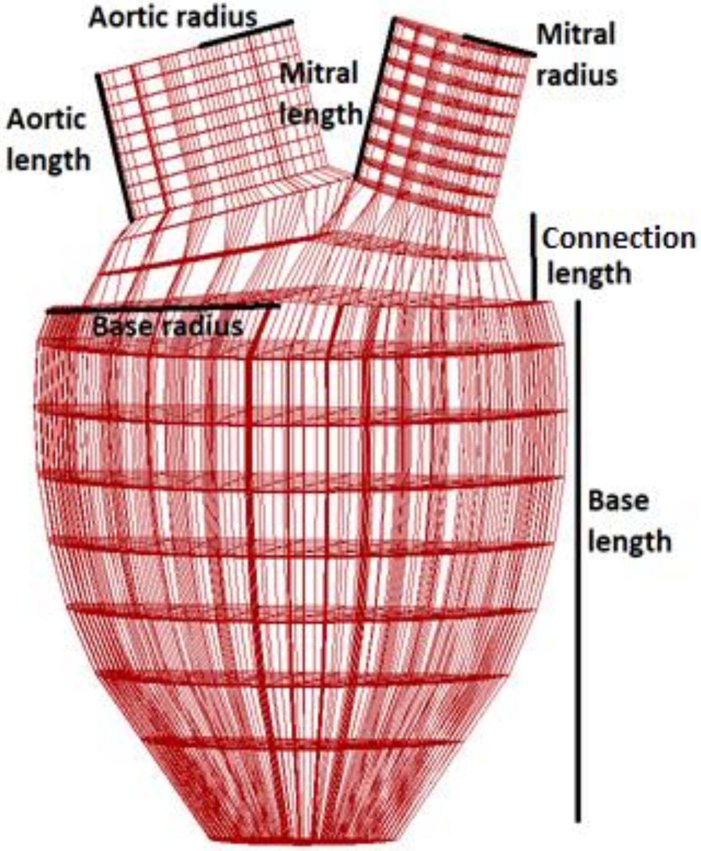
PAK module

- Example: Parametric structural model of Left ventricle



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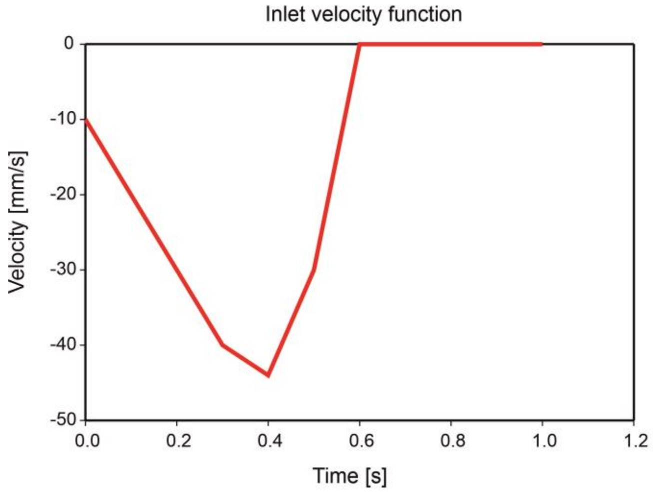
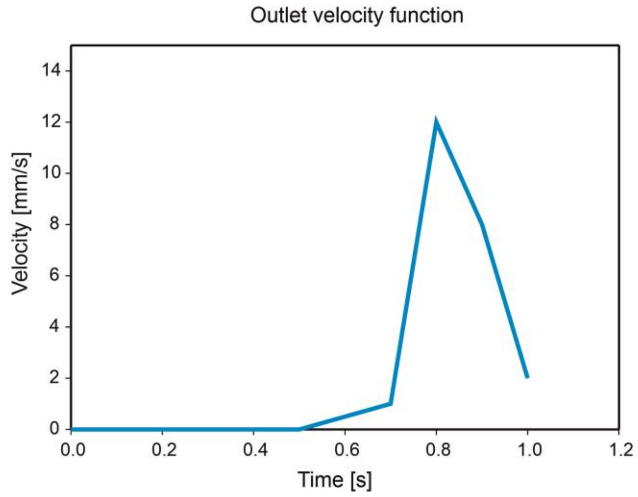
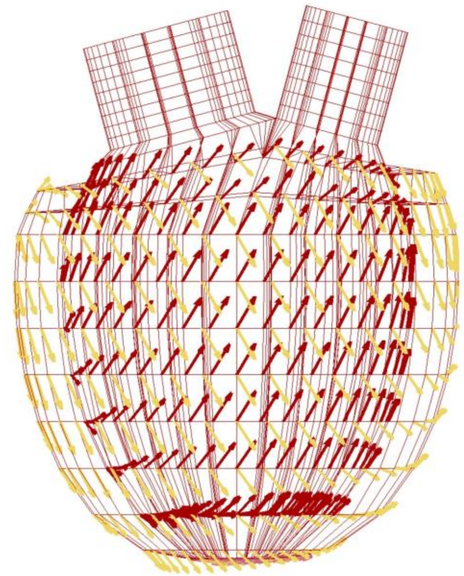


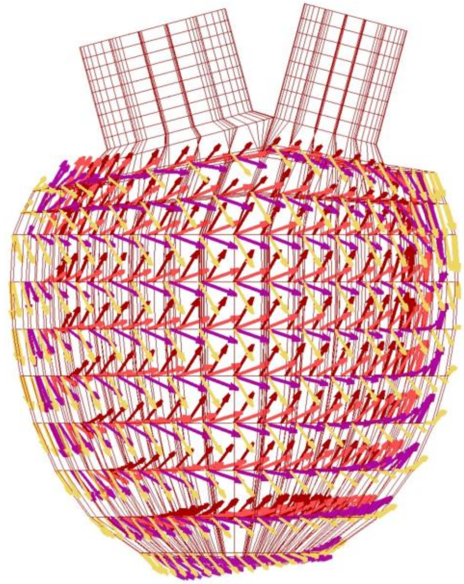
b)



c)



d)



e)

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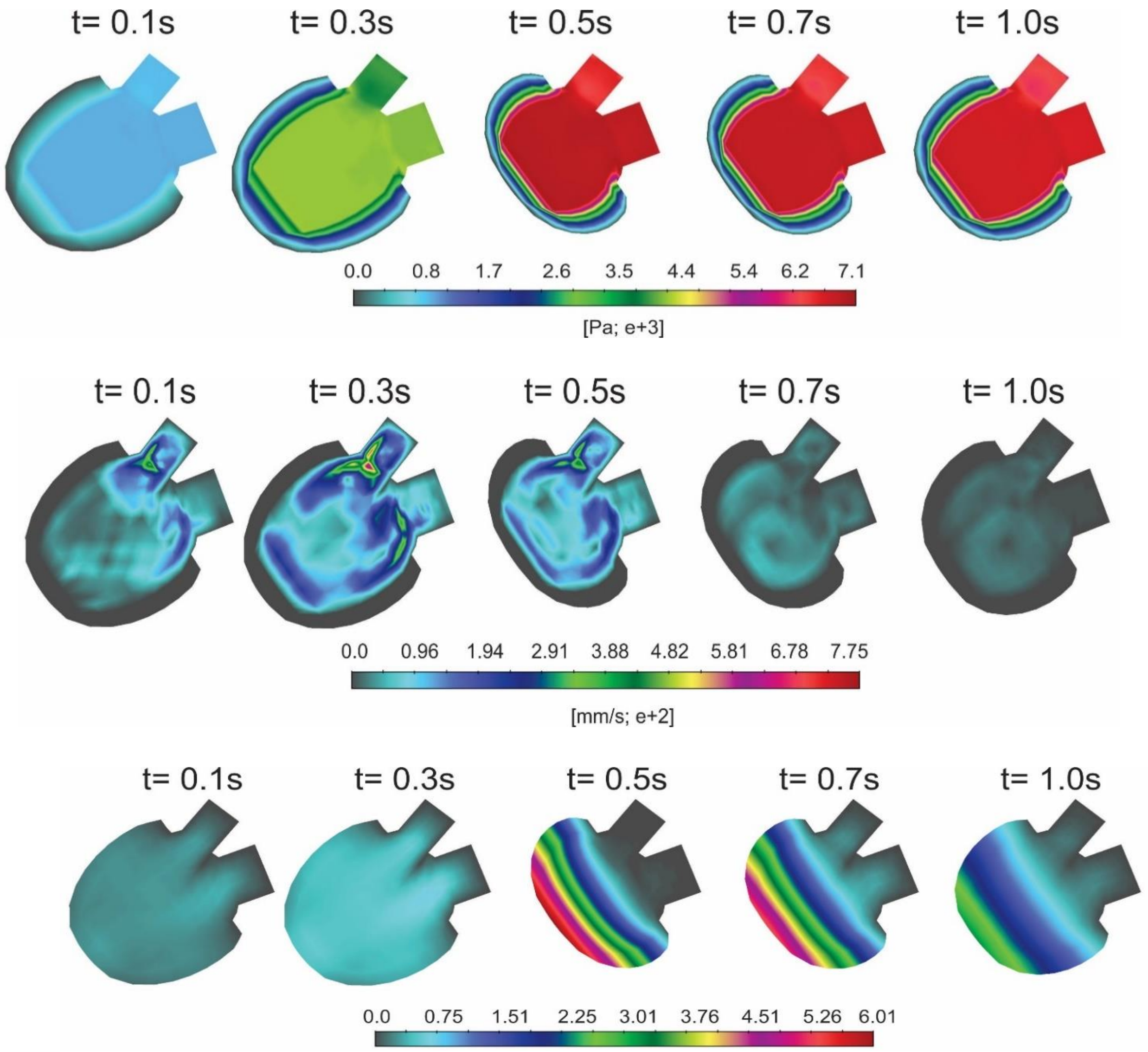
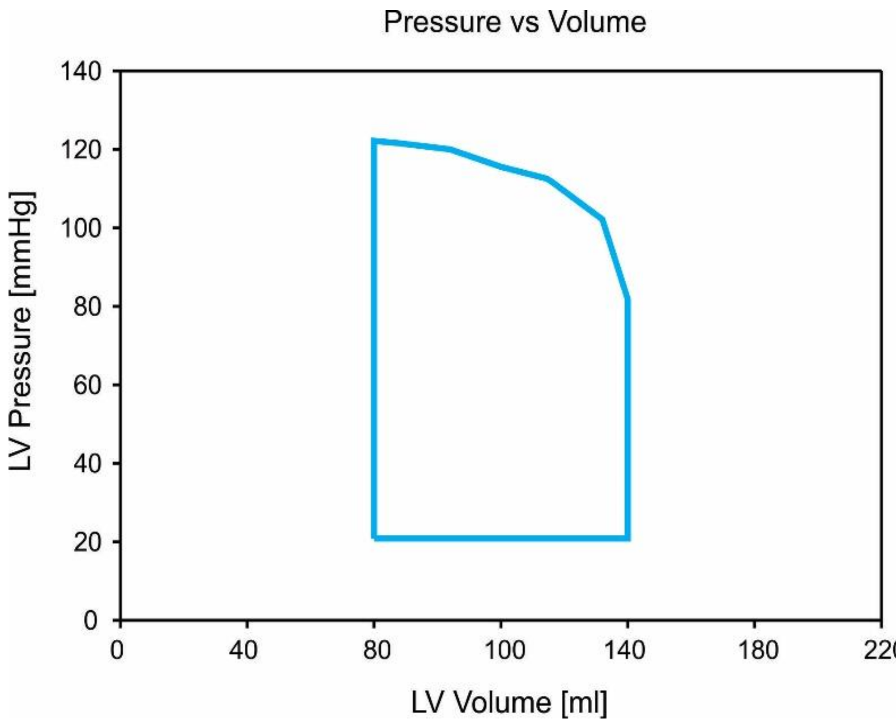
Example: Parametric structural model of Left ventricle



a)

b)

c)



d)

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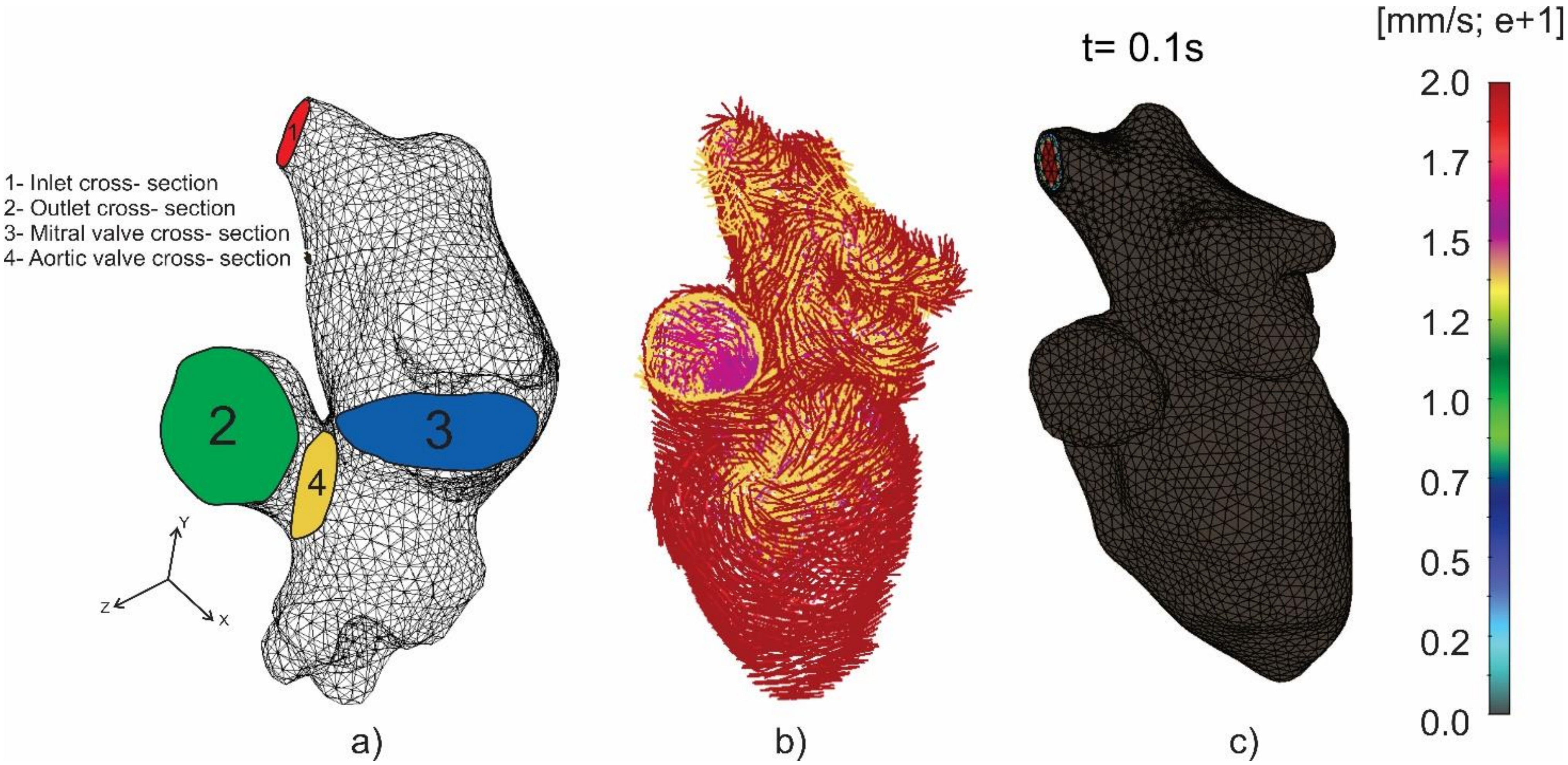
PAK module

- Example: Realistic heart model



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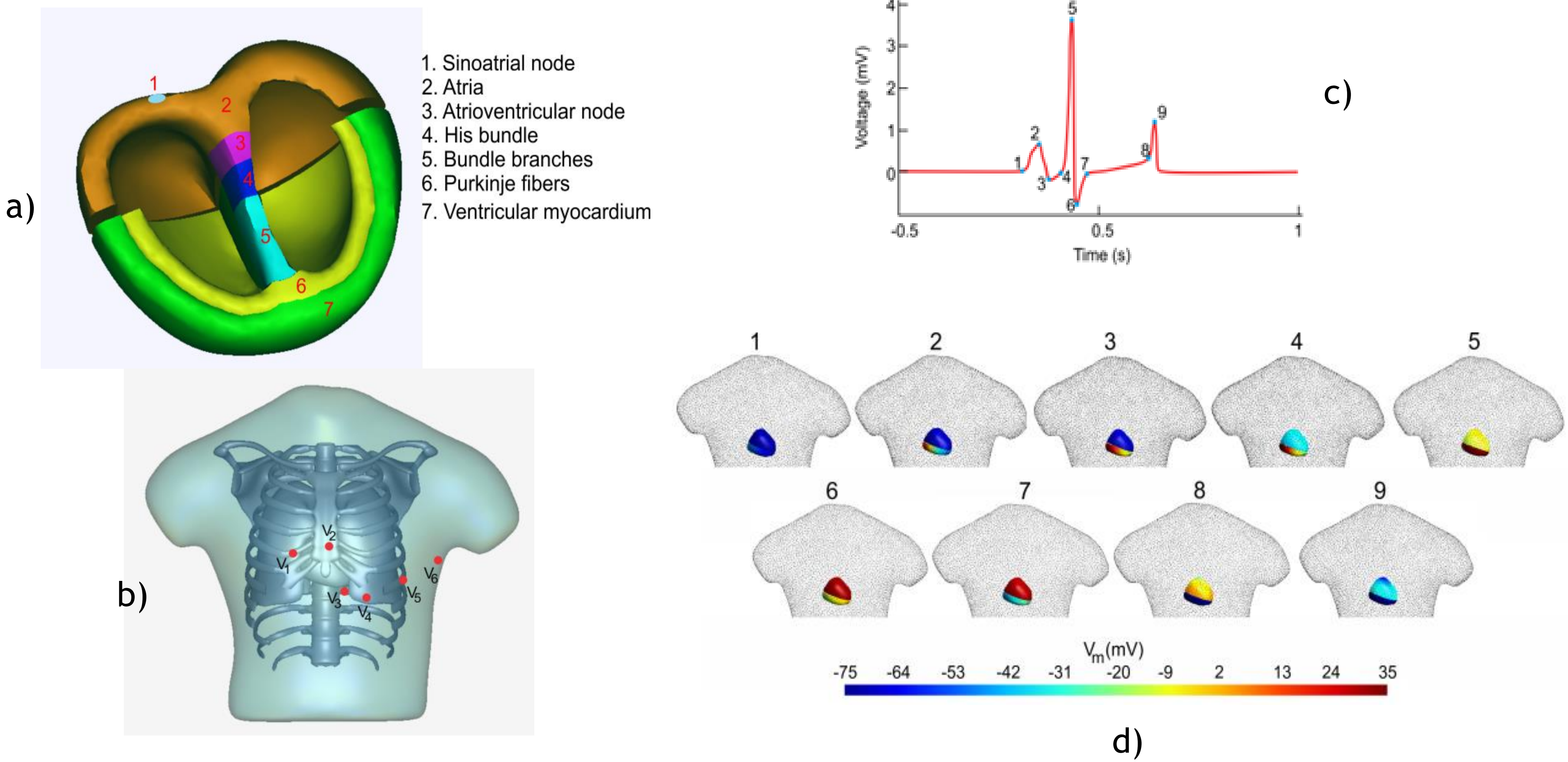
PAK module

