SILICOFCM

In Silico trials for drug tracing the effects of sarcomeric protein mutations leading to familial cardiomyopathy

OActive

OActive Workshop on "*Personalised predictive models*"

March 26th 2021, 10:00 - 12:00 CET

BioIRC

Prof. Nenad Filipovic, BIOIRC Kragujevac, Serbia

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

SILICOFCM Scope

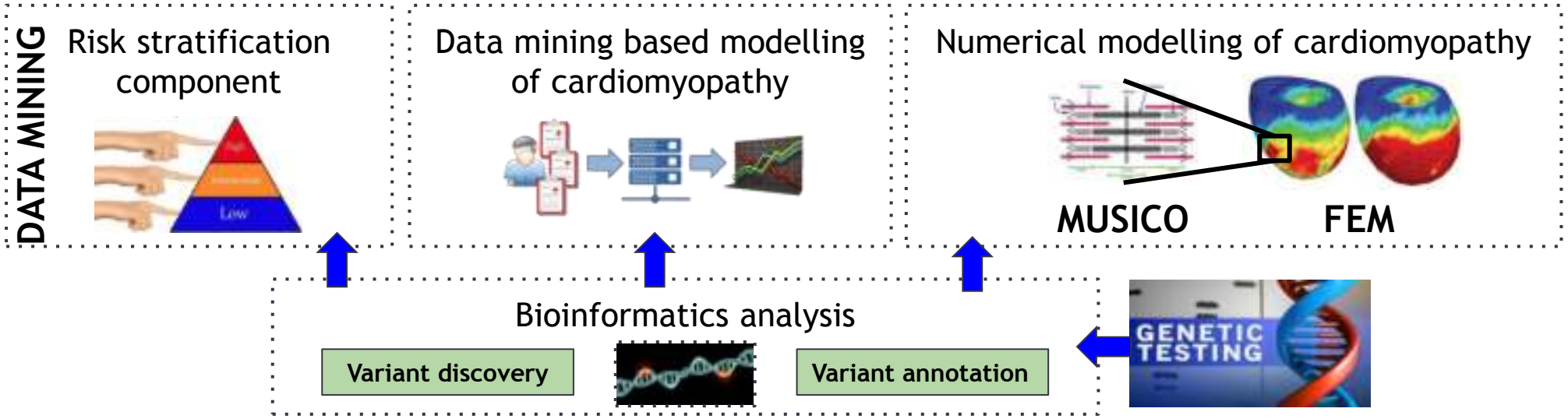
SILICOFCM aims to develop a computational platform for *in silico* clinical trials of Familial cardiomyopathies (FCMs) that would take into consideration comprehensive list of patient specific features (genetic, biological, pharmacologic, clinical, imaging and patient specific cellular aspects) capable 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.

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

The main vision of SILICOFCM project

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.



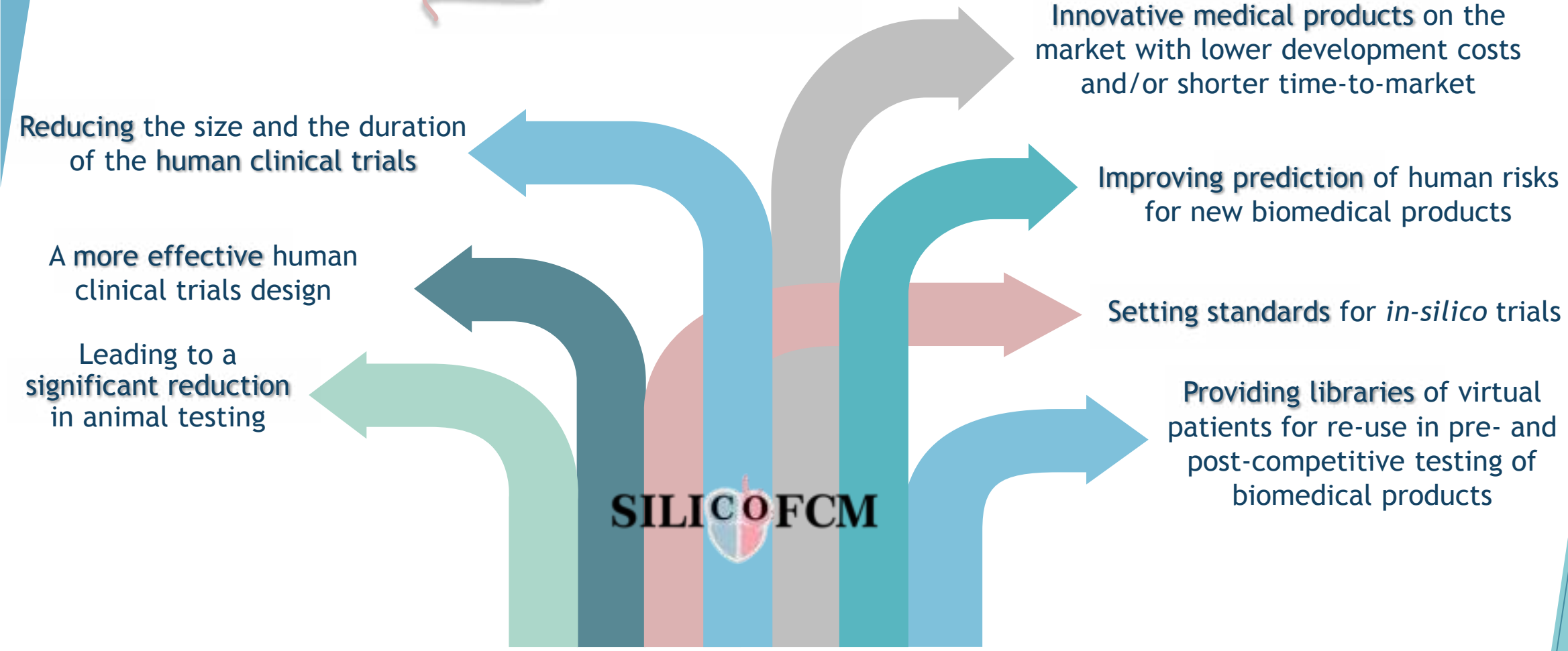
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

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)

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

SILICOFCM Impact



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

SILICOFCM

SILICOFCM Concept

Patient data (genetic, biological, pharmacologic, clinical, imaging and patient specific cellular aspects)