- Example: Torso model



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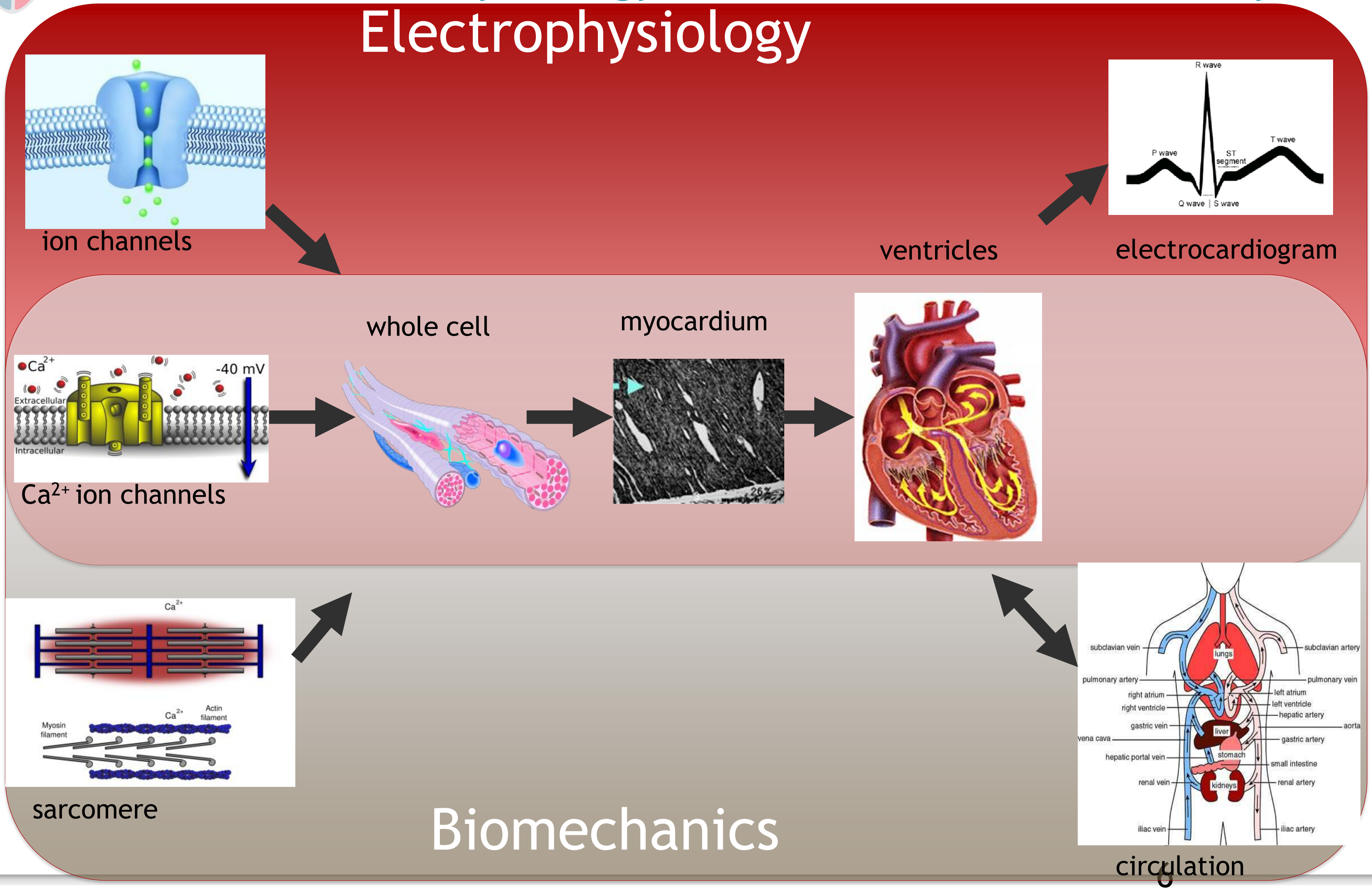
The Heart Physiology as an Electro-Mechanic System



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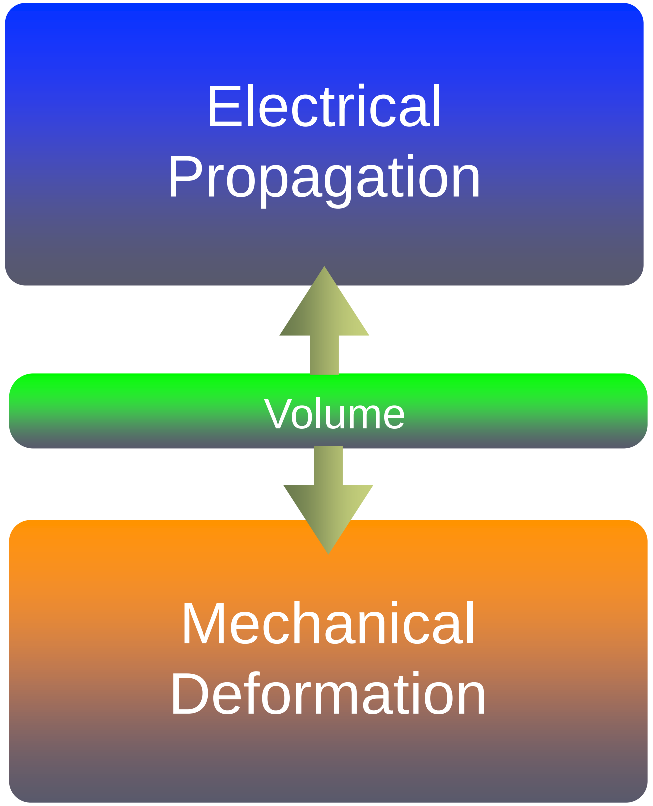
Fluid-Electro-Mechanic Cardiac Model - The Heart as a Multi-Physics Coupled System



Electrophysiology:

Linear anisotropic (fibers) diffusion + non-linear source terms

Rogers-McCulloch, O'Hara-Rudy, Ten Tuscher-Panfilov, Fenton-Karma,…

Electro-mechanical coupling, via Ca+ transient:

Hunter & McCulloch 1998, Land-Niederer 2017, Rice-Winslow 2006

Large deformations + non-linear, orthotropic material models: Holzapfel and Ogden 2009

ALE + Immersed Boundaries

Navier -Stokes for Incompressible Flow

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Models

I_{ion}: *Human EP model*

O'Hara- Rudy 2011

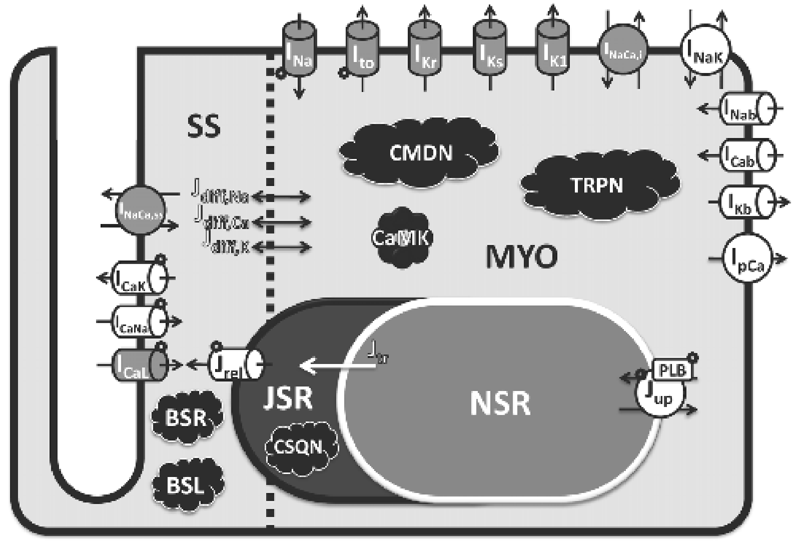
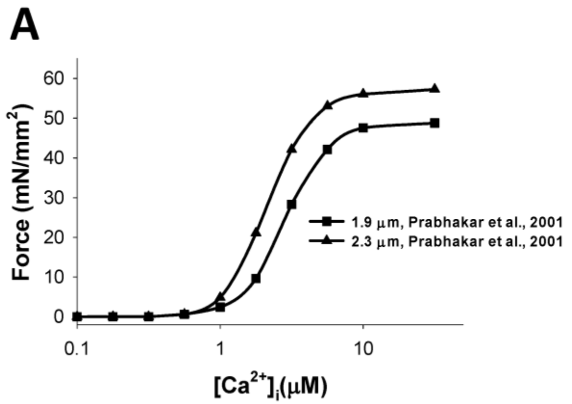
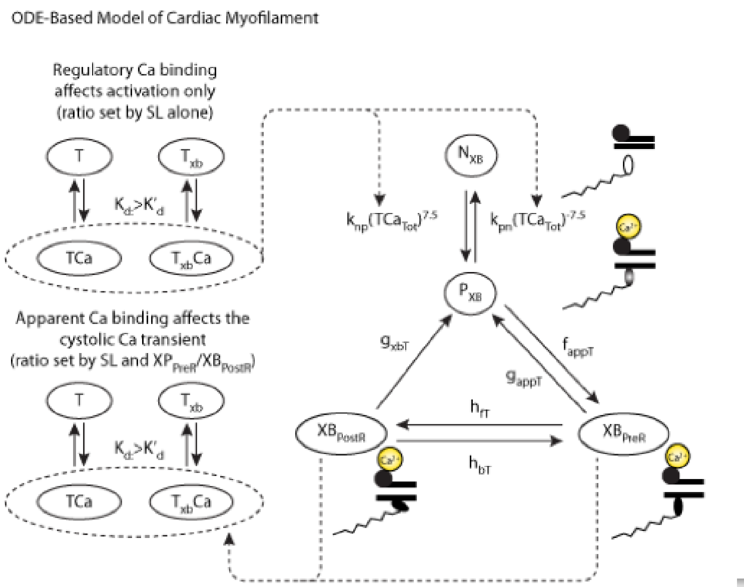


Figure 5. Schematic diagram of human ventricular myocyte model. Formulations for all currents and fluxes were based either directly (gray) or indirectly (white) on undiseased or nonfailing human experimental data. Model includes four compartments: 1) bulk myoplasm (myo), 2) junctional sarcoplasmic reticulum (JSR), 3) network sarcoplasmic reticulum (NSR), and 4) subspace (SS), representing the space near the T-tubules. Currents into the myoplasm: Na^+ current (I_{Na}; representing both fast and late components), transient outward K^+ current (I_{to}), rapid delayed rectifier K^+ current (I_{Kr}), slow delayed rectifier K^+ current (I_{Ks}), inward rectifier K^+ current (I_{K1}), 80% of Na^+/Ca^{2+} exchange current ($I_{NaCa,i}$), Na^+/K^+ pump current (I_{NaK}), background currents (I_{Nab}, I_{Cab} and I_{Kb}), and sarcolemmal Ca^{2+} pump current (I_{pCa}). Currents into subspace: L-type Ca^{2+} current (I_{CaL}, with Na^+ and K^+ components I_{CaNa}, I_{CaK}), and 20% of Na^+/Ca^{2+} exchange current ($I_{NaCa,ss}$). Ionic fluxes: Ca^{2+} through ryanodine receptor (J_{rel}), NSR to JSR Ca^{2+} translocation (J_{tr}), Ca^{2+} uptake into NSR via SERCA2a/PLB (J_{up}; PLB - phospholamban), diffusion fluxes from subspace to myoplasm ($J_{diff,Na}$, $J_{diff,Ca}$, and $J_{diff,K}$). Ca^{2+} Buffers: calmodulin (CMDN), troponin (TRPN), calsequestrin (CSQN), anionic SR binding sites for Ca^{2+} (BSR), anionic sarcolemmal binding sites for Ca^{2+} (BSL). Ca^{2+}/calmodulin-dependent protein kinase II (CaMK) and its targets are labeled.
doi:10.1371/journal.pcbi.1002061.g005

ECC: Hunter-McCulloch 1998



ECC: Rice et al. 2008



ECC: Land-Niederer 2017

$$\frac{\mathrm{dCaTRPN}}{\mathrm{d}t} = k_{\mathrm{TRPN}}\left(\left(\frac{[\mathrm{Ca}^{2+}]_{\mathrm{i}}}{[\mathrm{Ca}^{2+}]_{\mathrm{T50}}}\right)^{n_{\mathrm{TRPN}}}(1-\mathrm{CaTRPN})-\mathrm{CaTRPN}\right)$$

$$\frac{\mathrm{d}B}{\mathrm{d}t} = k_{\mathrm{b}}\cdot \mathrm{CaTRPN}^{-n_{\mathrm{Tm}}/2}\cdot U - k_{\mathrm{u}}\cdot \mathrm{CaTRPN}^{n_{\mathrm{Tm}}/2}\cdot B$$

$$\frac{\mathrm{d}W}{\mathrm{d}t} = k_{\mathrm{uw}}U - k_{\mathrm{wu}}W - k_{\mathrm{ws}}W - \gamma_{\mathrm{wu}}W$$

$$\frac{\mathrm{d}S}{\mathrm{d}t} = k_{\mathrm{ws}}W - k_{\mathrm{su}}S - \gamma_{\mathrm{su}}S$$

$$\frac{\mathrm{d}\zeta_w}{\mathrm{d}t} = A_w\frac{\mathrm{d}\lambda}{\mathrm{d}t} - c_w\zeta_w$$

$$\frac{\mathrm{d}\zeta_s}{\mathrm{d}t} = A_s\frac{\mathrm{d}\lambda}{\mathrm{d}t} - c_s\zeta_s$$

$$T_a = \frac{T_{\mathrm{ref}}}{r_s}\left(S(\zeta_s+1)+W\zeta_w\right)$$

$$\lambda = \mathrm{SL}/\mathrm{SL}_0 = \|\mathbf{Ff}\| \quad \text{(in multiscale simulations)}$$

$$U = (1-B)-S-W$$

$$\gamma_{\mathrm{wu}} = \gamma_w|\zeta_w|$$

$$\gamma_{\mathrm{su}} = \begin{cases}\gamma_s(-\zeta_s-1) & \text{if } \zeta_s+1<0\\ \gamma_s\zeta_s & \text{if } \zeta_s+1>1\\ 0 & \text{otherwise (if } \zeta_s+1\in[0,1])\end{cases}$$

$$A_s = A_w = A_{\mathrm{eff}}\cdot r_s/((1-r_s)r_w+r_s)$$

$$k_{\mathrm{wu}} = k_{\mathrm{uw}}(1/r_w-1)-k_{\mathrm{ws}}$$

$$k_{\mathrm{su}} = k_{\mathrm{ws}}r_w(1/r_s-1)$$

$$k_{\mathrm{b}} = k_{\mathrm{u}}\mathrm{CaTRPN}^{n_{\mathrm{Tm}}}/(1-r_s-(1-r_s)r_w)$$

$$c_w = \phi\cdot k_{\mathrm{uw}}\cdot U/W = \phi\cdot k_{\mathrm{uw}}\cdot((1-r_s)(1-r_w))/((1-r_s)r_w)$$

$$c_s = \phi\cdot k_{\mathrm{ws}}\cdot W/S = \phi\cdot k_{\mathrm{ws}}\cdot((1-r_s)r_w)/r_s$$

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Fully Coupled Electro-Mechanic-Fluid simulation

Number of elements: 4M total
240 cores, 12 hrs, 400 ms

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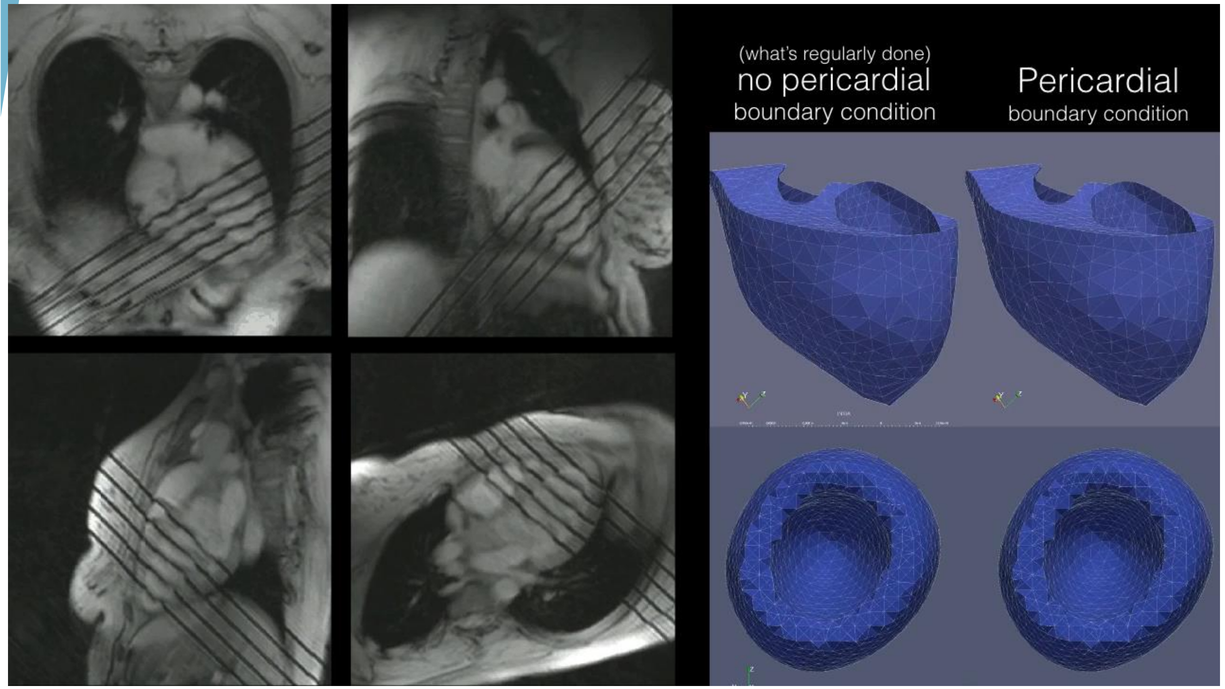
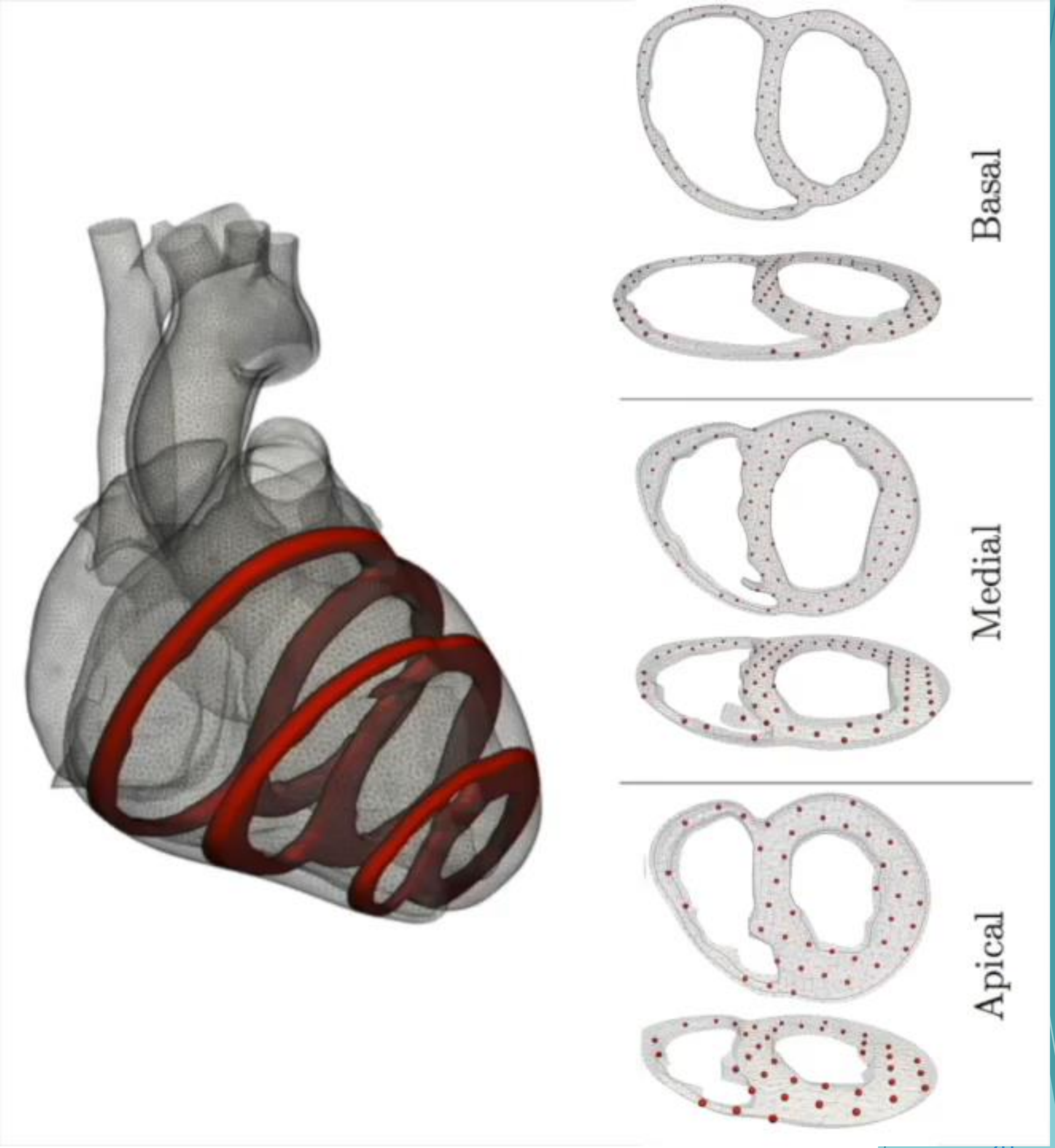
Boundary Conditions and Physiological motion





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Human Biventricular Geometry Reconstruction

High Resolution MRI of Male and Female Human Hearts

Courtesy of The Visible Heart ® Lab

- *Male Heart*
- *Female Heart*

Segmentation and Surface representation

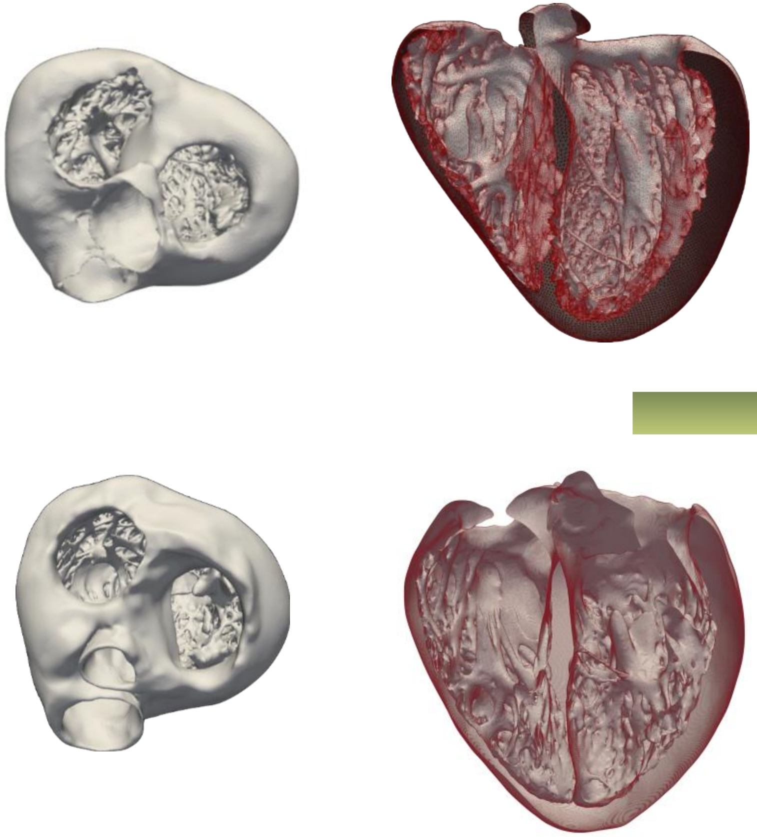
Endocardial structures included are ≥ 1 mm^2 cross-section

AUTODESK MESHMIXER

Fiji Is Just ImageJ

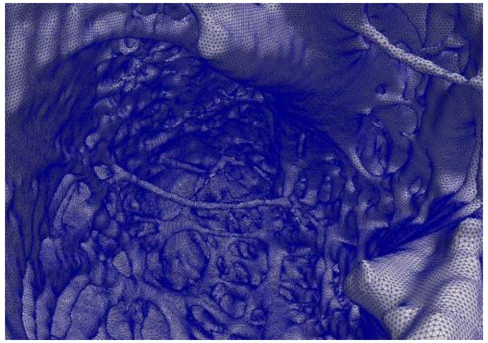
Seg3D

ReMESH

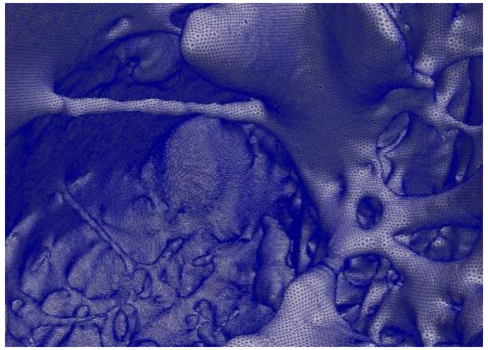


Biventricular Detailed Octree Volumetric Meshes

MAXIMUM ELEMENT SIDE LENGTH: 0.4 mm



n° elements: 86.318.429
Volume: 394.2 cm^3
n° points: 14.994.563



n° elements: 65.501.799
Volume: 299.2 cm^3
n° points: 11.416.445

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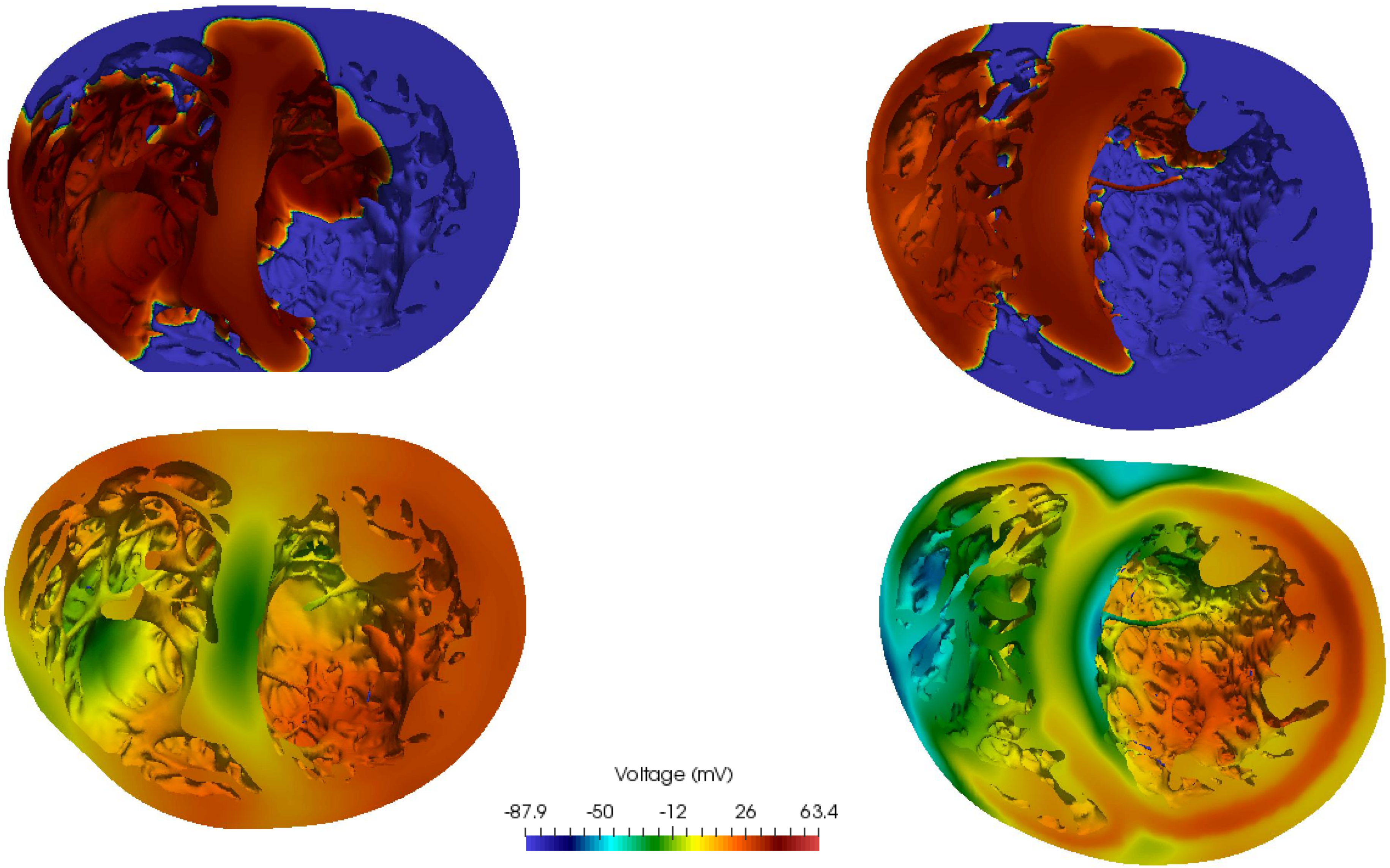
Female Phenotype Male Phenotype



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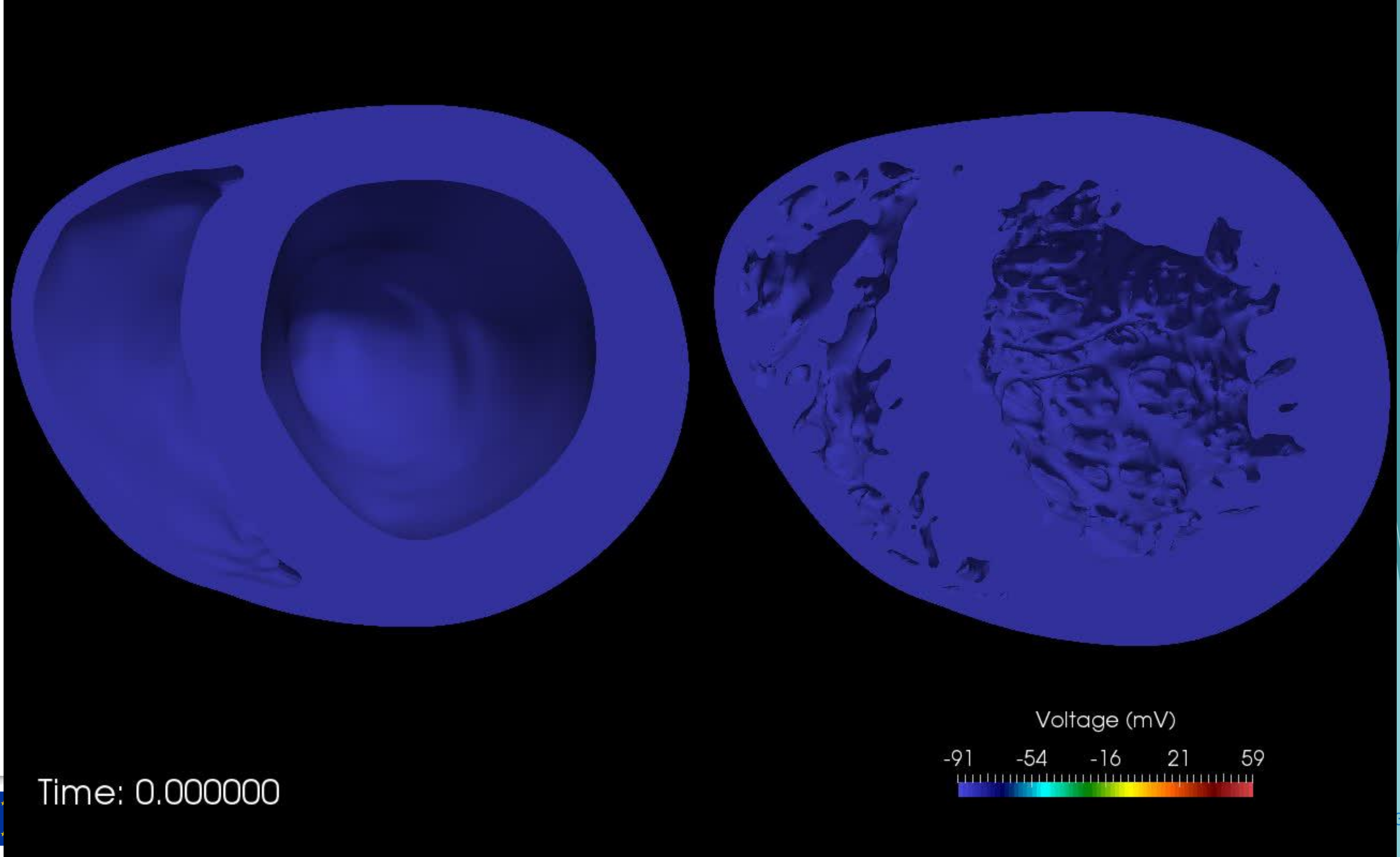

Voltage (mV)
-91 -54 -16 21 59
Time: 0.000000

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Drug selection

Drug Database

Signaling Pathway selection

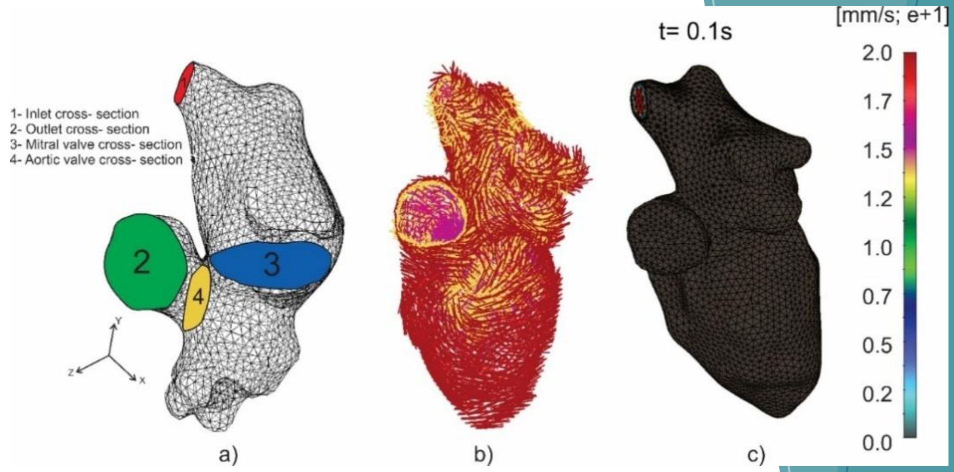
Minerva

Drug/Protein Interactions

Data Collection

Molecular data

SILICOFCM MUSICO model



SILICOFCM finite element model

Clinical decision for patient therapy

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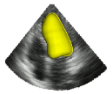
SILICOFCM Tools - Specific impact on Medical doctors, Pharmaceutical companies and Researchers