USER 1: Medical doctor

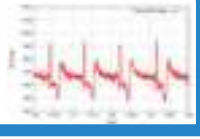
3D IMAGE SEGMENTATION tool

USER 2: Pharmaceutical company

USER 3: Researcher

Virtual experiments database

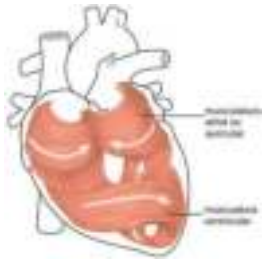
Experiments



Virtual population database

BIOINFORMATICS tool

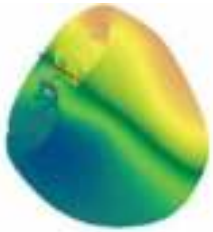
MUSICO tool

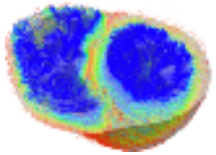


DATA ANALYTICS tool

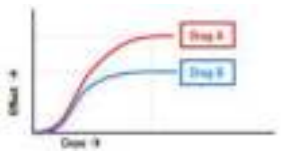
RISK STRATIFICATION tool

Finite element solver (ALYA, PAK)





Drug efficacy



Cardiomyopathy disease progression

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

SILICOFCM

USE CASE 1

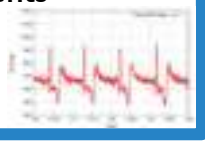
Patient data (genetic, biological, pharmacologic, clinical, imaging and patient specific cellular aspects)

USER 1: Medical doctor

3D IMAGE SEGMENTATION tool

Virtual experiments database

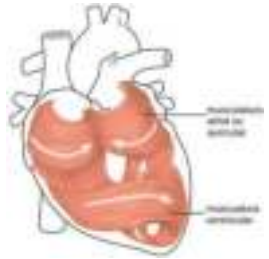
Experiments



Virtual population database

BIOINFORMATICS tool

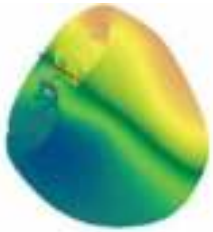
MUSICO tool

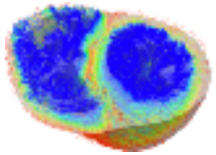


DATA ANALYTICS tool

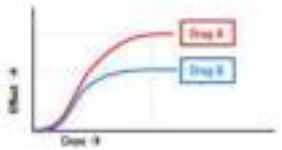
RISK STRATIFICATION tool

Finite element solver (ALYA, PAK)





Drug efficacy



Cardiomyopathy disease progression

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

SILICOFCM

USE CASE 2

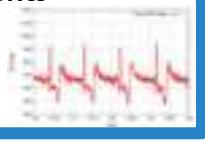
Patient data (genetic, biological, pharmacologic, clinical, imaging and patient specific cellular aspects)

3D IMAGE SEGMENTATION tool

USER 2: Pharmaceutical company

Virtual experiments database

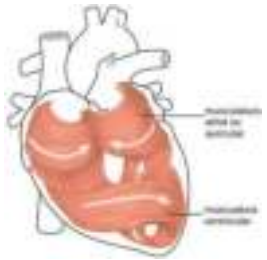
Experiments



Virtual population database

BIOINFORMATICS tool

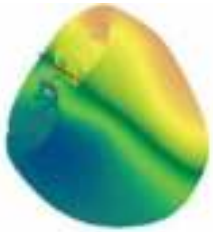
MUSICO tool

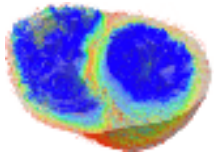


DATA ANALYTICS tool

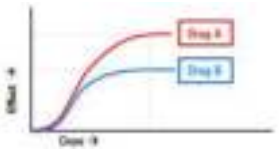
RISK STRATIFICATION tool

Finite element solver (ALYA, PAK)





Drug efficacy



Cardiomyopathy disease progression

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

USE CASE 3

Patient data (genetic, biological, pharmacologic, clinical, imaging and patient specific cellular aspects)

3D IMAGE SEGMENTATION tool

USER 3: Researcher

Virtual experiments database

Experiments

Virtual population database

BIOINFORMATICS tool

MUSICO tool

DATA ANALYTICS tool

RISK STRATIFICATION tool

Finite element solver (ALYA, PAK)