3D IMAGE SEGMENTATION tool



- *Fast 3D reconstruction*
- *Suitable heart models for further simulations*

VIRTUAL EXPERIMENTS database

- Optimisation of clinical trials
- Break-through pharmacological treatment for heart failure

VIRTUAL POPULATION

- Reusable and plausible libraries
- Geometrical and clinical features
- Testing of a new drug under different boundary conditions

DATA ANALYTICS tool

- Improved prediction of patients risks
- Estimation of disease progression
- Estimation of drug efficacy

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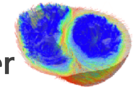
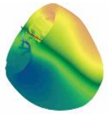
ALYA Finite element solver



- Simulations from the sarcomere dynamics up to the whole heart behavior
- Determination of drug efficacy

PAK Finite element solver

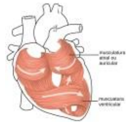


- Drug distribution, stress distribution and deformations of heart tissue

BIOINFORMATICS tool

- Identified variants contributing to the disease

MUSICO tool



- Simulation of a wide variety of experimental muscle behavior

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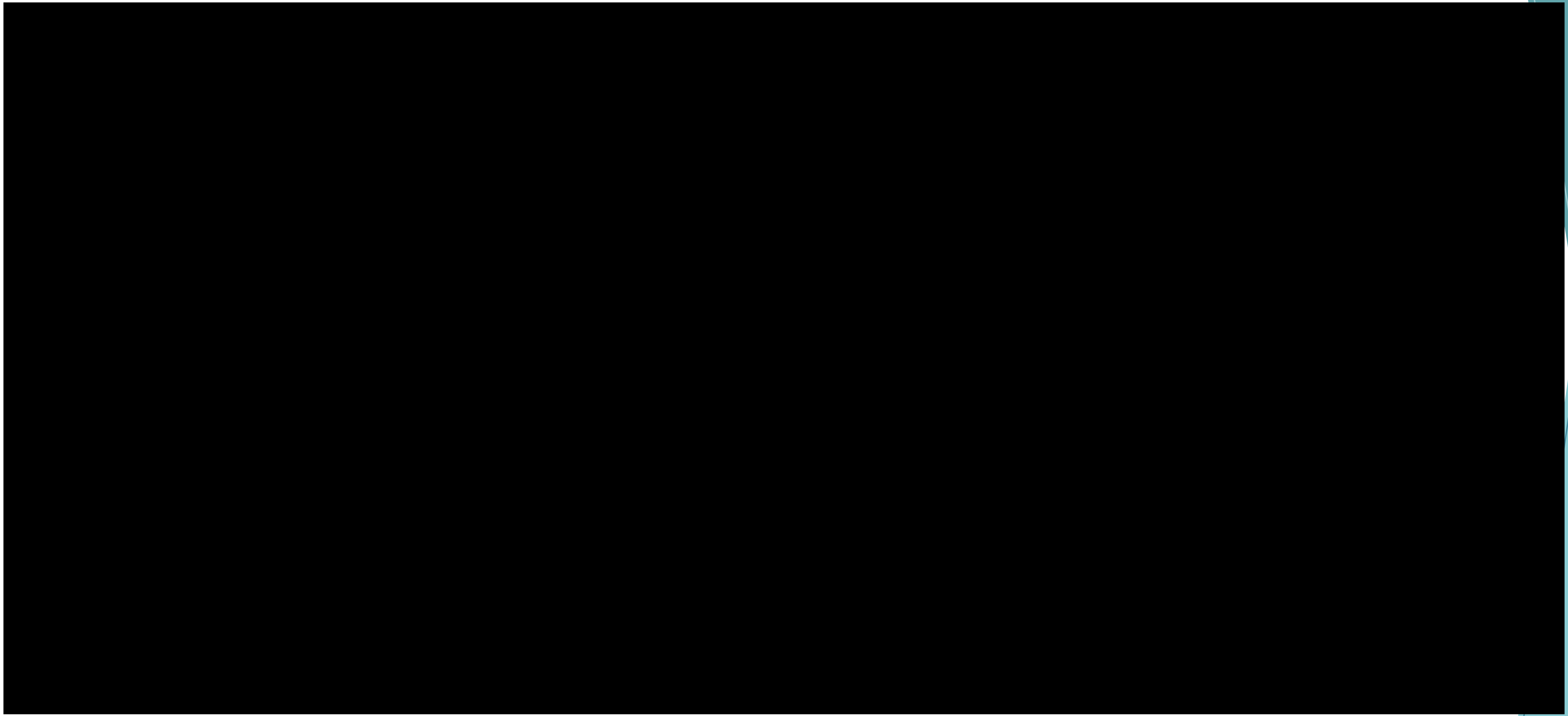
DEMO



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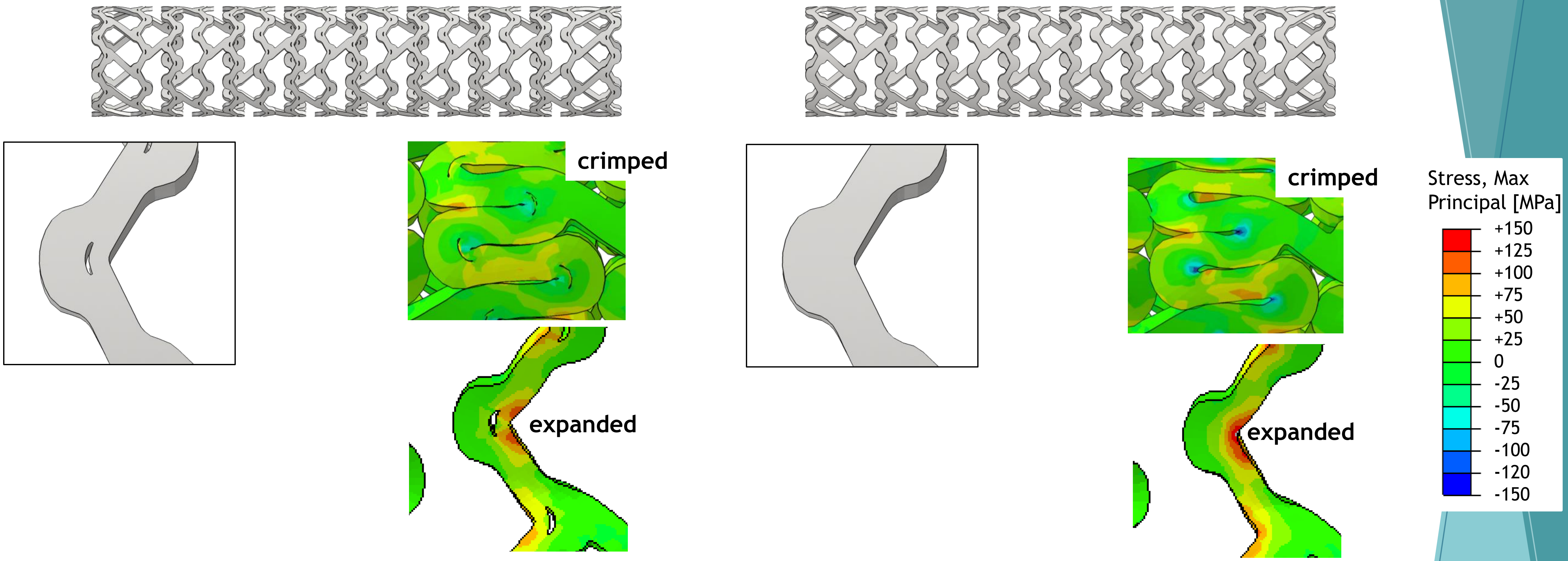
Finite element modelling of the BVS implantation system

PLLA prototype-V2 vs PLLA prototype



Antonini L., Poletti G., Mandelli L. , Dubini G. , Pennati G. , Petrini L. **Comprehensive computational analysis of the crimping procedure of PLLA BVS: effects of material viscous-plastic and temperature dependent behavior** *J Mech Behav Biomed Mater,* 2021 (minor revisions)

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Task 5.1 Overview - DoA

DoA	1-18	19-24
“detailed material characterization based on classical tests for viscoplastic materials… information obtained from **experiments performed in Task 3.1** (Group 2) … FE simulations for calibrating the viscoplastic parameters of the specific material”	▪ Synergy: material parameter definition from BSL data ▪ PLLA prototype: tests on dogbones and material parameter definition ▪ BVS-1: material parameters based on literature data	**BVS-2**: **calibration** of nine material parameters based on device experimental tests (WP3) & response surface creation
“The **accuracy** of these models will be assessed“	▪ Synergy: preliminary validation ▪ PLLA prototype: preliminary validation ▪ BVS-1: validation using literature data	**Complete validation** for : ▪ Synergy ▪ PLLA prototype ▪ PLLA prototype-V2 ▪ BVS-2

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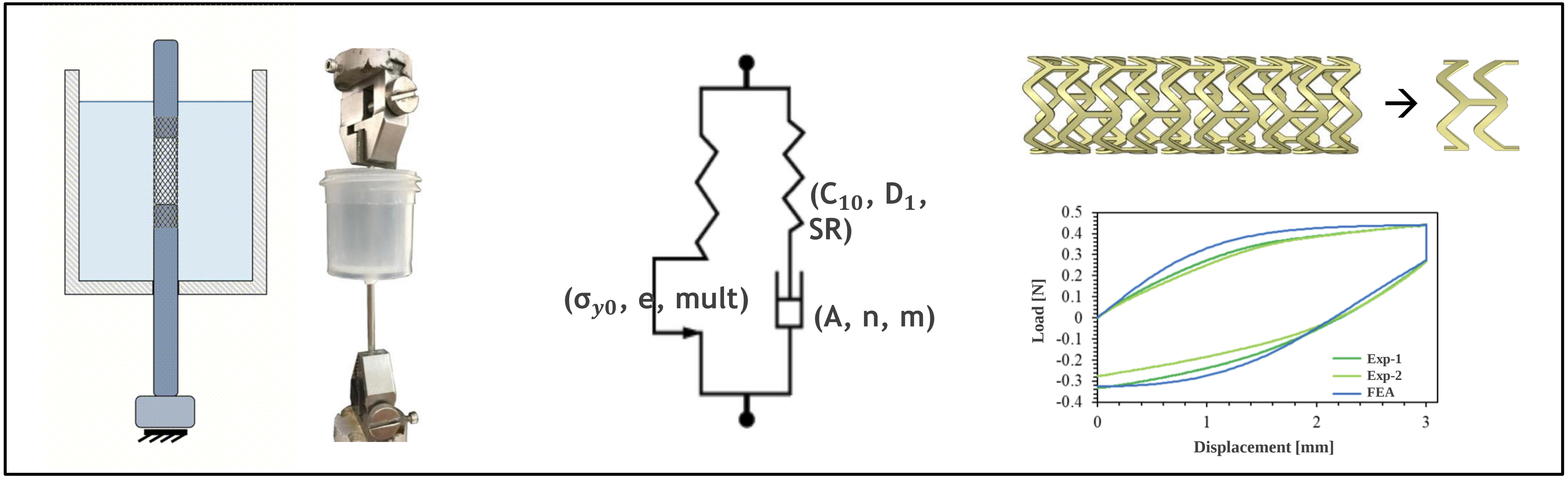
BVS-2 calibration of material model

Experimental Tests → Selection of material model → Calibration of model parameters



Antonini L., Berti F., Isella B., Hossain D., Mandelli L., Pennati G., Petrini L.
From the real device to the digital twin: a coupled experimental-numerical strategy to investigate a novel bioresorbable vascular scaffold.
PLOS ONE 2021 16(6): e0252788.
https://doi.org/10.1371/journal.pone.0252788

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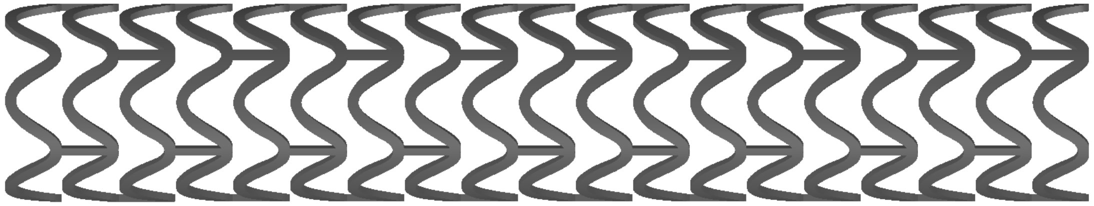
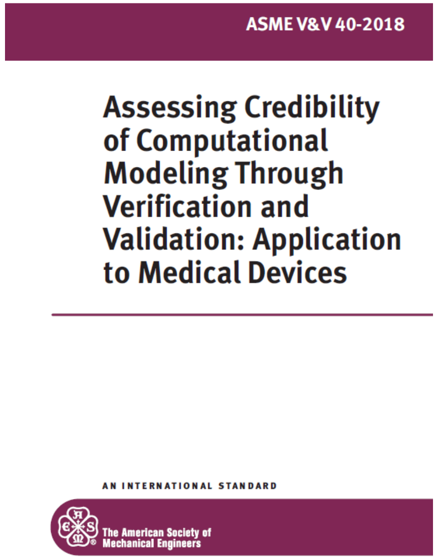
Validation of stent mod

Free Expansion

BVS-2



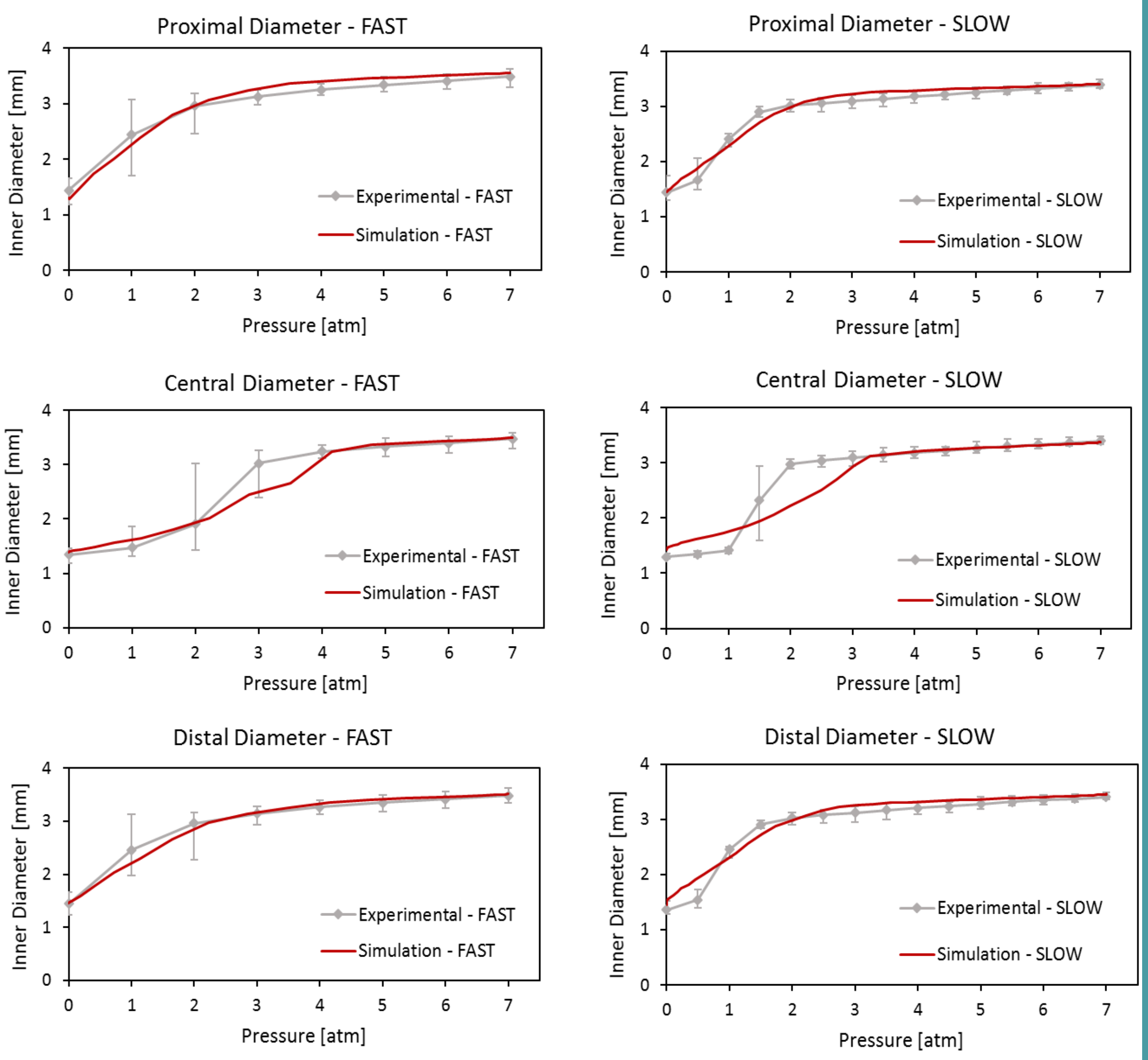

ASME V&V 40-2018

Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices

AN INTERNATIONAL STANDARD

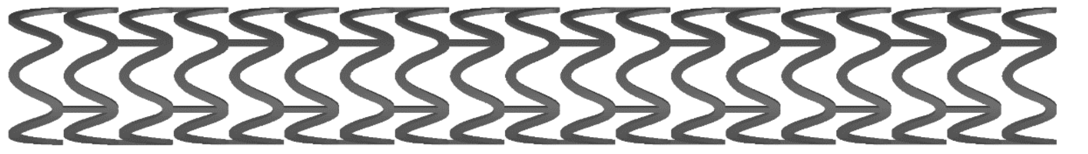
The American Society of Mechanical Engineers