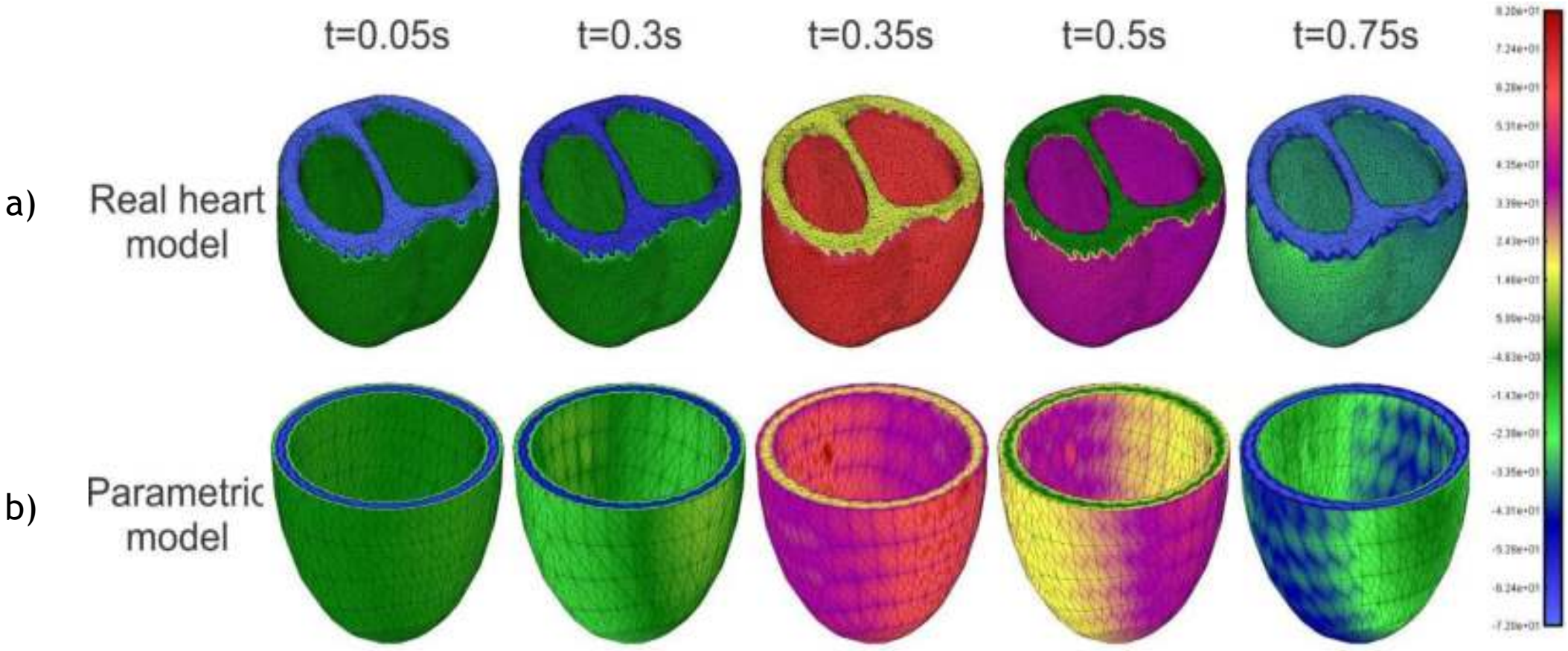
Drug efficacy

Cardiomyopathy disease progression

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

PAK module

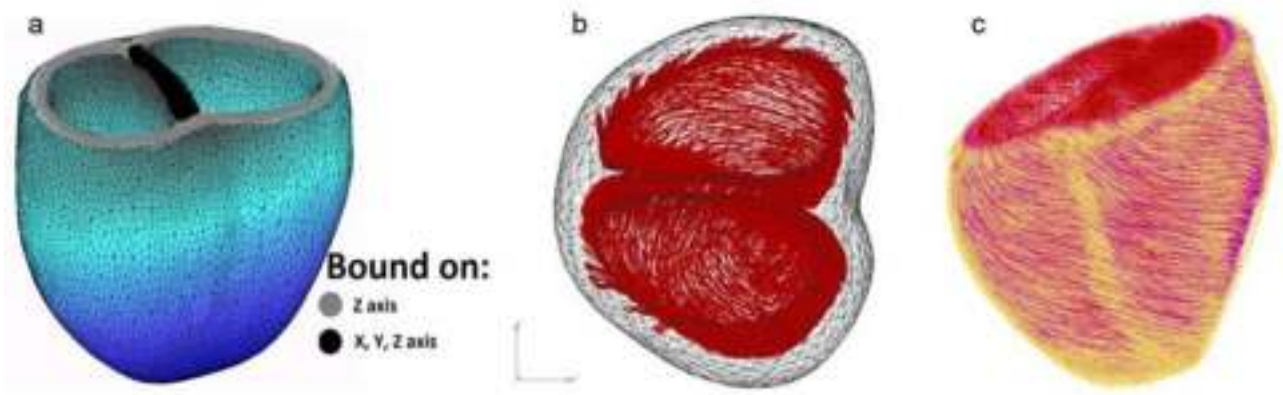
- Example: Realistic models for electrical field and electromechanical coupling



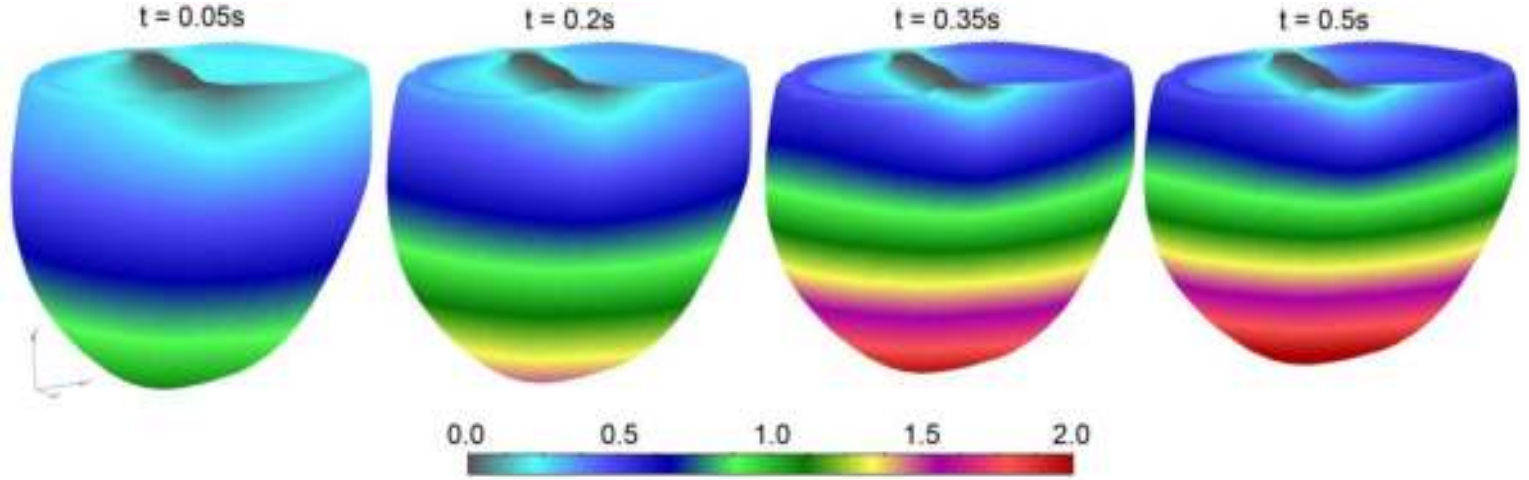
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

PAK module

- Example: Realistic models for electrical field and electromechanical coupling



Boundary conditions in the model. (a) Orientation of the fibers in top (b) and side (c) view.