Diameter Error < 5%

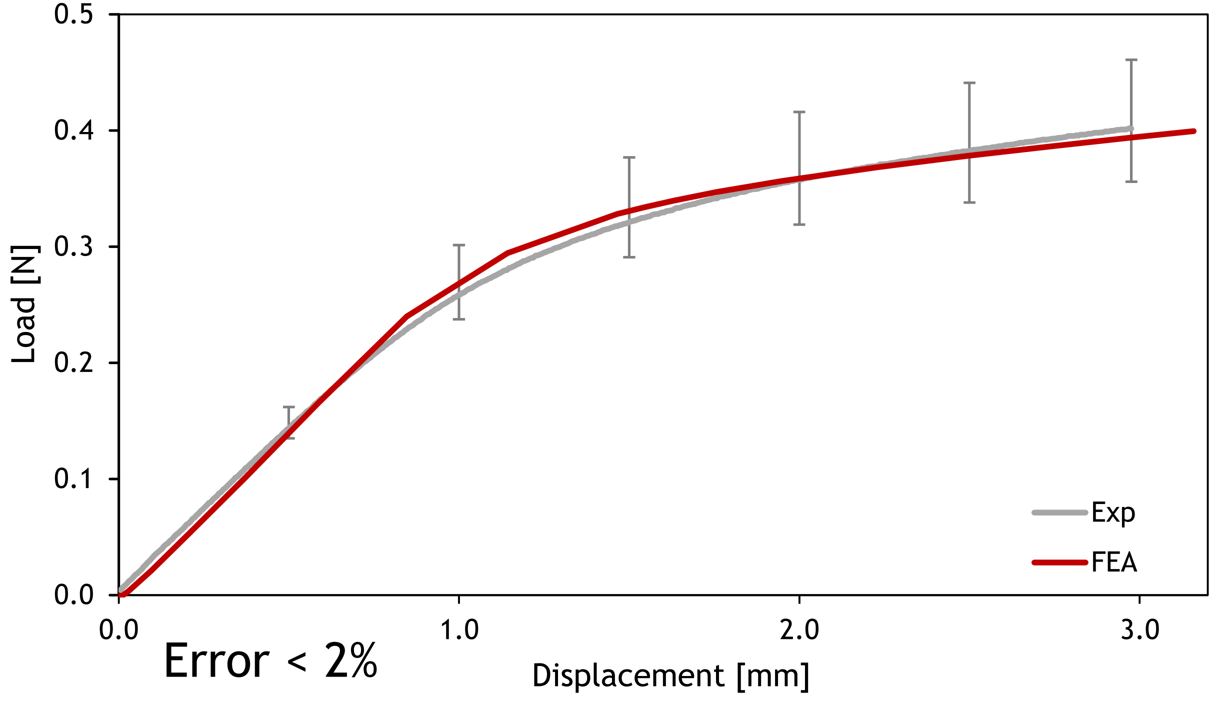


This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

Validation of stent models

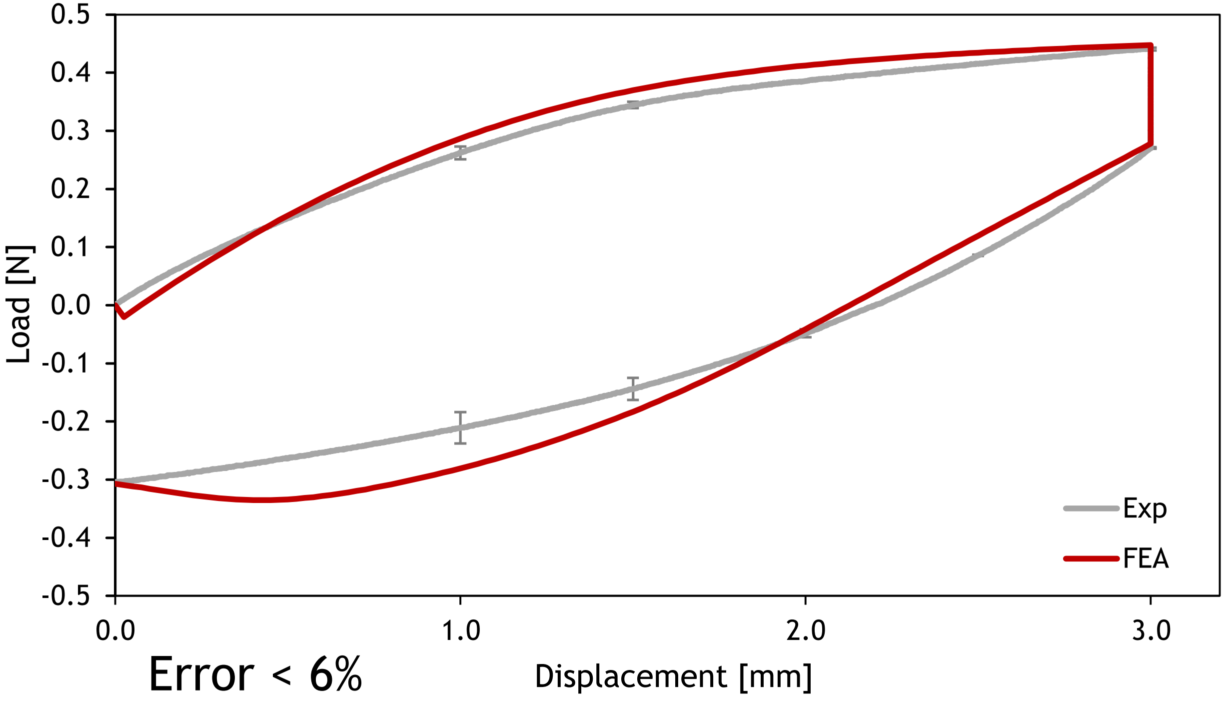


SYNERGY Uniaxial tensile test



Error < 2%

BVS-2 Uniaxial tensile test



Error < 6%

Antonini L., Mandelli L., Berti F., Pennati G., Petrini L. **Validation of the computational model of a coronary stent: a fundamental step towards in-silico trials** J Mech Behav Biomed Mater, 2021 (accepted)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

Challenges & Beyond the state-of-the-art

Challenges

- Creation of a **database of virtual coronary devices** with **realistic behavior** to be used for in silico stenting

Beyond the state of the art

- **Material** (metal and polymer) **properties specifically characterized** for each delivery system
- **Extensively validated models (V & V40)** of BVS and DES delivery systems
- **Large database of virtual stenting devices:** BVS, DES delivery systems and angioplasty balloons

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

Mechanical Modelling Module

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Task 5.2 Overview - DoA

DoA	1-18	19-24
"The creation of the **Mechanical Modelling Module**, consisting of a number of FE simulations **mimicking the in vitro mechanical testing** performed in Task 3.1 (Group 1). All the in vitro tests required by technical standards will be systematically reproduced by corresponding in-silico mechanical testing"	**Preliminary In silico testing** has been performed for the following commercial and prototype stents: - Synergy - PLLA prototype	**Development** of a **Mechanical Modelling Module** capable of performing all necessary simulations of mechanical tests with different material models requested by appropriate **ISO standards** for testing stent devices.
"The **coronary BVS implantation** systems developed in Task 5.1 are **coupled to proper models of the experimental set-ups** adopted in Task 3.1. "	**New material model** has been developed and tested on the results from Task 3.1.	**Material models of BVS material**, integrated in PAK (in-house solver) A newly developed material model for simulation of PLLA or other similar polymer materials based on the original experimental curves from BSL partner

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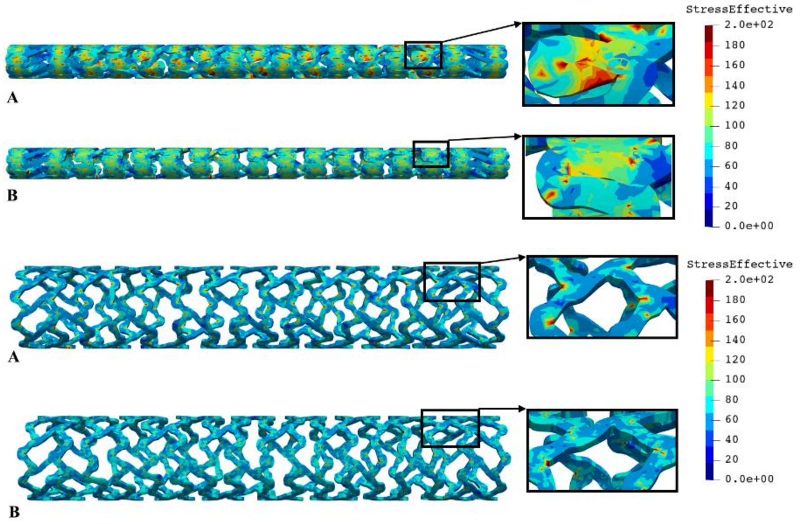
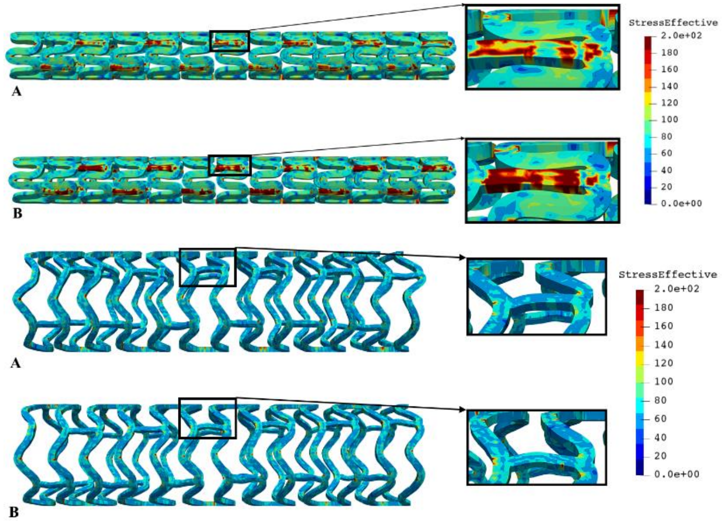
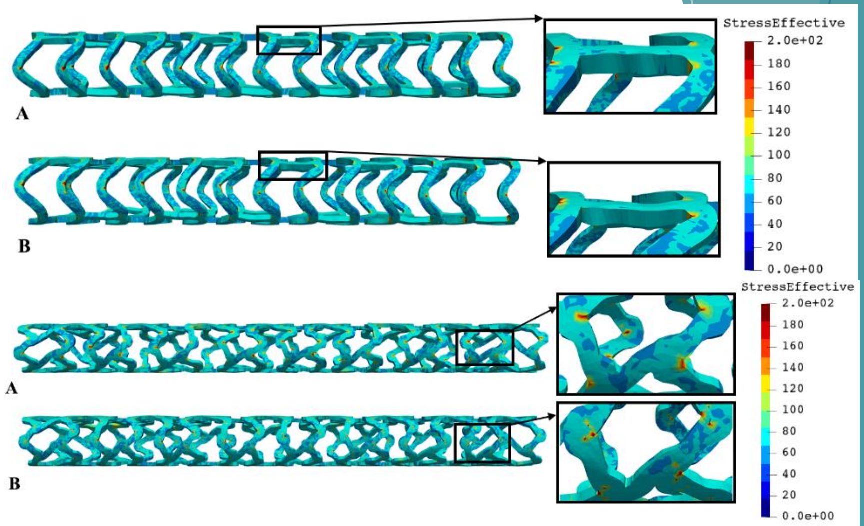
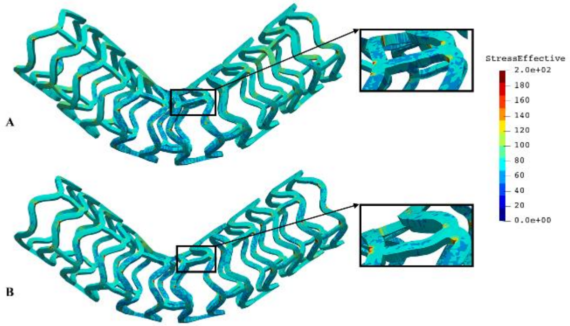
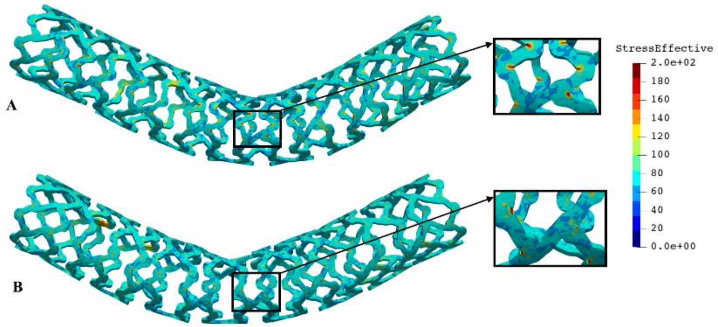
Mechanical module for BVS device testing











Mechanical module

Comparison of two BVS designs

Filipovic N, Nikolic D, Isailovic V, Milosevic M, Geroski V, Karanasiou G, Fawdry M, Flanagan A, Fotiadis D, Kojic M.
In vitro and in silico testing of partially and fully bioresorbable vascular scaffold. *J Biomech*. 2021;115:110158

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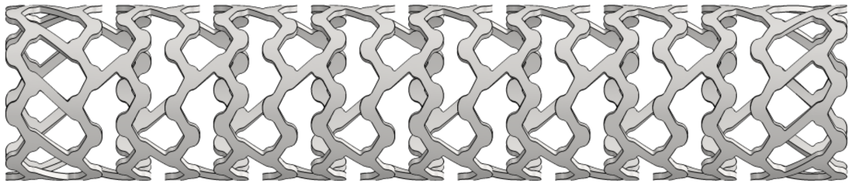
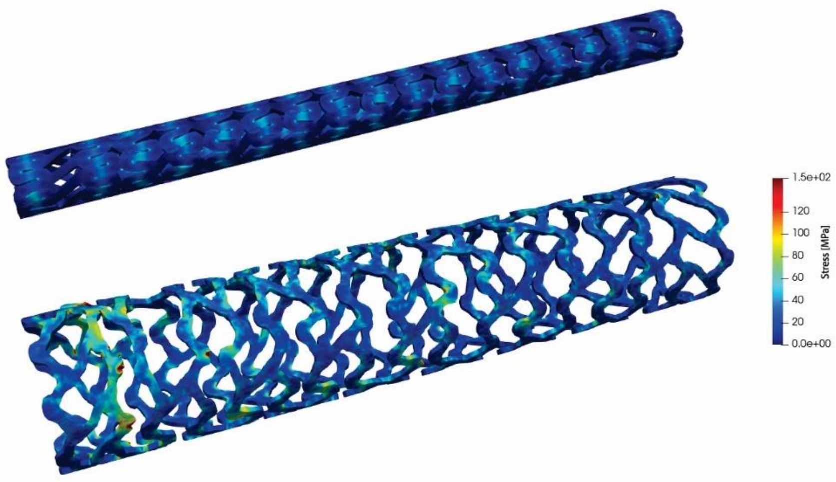
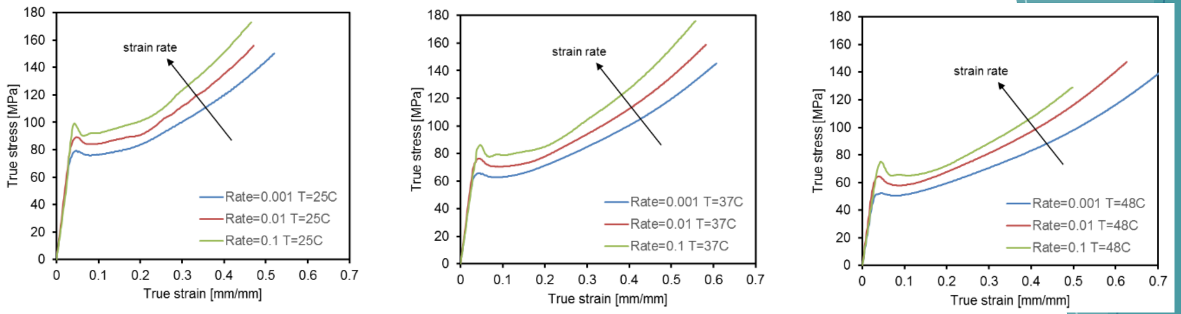
PLLA material model

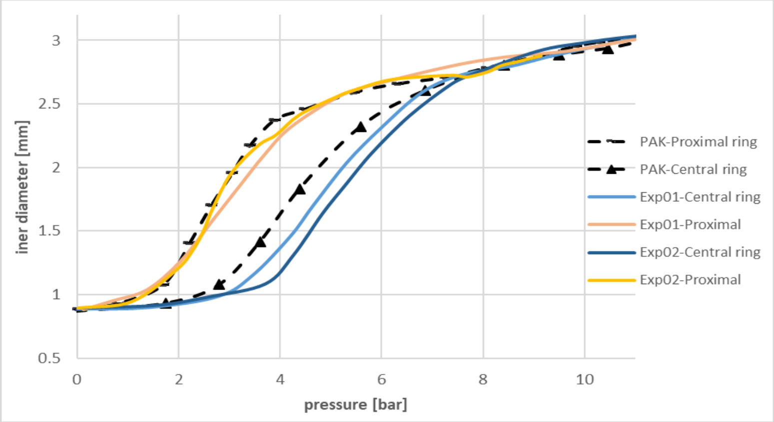




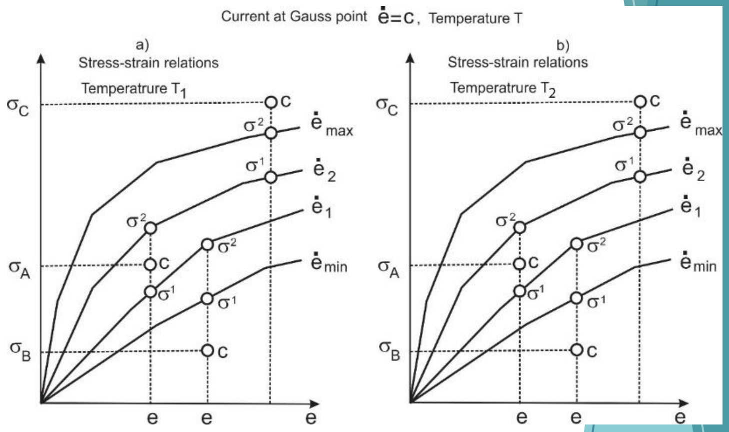
Stress distribution – BVS prototype device, inflation test