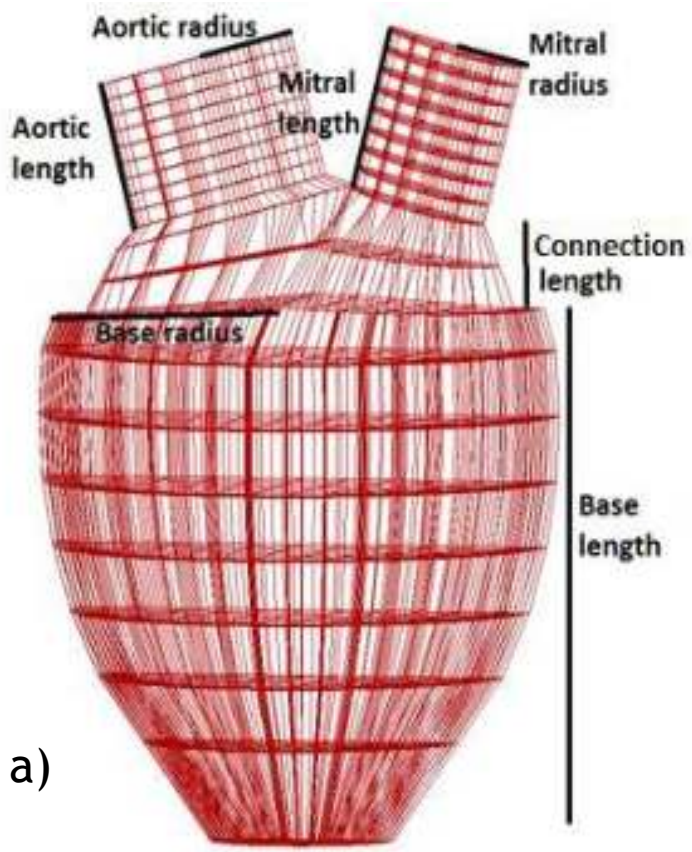


Displacements in coupled electro-mechanical realistic model of biventricular heart.

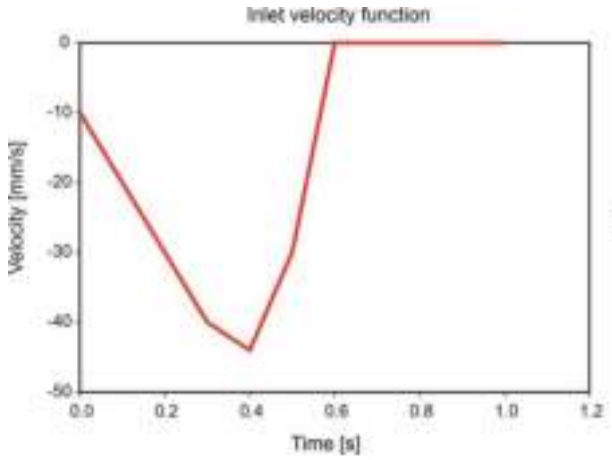
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

PAK module

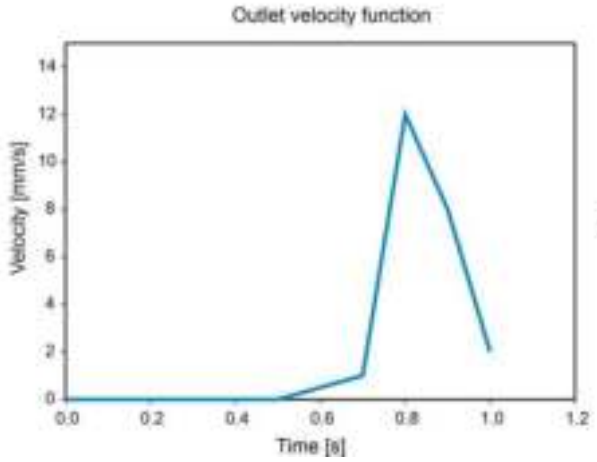
- Example: Parametric structural model of Left ventricle



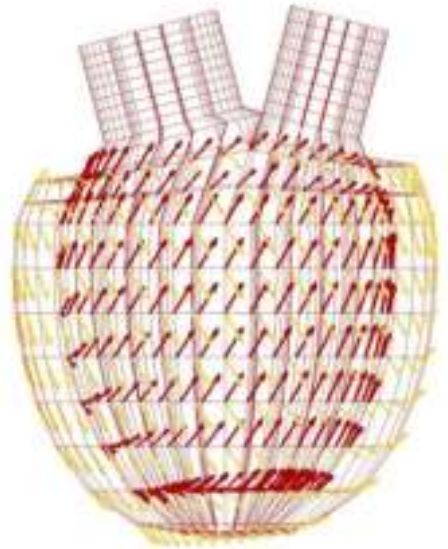
a)



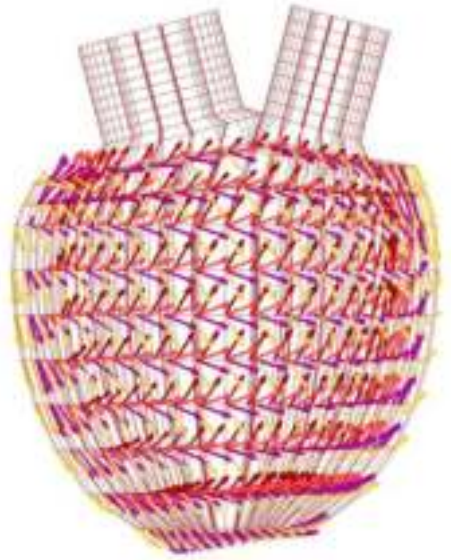
b)



c)



d)



e)

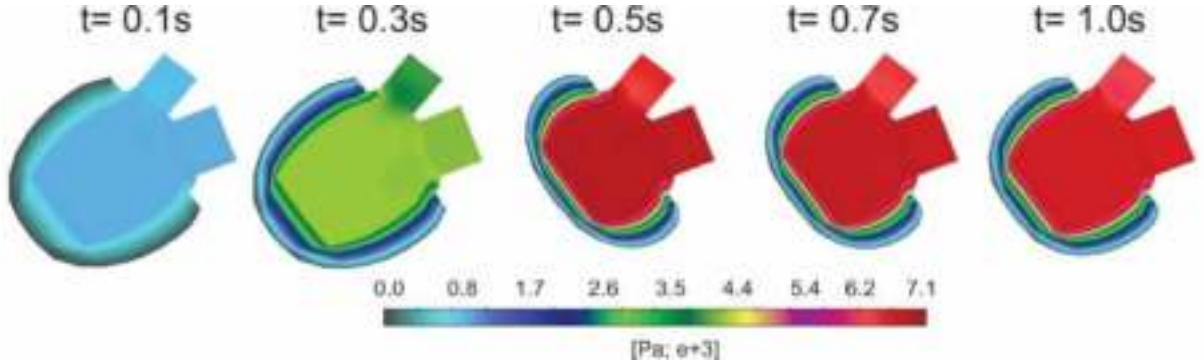
a) Parametric heart model with structural mesh and valves, b) inlet and c) outlet velocities functions. Automatic calculation of fiber direction. d) One-layered and e) three-layered solid wall representation.

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

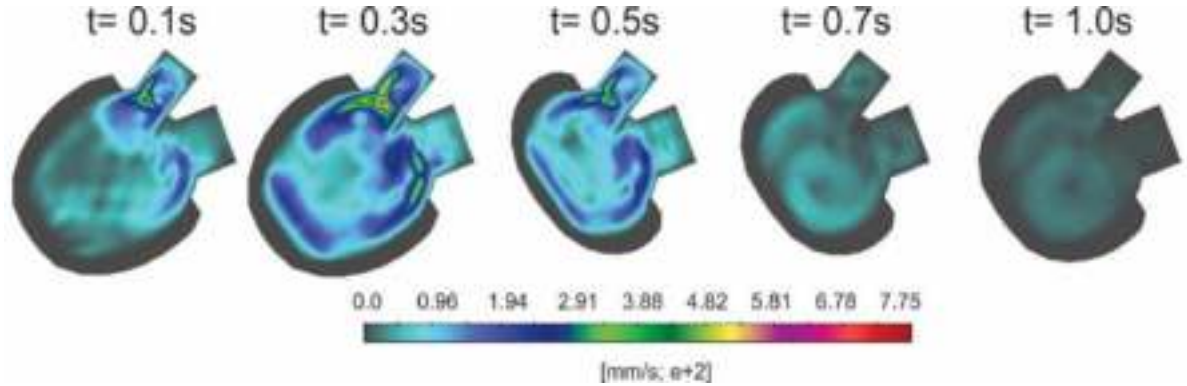
PAK module

- Example: Parametric structural model of Left ventricle

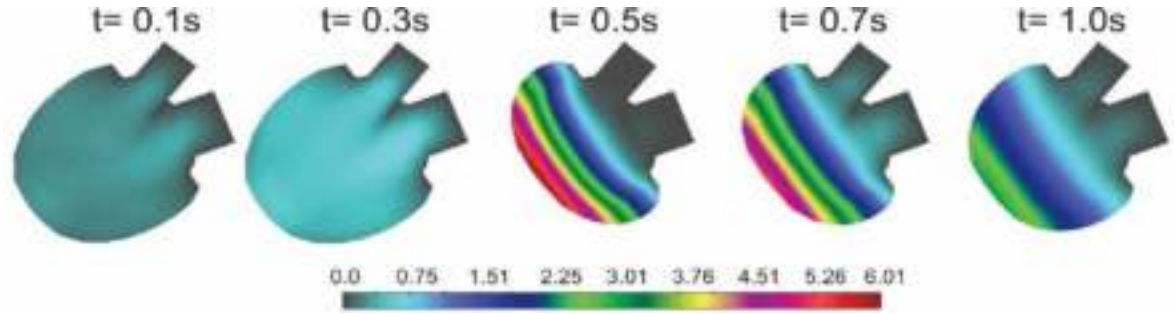
a)

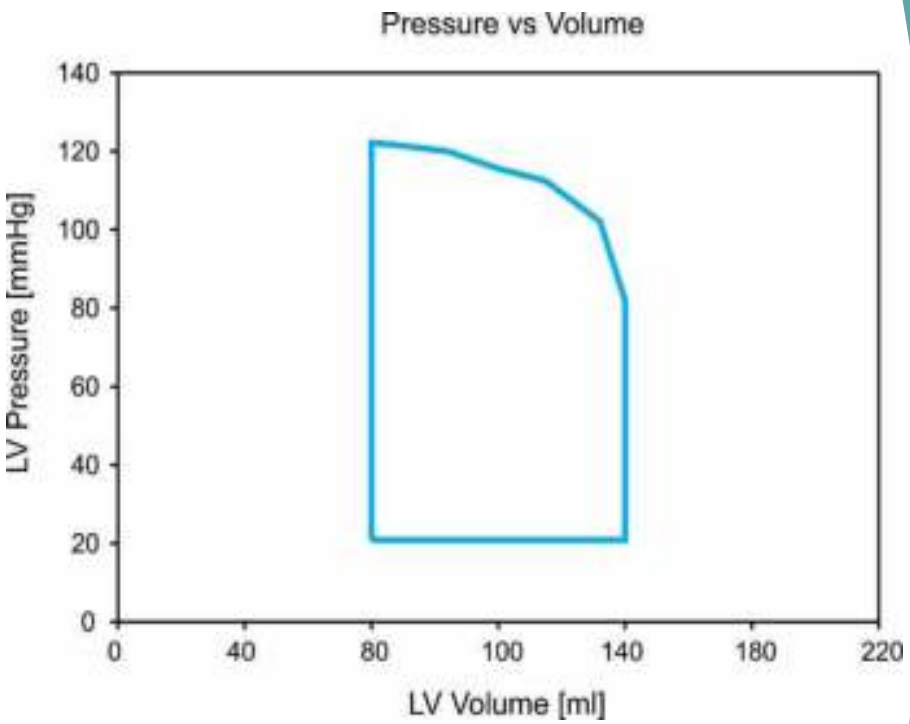


b)



c)





d)