Average tensile test results provided by BSL at different temperatures and strain rates



Comparison of diameter-pressure curves,
PAK vs experiment for BVS prototype device, inflation test



Uniaxial stress-strain curves for different strain rates and two temperatures

Filipovic N, Nikolic D, Isailovic V, Milosevic M, Geroski V, Karanasiou G, Fawdry M, Flanagan A, Fotiadis D, Kojic M.
In vitro and in silico testing of partially and fully bioresorbable vascular scaffold. *J Biomech*. 2021;115:110158

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Task 5.2 Overview - DoA

DoA	1-18	19-24
"Among the ***in silico* tests** are the dimensional verification, foreshortening, dog boning, radial force, local compression, crush resistance with parallel plates, three-point bending and fatigue. Risk of fatigue failure is also calculated."	The following **tests** were **simulated on DES:** Inflation test , Radial compression test, Crush test, Local compression test, Three-point bending test, Tensile test, Flex/kink test, Radial fatigue test, Simulated use test.	The following **tests** were **simulated on fully <u>BVS prototype device</u> :** - Three-point bending of BVS device - Longitudinal tensile strength of BVS device - Flex-kink of BVS device
"The **comparison** between in vitro tests and in-silico results will allow **accurate validation** of the in-silico protocol **to simulate a complete bench mechanical testing for BVSs.**"	Performed simulations and their **validation by comparison with the results from real mechanical tests** showed that it is possible to replace all in vitro mechanical tests with **faster and cheaper in silico tests**.	The **simulations of mechanical tests** are performed on two different types of stent devices. The **comparison** of the tests results interpreted in form **of graphs (displacement-force curve)** obtained from the fully BVS devices (PLLA prototypes) show <u>**very good matching**</u> with results from real mechanical tests.

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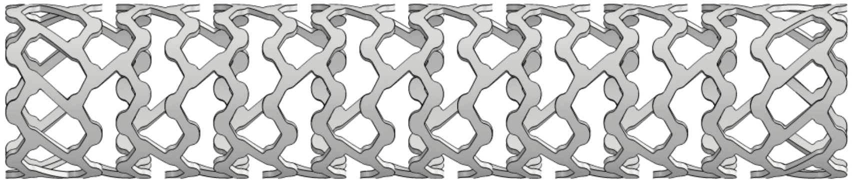
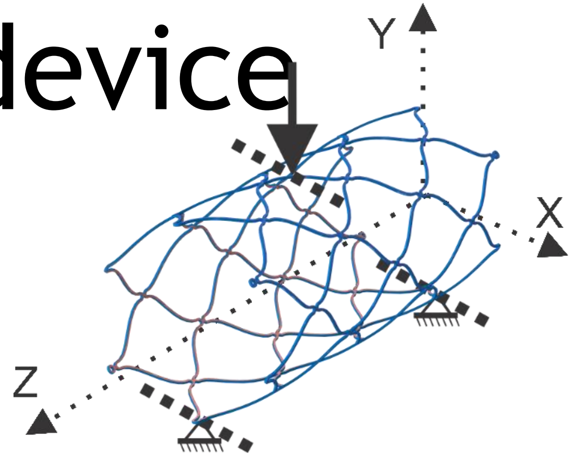
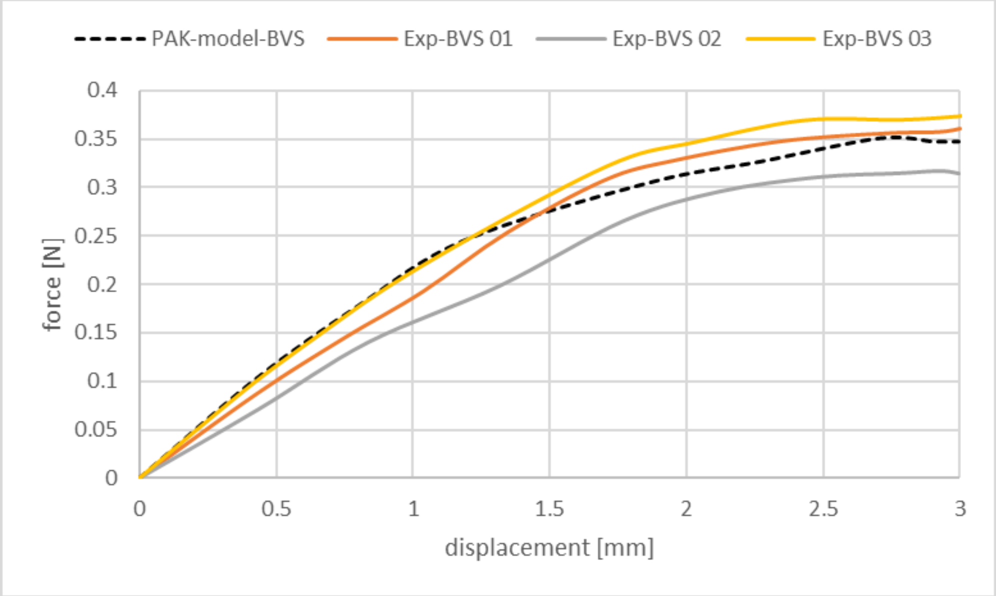
Three-point bending of BVS device

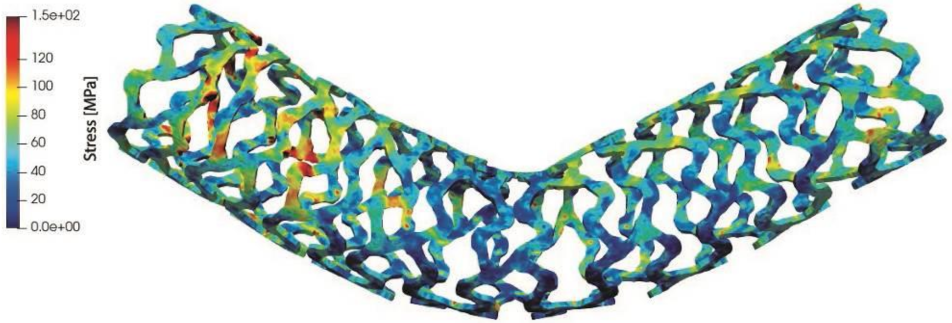




Real mechanical test setup for three point bend test (left);
three point bend test simulation - boundary condition (right)



Comparison of displacement-force curves,
PAK vs experiment for BVS prototype device, three-point bending test



Stress distribution – BVS prototype device, three-point bending

Model	BVS prototype devices N=4
Coefficient of determination - R^2	0.9900
Correlation coefficient R	0.995
Significance level	P<0.0001

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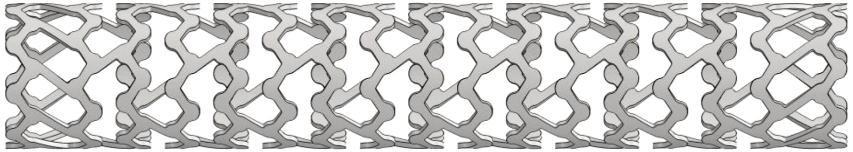
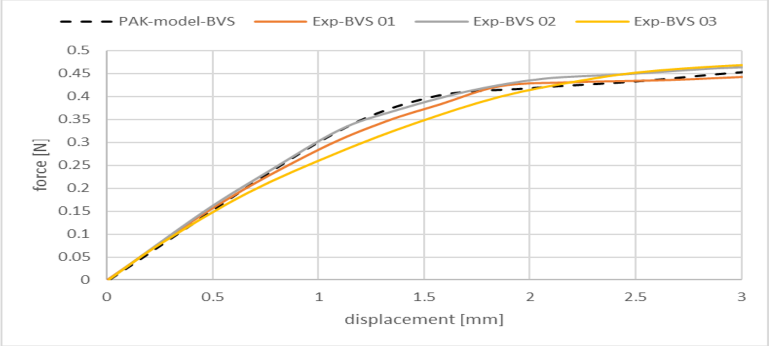
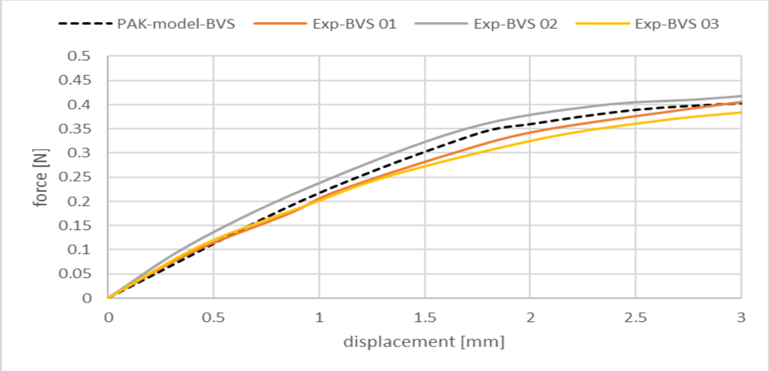
Longitudinal tensile strength of BVS device

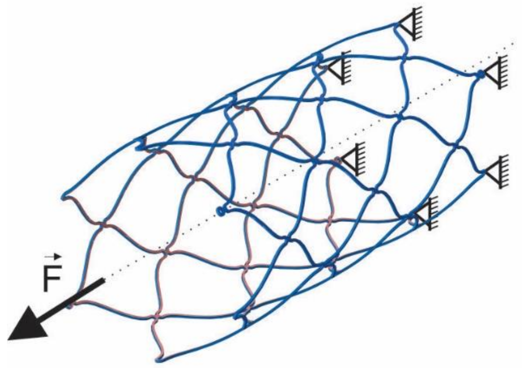




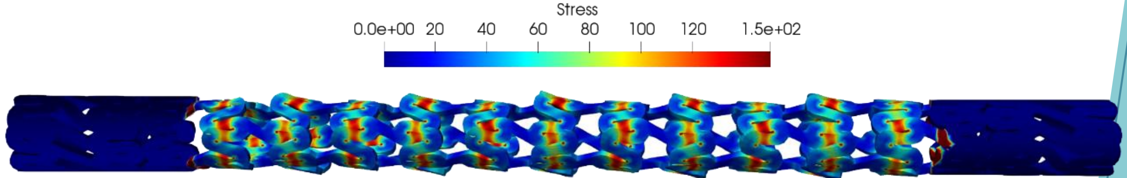
Comparison of displacement-force curves – Fast protocol,
PAK vs experiment for BVS prototype device, longitudinal tensile strength test



Comparison of displacement-force curves – Slow protocol,
PAK vs experiment for BVS prototype device, longitudinal tensile strength test



Real mechanical test setup for longitudinal tensile test (left); longitudinal tensile test simulation - boundary condition (right)



Stress distribution – BVS prototype device, longitudinal tensile strength test

Model	BVS prototype devices N=4
Coefficient of determination - R^2	0.9944
Correlation coefficient R	0.9984
Significance level	0.0001

Coefficient of determination (R2) – longitudinal tensile test, fast protocol

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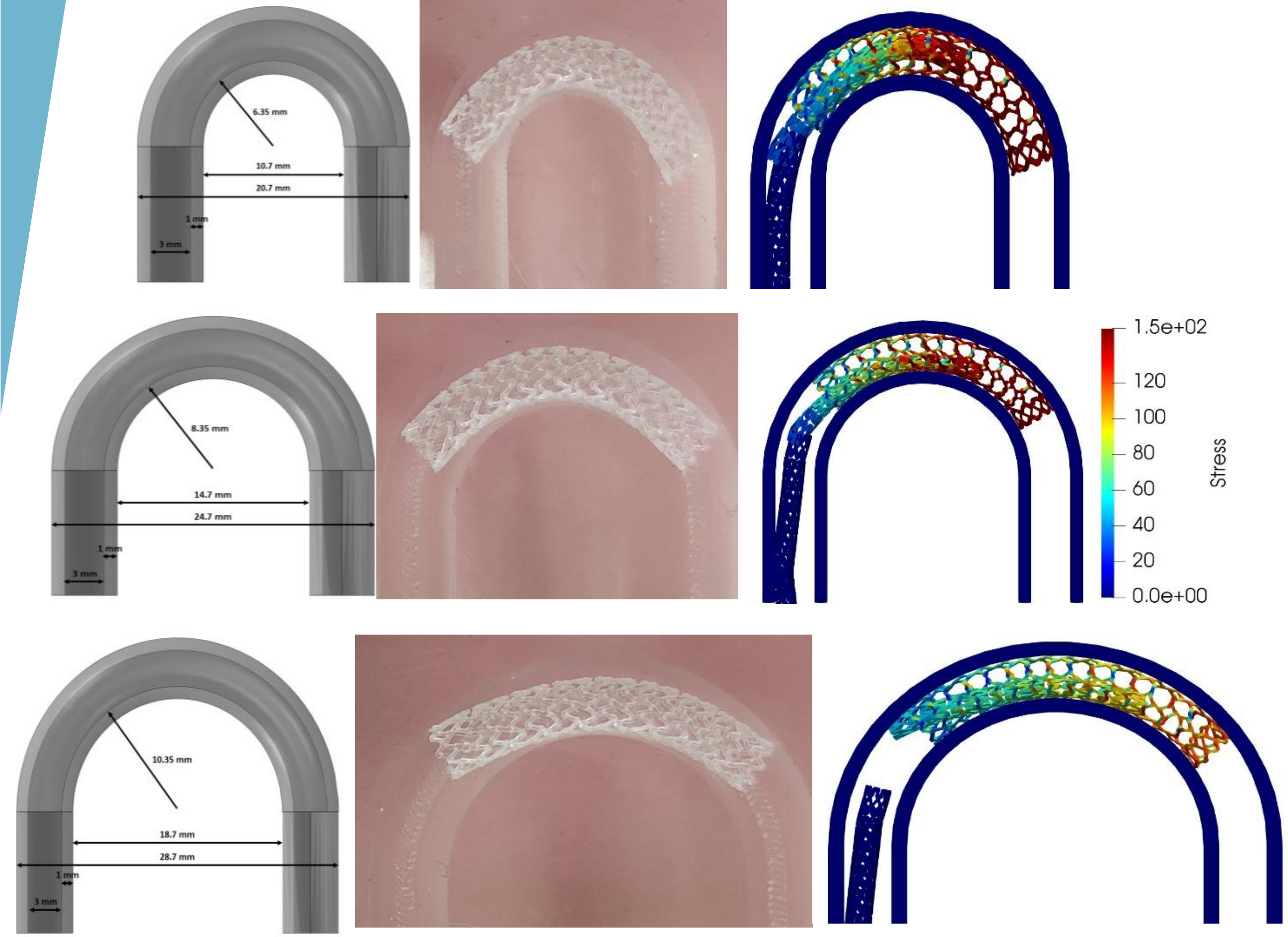
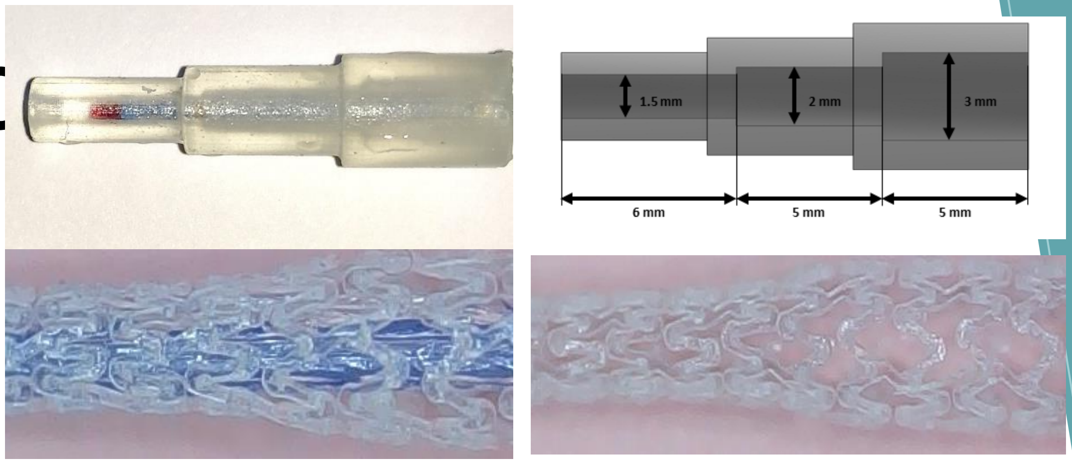
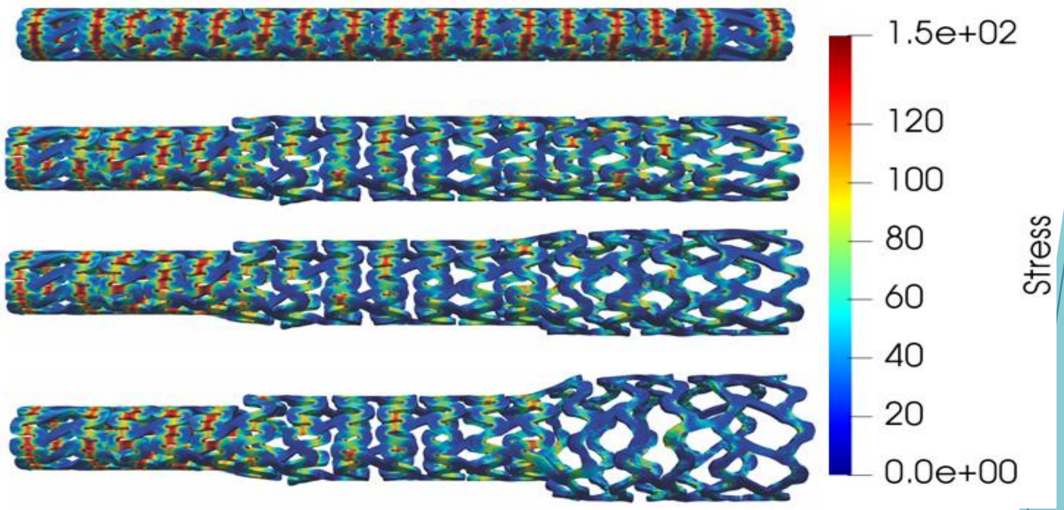
Flex-kink of BVS devic