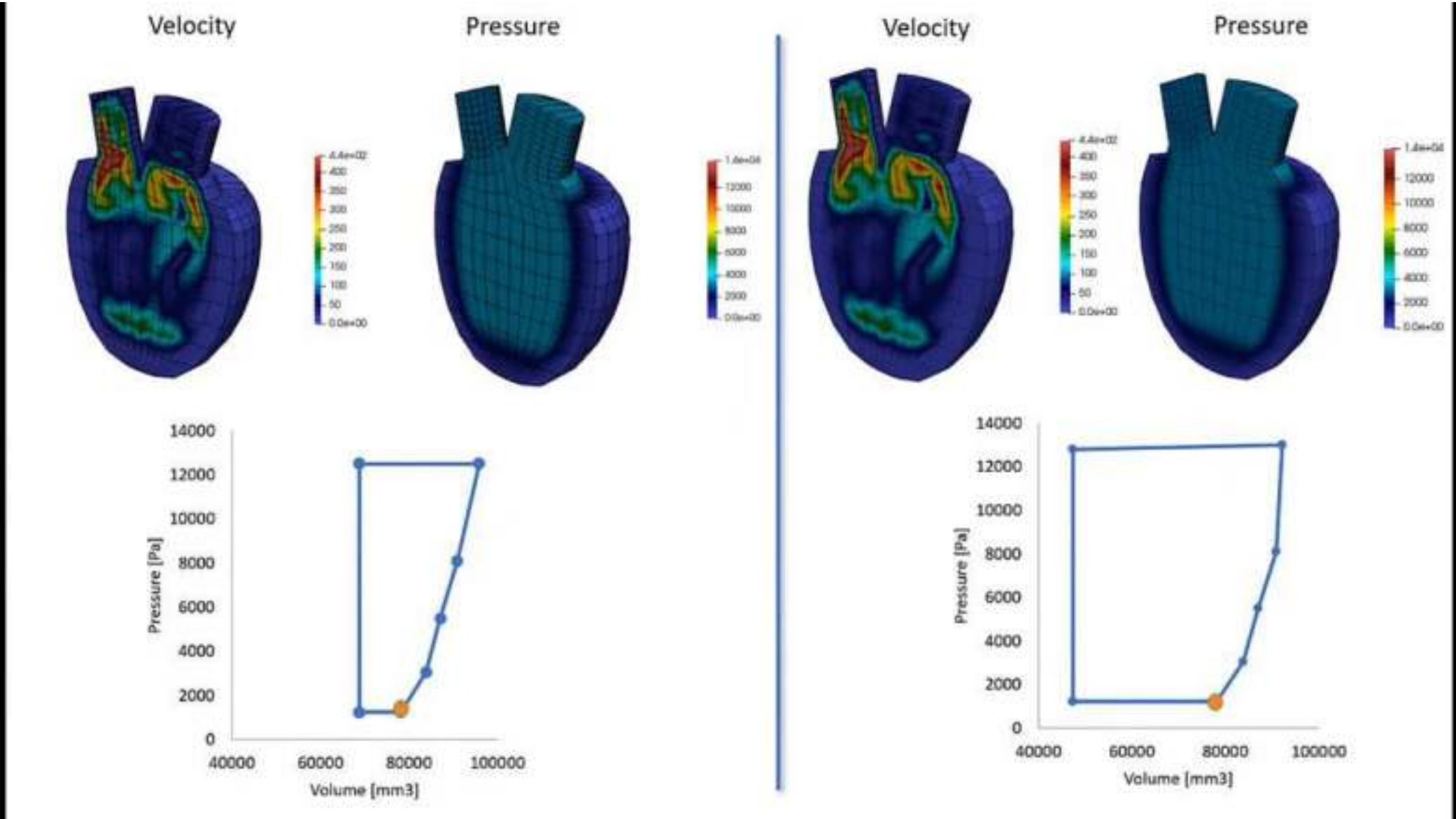
a) Pressure field, b) velocity field, c) displacements inside parametric model of left ventricle (five different time steps) and d) P-V diagram.

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

SILICOFCM

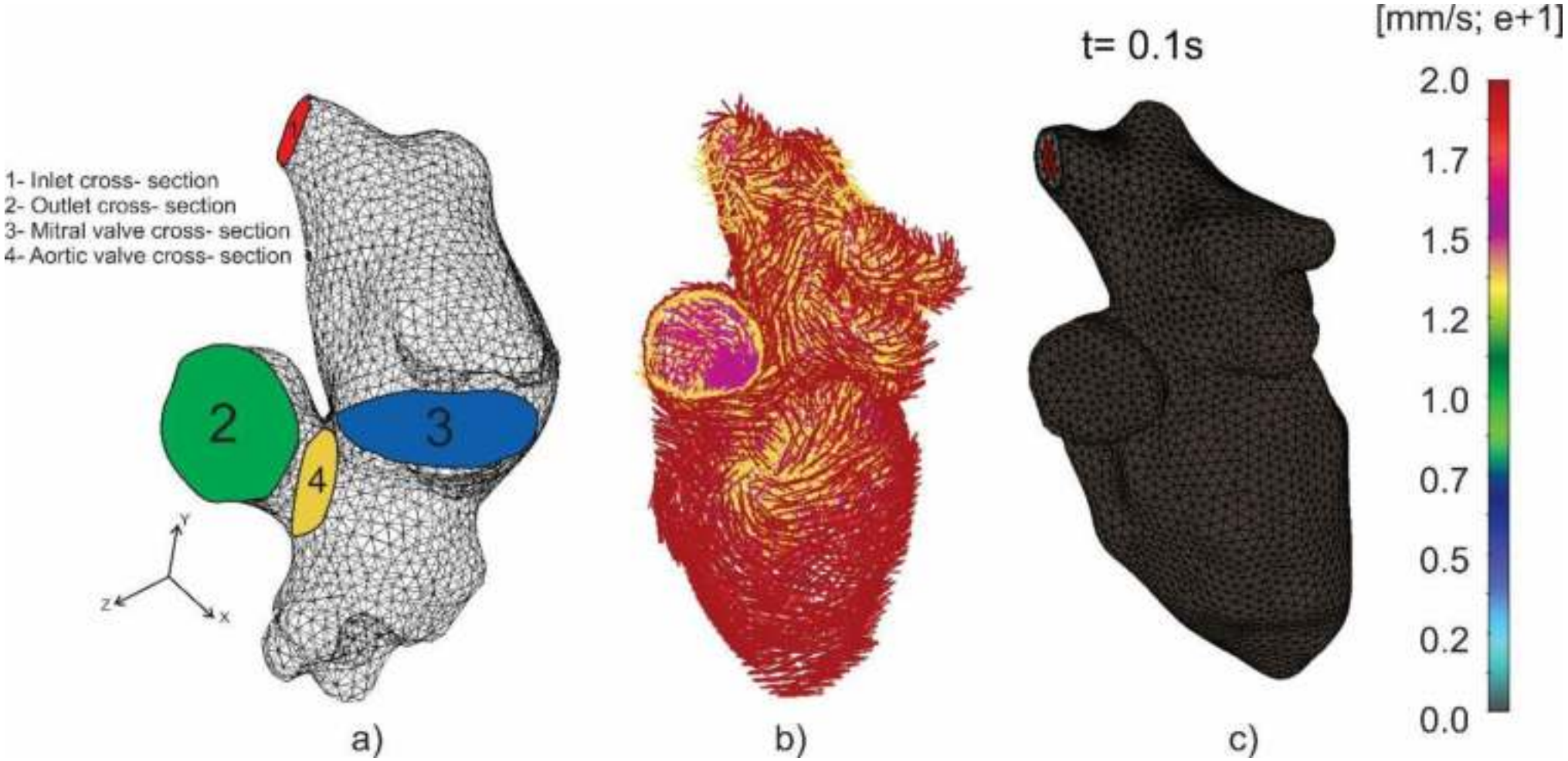
PAK module

- Scenario for creating PV Diagram



PAK module

- Example: Realistic heart model



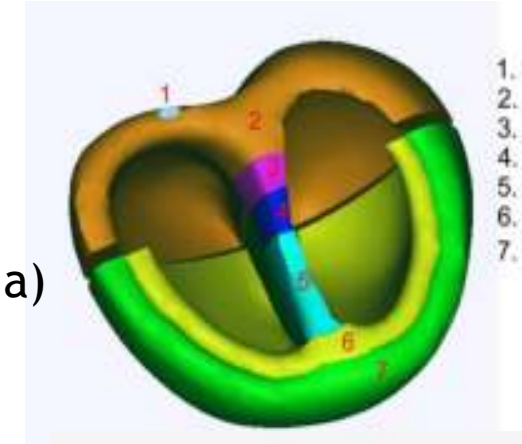
a) Realistic heart FE model with representative cross-section, b) fibers direction in solid part of realistic model and c) fluid velocity field at 0.1s

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

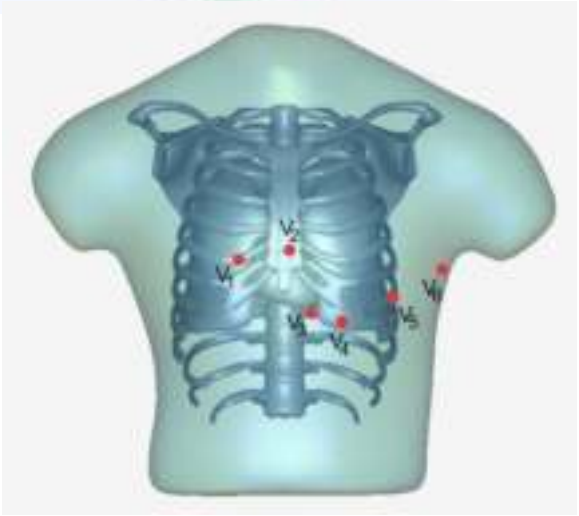
PAK module

- Example: Torso model

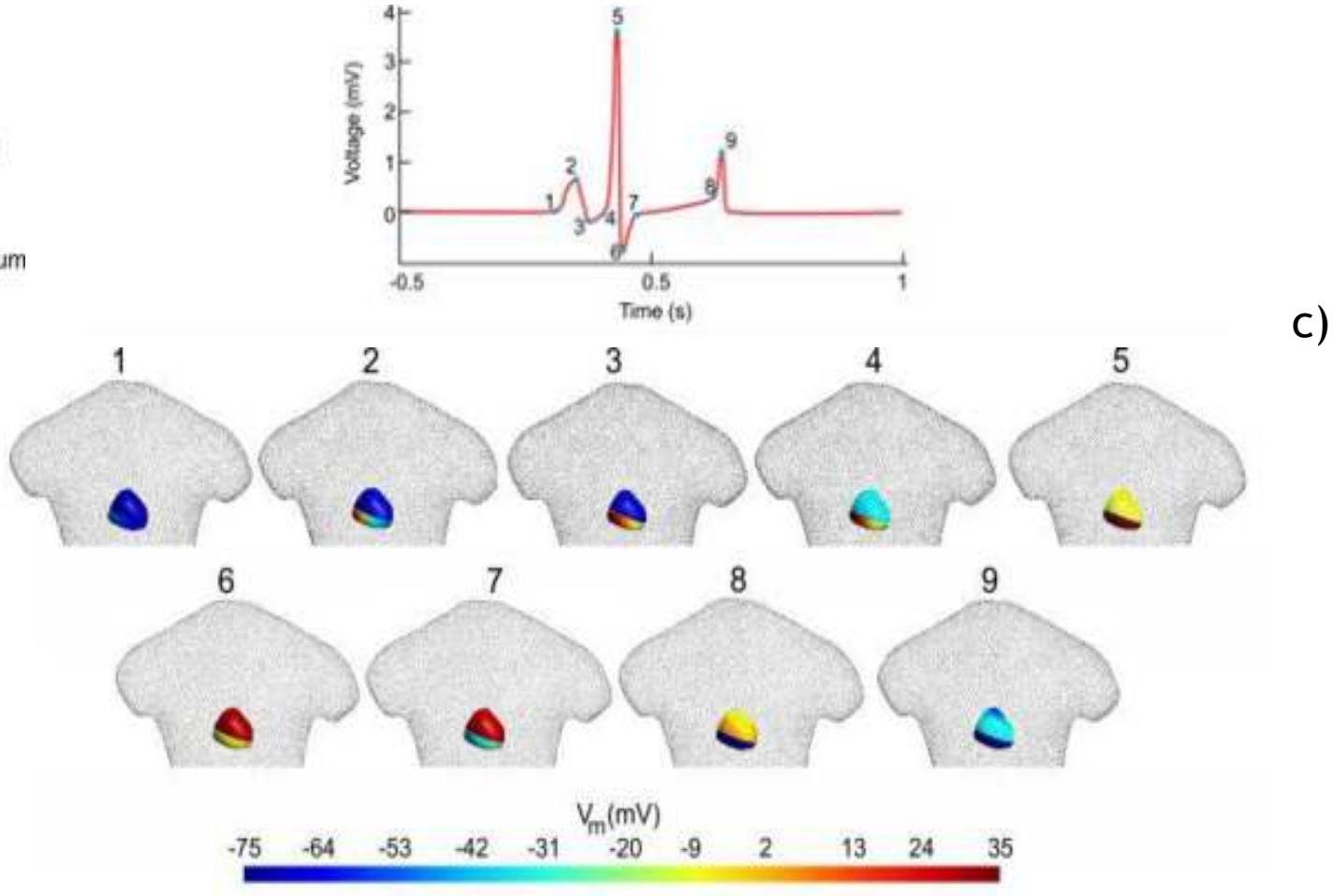
a)



b)



c)