Flex test simulation - boundary condition (left)
Real mechanical test setup for flex test (middle);
Flex test simulation – results stress distribution (right)



Real mechanical test setup for kink test (top left);
kink test simulation - boundary condition (top right)
BVS devices after kink tests were performed – kinking not observed (bottom)



Stress distribution – BVS prototype device,
Shape of expanded BVS prototype device, kink test

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

Challenges & Beyond the state-of-the-art

Challenges

- The development of material model and methods for in silico **mimicking the real mechanical tests** on BVS and DES devices.
- The **developed module** is capable of performing all necessary simulations of mechanical tests with different material models requested by appropriate **ISO standards** for testing stent devices.
- **To validate** in silico module results

Beyond the state of the art

- **Newly developed material model** for simulation of PLLA or other similar polymer materials show **very satisfying performance and results.**
- A **Mechanical Modelling Module** with a **full set of in silico mechanical test benches**
- **Validated material** and **test-bench models** for BVS and DES delivery systems

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Deployment Module

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Task 5.3 Overview - DoA

DoA	6-18	19-41
SubTask 5.3.1 - Implementation and validation of in-silico stenting procedure "The real **BVS samples** will be deployed within the **mock coronary vessels**… different geometries (including bifurcations) obtained by rapid prototyping (…mimicking also possible wall **calcifications**)"	▪ Design of several **mock vessels** to be 3D printed ▪ Design of the experimental set-up and **measurement system** ▪ Deployment of **Synergy** samples in **3D printed single** vessels	▪ Design of **new** mock vessels with **markers** and **calcifications** ▪ Deployment of **Synergy** and **BVS-2** samples in 3D printed single and **bifurcated** vessels
The **BVS models** will be used to **simulate** the deployment inside mock coronary segments	▪ **FE models** of mock-up vessels ▪ **Preliminary simulations** of Synergy deployment within the mock-up vessels	▪ **FE models** of the final mock vessels ▪ **Final simulations** of Synergy and BVS-2 deployment mimicking all the in vitro experiments

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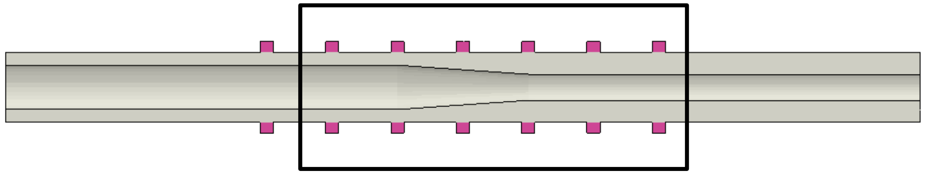
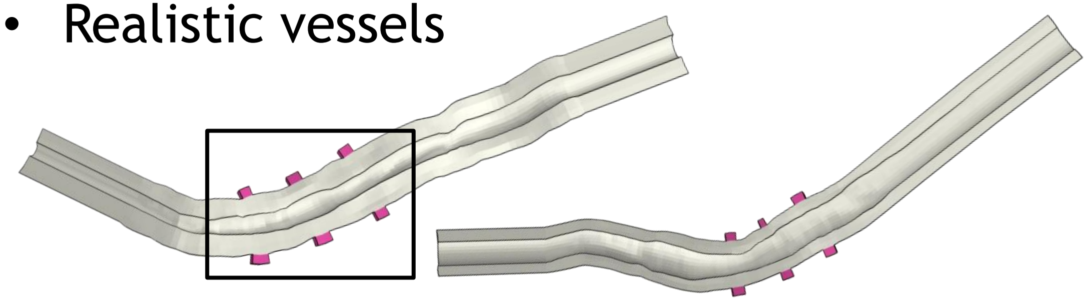
Mock-vessels & In-vitro vs. In-silico deployment

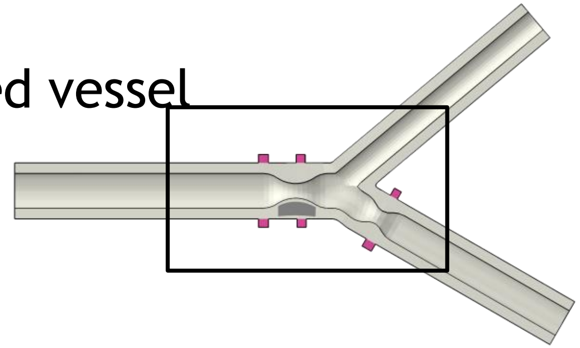
- Idealized vessel



- Realistic vessels



- Bifurcated vessel



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Task Overview - DoA SubTask 5.3.1

DoA	6-18	19-41
"The comparison of FEA and in vitro results will allow an effective **validation** of the BVS implantation stenting system and the in-silico deployment procedure"	Analysis of **V & V40**	▪ Analysis of **uncertainties** for model inputs and comparators for validation ▪ Comparison of in vitro and in silico results in terms of pressure-diameter curves at several vessel locations and **error evaluations**
"...by using data deriving from **animal studies** (Task 3.2) a more complete validation will be accomplished"	**Selection** of animal cases (from Task 3.2) to simulate	▪ **FE models** of animal arteries (reconstructed in WP4) ▪ **Simulations** of Synergy and PLLA prototype deployment ▪ Analysis of **uncertainties** for model inputs and comparators for validation ▪ Comparison with animal OCT data (Task 3.2) and **error evaluations**

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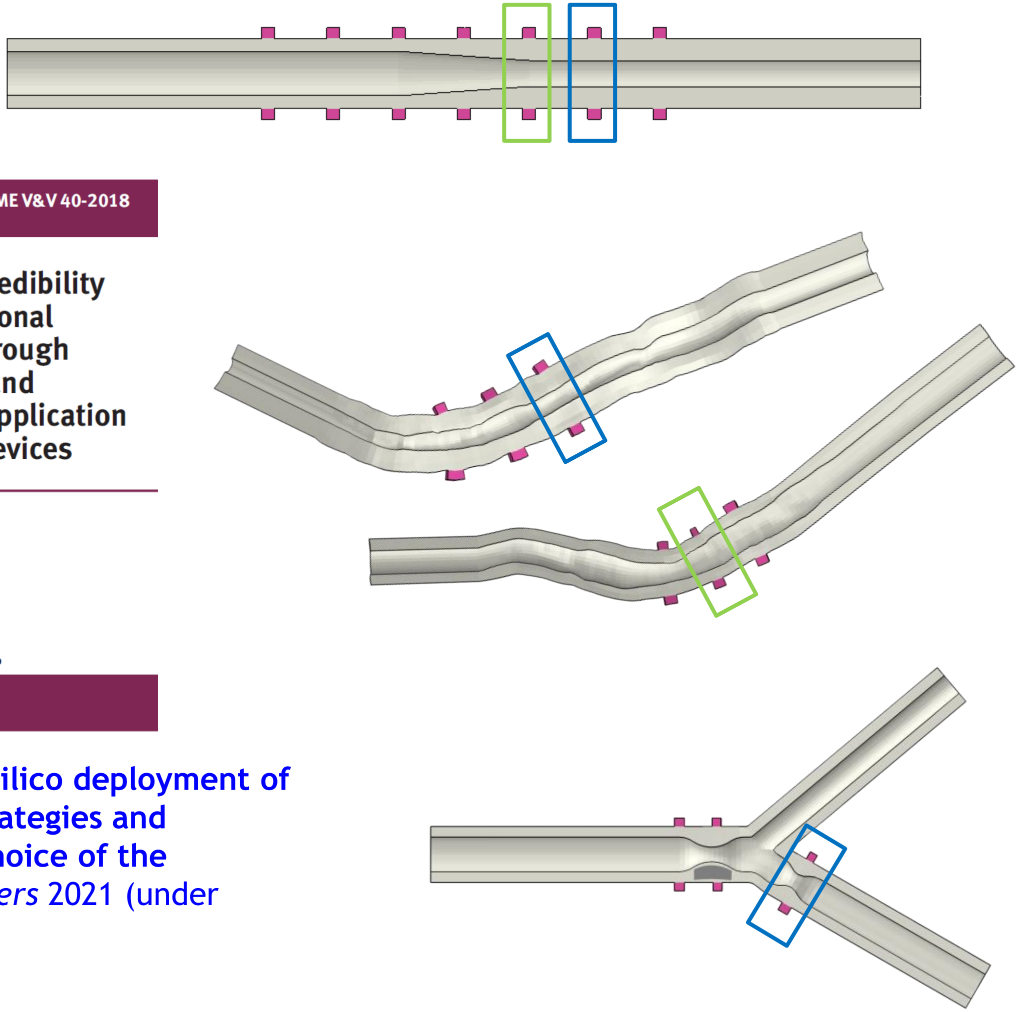
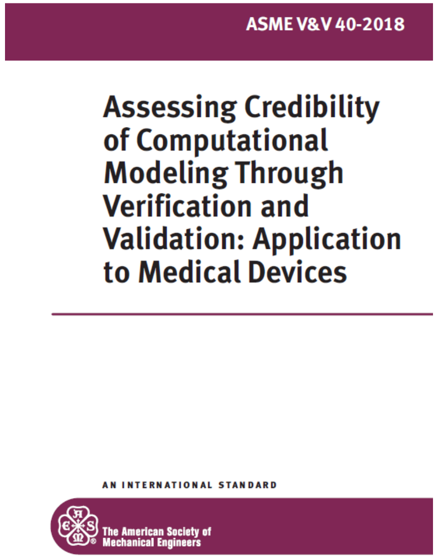
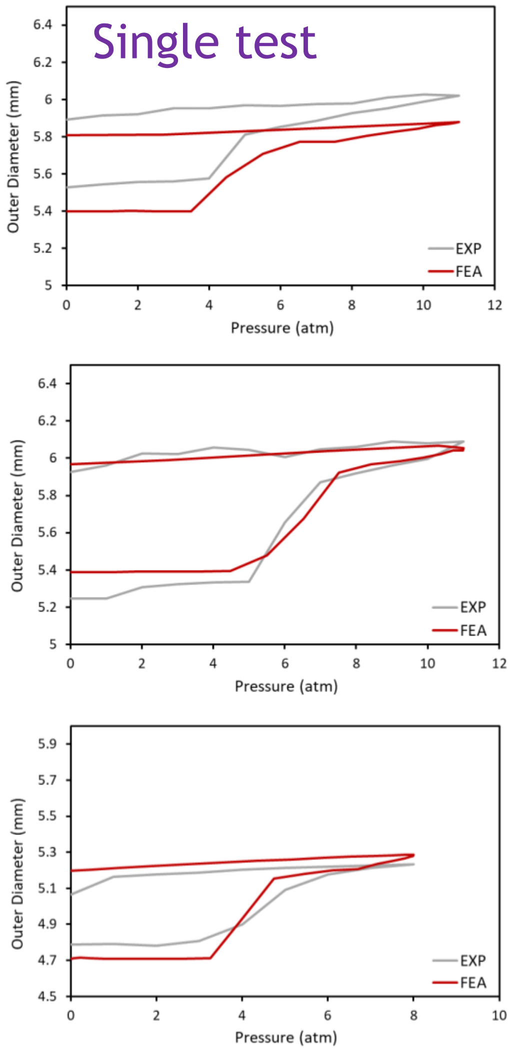
Validation of In-silico deployment

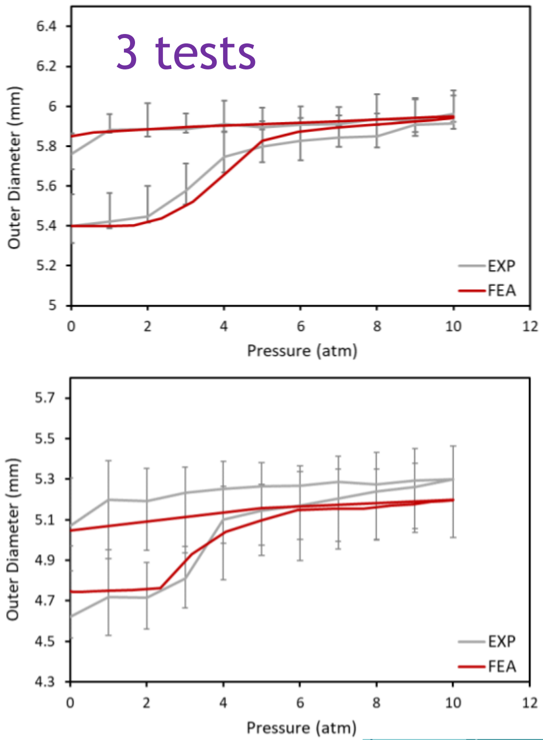




SYNERGY



BVS-2



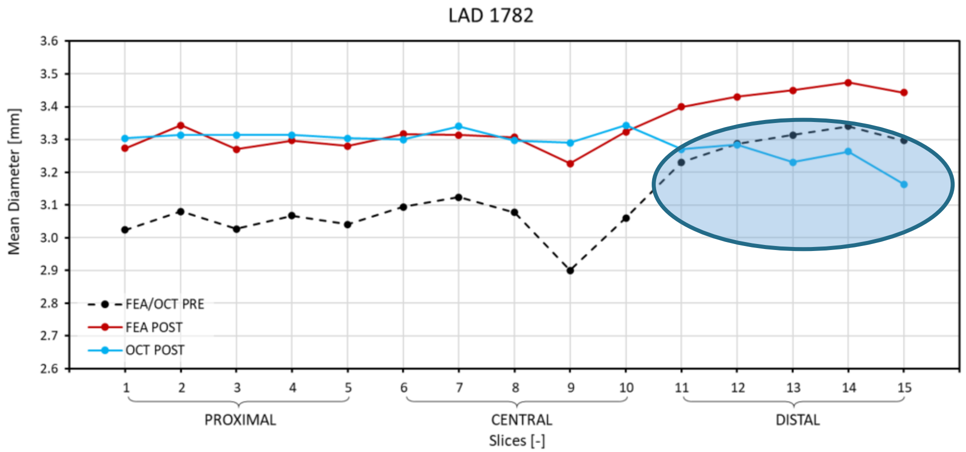
Diameter errors < 3%

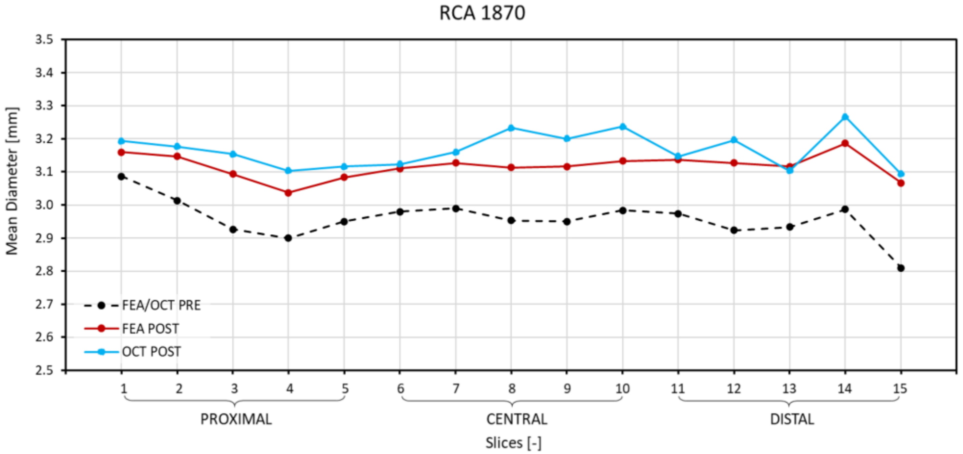
How to validate in silico deployment of coronary stents: strategies and limitations in the choice of the comparator – *Frontiers* 2021 (under review)

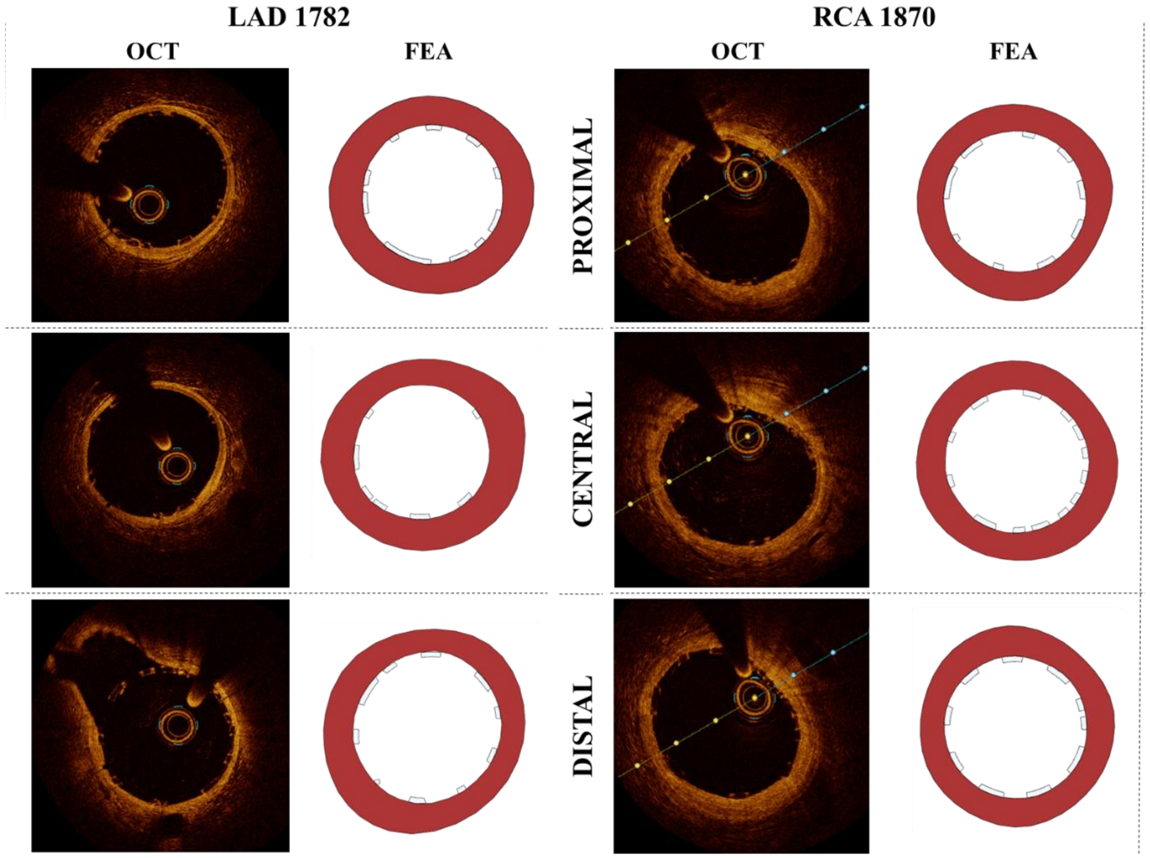
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

Animal studies

In vivo comparator uncertainty







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Task 5.3 Overview - DoA

DoA	6-18	19-41
Subtask 5.3.2 - Deployment Module development and integration in the Cloud platform "**accurate simulations** of the BVS deployment within **human stenosed coronary arteries** will be performed… **geometrical and mechanical information** based on **retrospective** (Task 4.1) and **prospective** (Task 8.1) clinical data will be applied to model the coronary artery and the atherosclerotic plaque."	▪ **Strategy** to model different layers of arterial wall based on OCT data ▪ **Mesh** sensitivity ▪ Preliminary **use cases**	**Several patient-specific cases** (from Task 8.1) were modelled based on reconstructed anatomies (in WP4)
… **detailed constitutive models** … will be used for the **coronary wall…** for the plaque we will consider different biomechanical models for the **various plaque constituents**"	**Parameter calibration** for material constitutive models (healthy wall, plaque, calcifications) using literature data	Novel **optimized strategy** to model the coronary artery wall and plaque components based on clinical images

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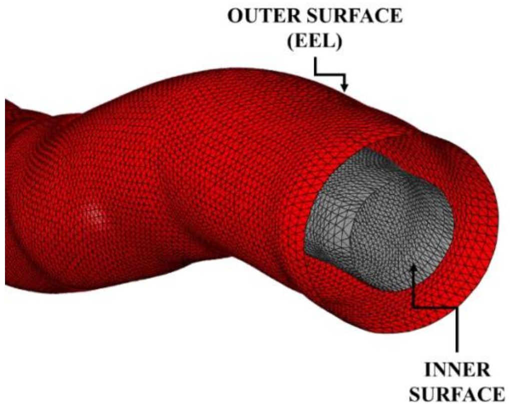
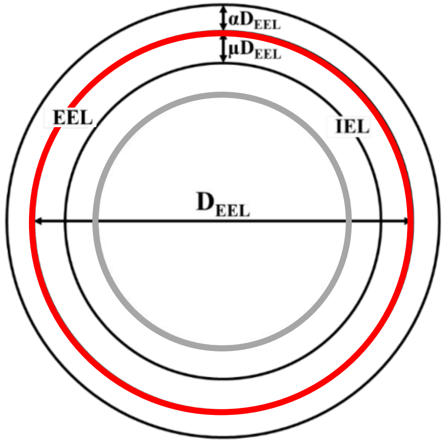
Patient-specific cases

Detectable from images
(two surfaces)

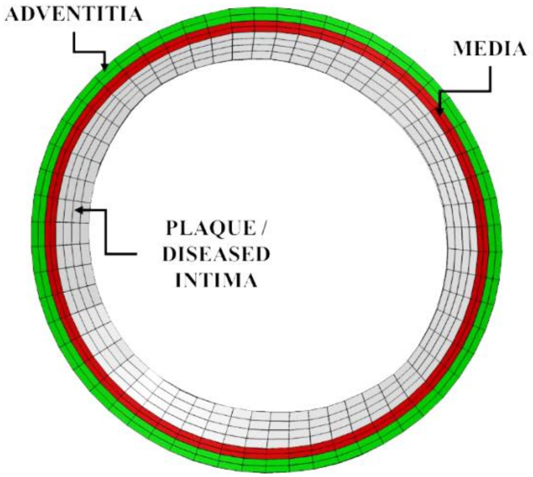


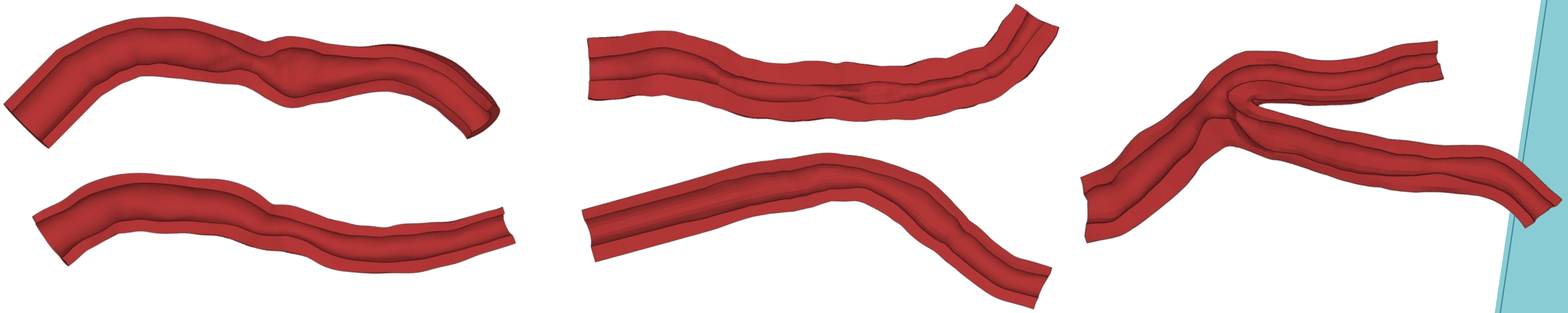


Biomechanical model
(three layers)

$$t_{MEDIA} = \mu \, D_{EEL}$$

$$t_{ADVENTITIA} = \alpha \, D_{EEL}$$





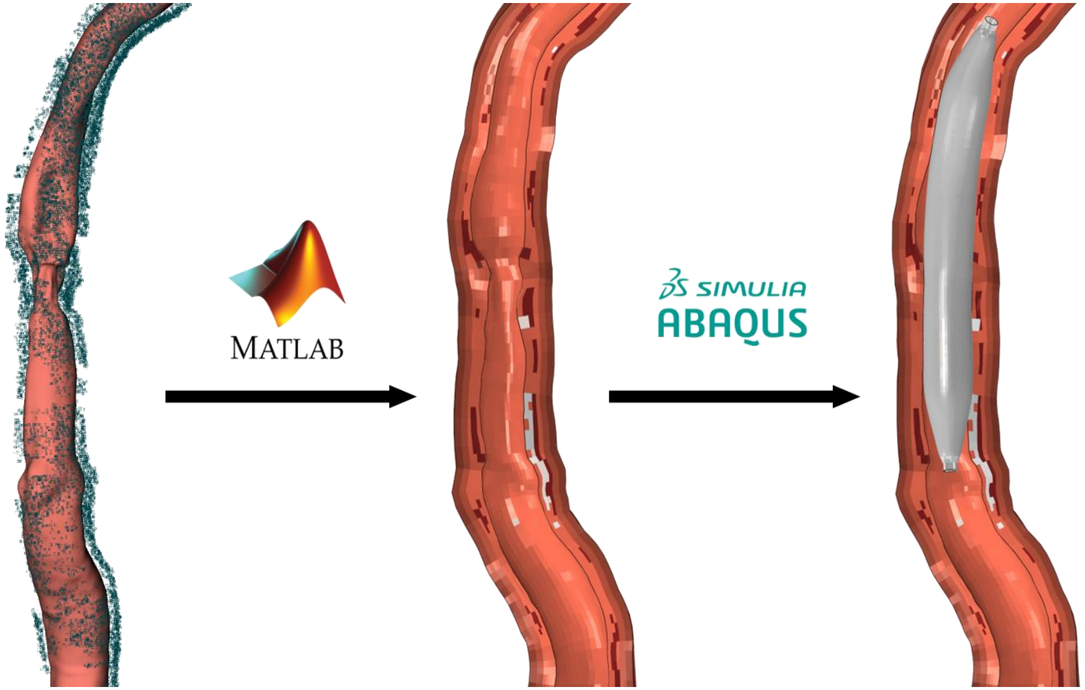
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

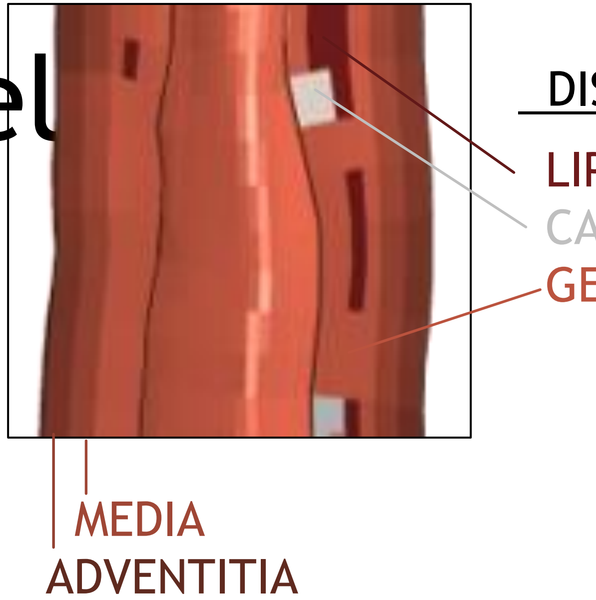
Coronary artery model

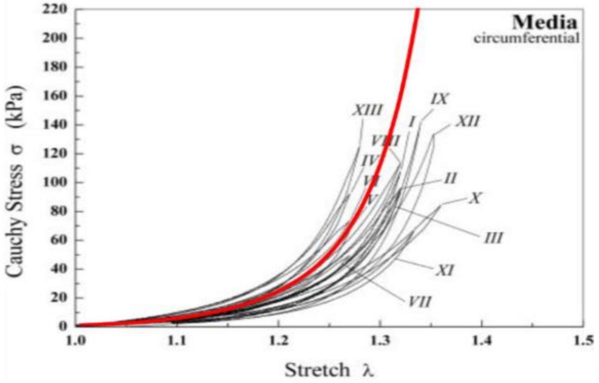
Detectable from images (clouds of points)

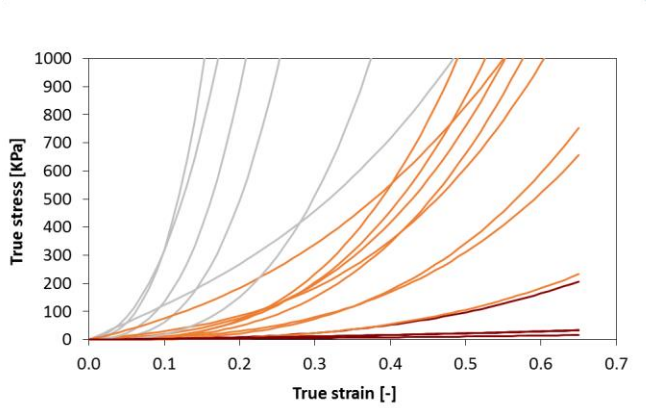
Plaque components

Mechanical properties









- **Material constitutive models**
  - *in vivo* blood pressure & axial pre-stretch → nonlinear **elastic** behavior, **properly adapted** from literature
  - permanent deformations → **plastic models** for **inelastic** behavior

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Task Overview - DoA SubTask 5.3.2

DoA	6-18	19-41
"the Deployment Module will be **integrated** in the whole platform to **provide input data** for the other modelling modules"	▪ Definition of **basic simulation steps for stenting** (positioning, inflation, deflation & deployment) ▪ **Preliminary automation** of the simulation steps ▪ Definition of module **inputs** and **outputs**	▪ **Full automation** of the simulation steps and **integration** of the "accurate" Deployment Module on the platform ▪ Development of a **"simplified deployment"** to create inputs for other modules when the accurate deployment is unfeasible
"…identification of specific zones, where the interaction between drug-eluting BVS and tissue is very pronounced (**high level of injury**) and may induce restenosis. …**BVS malapposition**, which correlates with increased the risk of late stent thrombosis, will be assessed."	Analysis of possible **acute endpoints**	Final definition of **acute endpoints** visible on the platform: i) **mimicking** clinical endpoints ii) **refining** some aspects, exploiting potentialities of in silico stenting

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Deployment Module

Accurate deployment
(based on OCT pre, stent design & **stenting procedure**)

→ Mimicking of all clinical procedural steps
→ **stented artery, stresses & strains**

Simplified deployment
(based on OCT post & stent design)
→ **stented artery**

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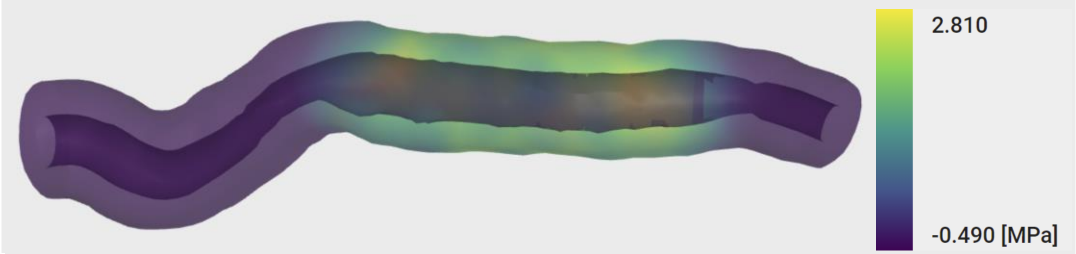
Acute Endpoints on the Platform

Clinical Endpoints

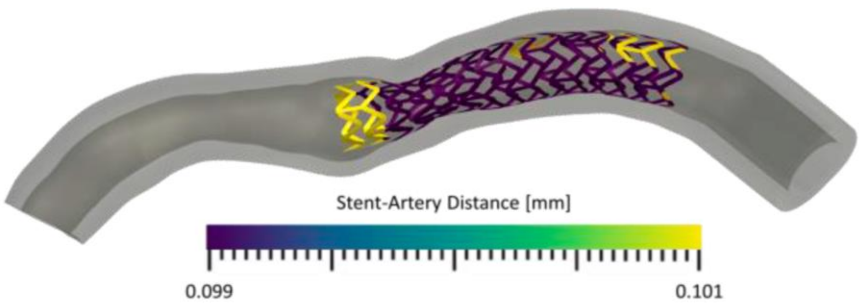
Pre	Minimum Lumen Diameter - Pre-procedural [mm]	1.43
	Reference Vessel Diameter [mm]	2.25
	Lesion Length [mm]	54.10
	Diameter Stenosis - pre-procedural [%]	36.30
Post	Minimum Lumen Diameter - post-procedural [mm]	2.16
	Lumen Gain - post-procedural [mm]	0.73
	Diameter Stenosis - post-procedural [%]	4.15
	Minimum Stent Area - post-procedural [mm2]	3.65
	Eccentricity Index - post-procedural [-]	0.71
	Asymmetry Index - post-procedural [-]	0.29

Potentialities of in silico stenting

- Artery wall injury (stresses at max inflation)



- BVS malapposition (stent-artery distance)



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Task 5.3 Overview - DoA SubTask 5.3.2

DoA	6-18	19-41
"the Deployment Module will be used for the **in-silico simulation of drug-eluting BVS in the "virtual" patients"**	▪ First Scenarios ▪ **Retrospective** patients: Absorb ▪ **Perspective** patients: Fantom Encore	Creation of a large number of **"What if" and comparative Scenarios**, investigating various aspects of stenting (later on…)
The **numerical predictions will be verified** against the post-treatment retrospective and prospective **clinical data generated by the project.**	---	Definition of a **methodology for an effective use of in vivo data** (OCT slices) to verify in silico predictions (later on…)

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Challenges & Beyond the state-of-the-art

Challenges

- To develop a **Deployment Module to be included in** **an in silico pipeline** for investigating both **acute** and **short/medium/long term** outcomes of stented coronary arteries

Beyond the state of the art

- An **effective, robust and automatic** numerical framework to be used for **in silico coronary stenting in patient-specific arteries**, where all the clinical procedures (from the simple angioplasty to the complex treatment of coronary bifurcations) are modelled as combination of **few basic simulation steps** (positioning, inflation, deflation/deployment)
- An **extensive validation of the Deployment Module**, based on in vitro tests, animal studies and patient-specific data
- A **versatile tool** able to predict both the **acute behavior of stents** after implantation (clinical endpoints) in stenotic arteries (not exclusively coronaries)
- A **mature in silico module** able to **provide inputs** for the other modules on the **InSilc platform** to foresee also short/medium/ long term response.
- A **simplified approach based on post-treatment images** to obtain suitable models of the stented artery to be used by other InSilc modules to investigate short/medium/ long term response

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