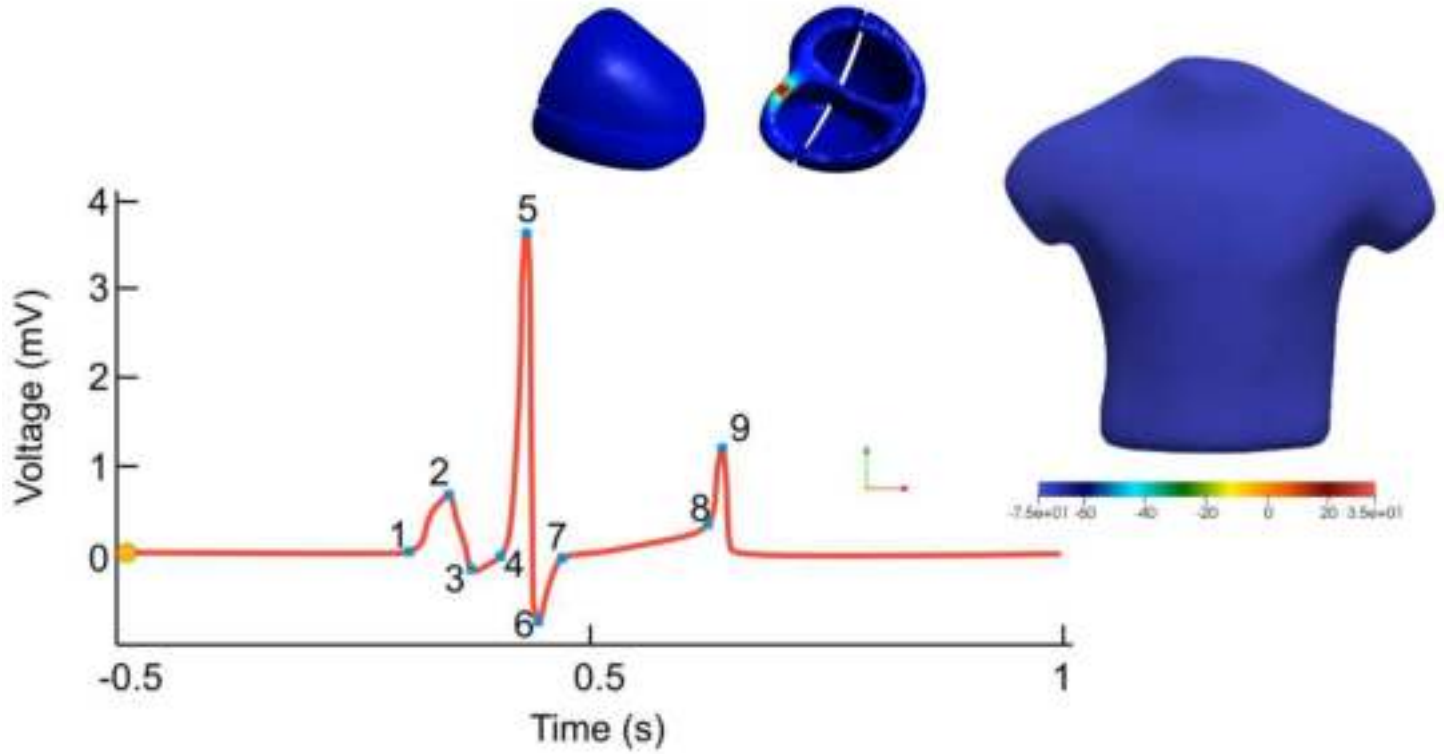


a) Heart geometry and seven different regions of the model; b) Six electrodes (V1-V6) which are positioned at the chest to model the precordial leads; c) Whole heart activation simulation from lead II ECG signal at various time points on the ECG signal. There are 1-9 activation sequences which are corresponding to ECG signal above. The color bar denotes mV of the transmembrane potential.

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

PAK module

- Body surface potential maps with heart activation simulation

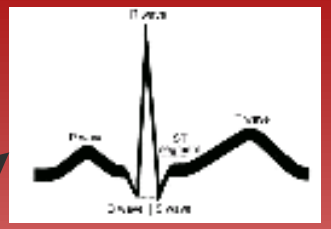


This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

The Heart Physiology as an Electro-Mechanic System

Electrophysiology

ion channels

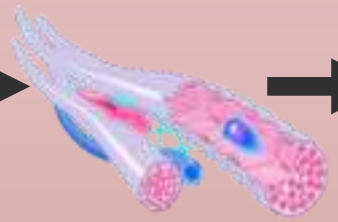


electrocardiogram

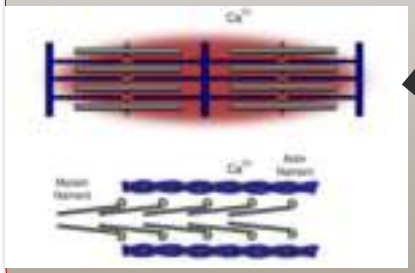
ventricles

Ca^{2+} ion channels

whole cell

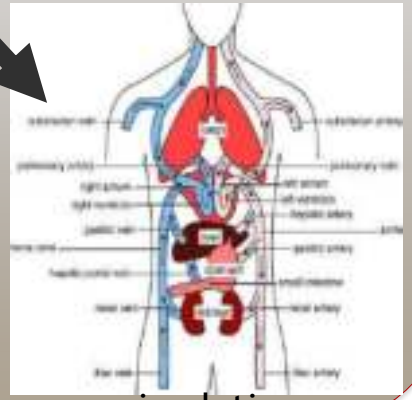


myocardium



sarcomere

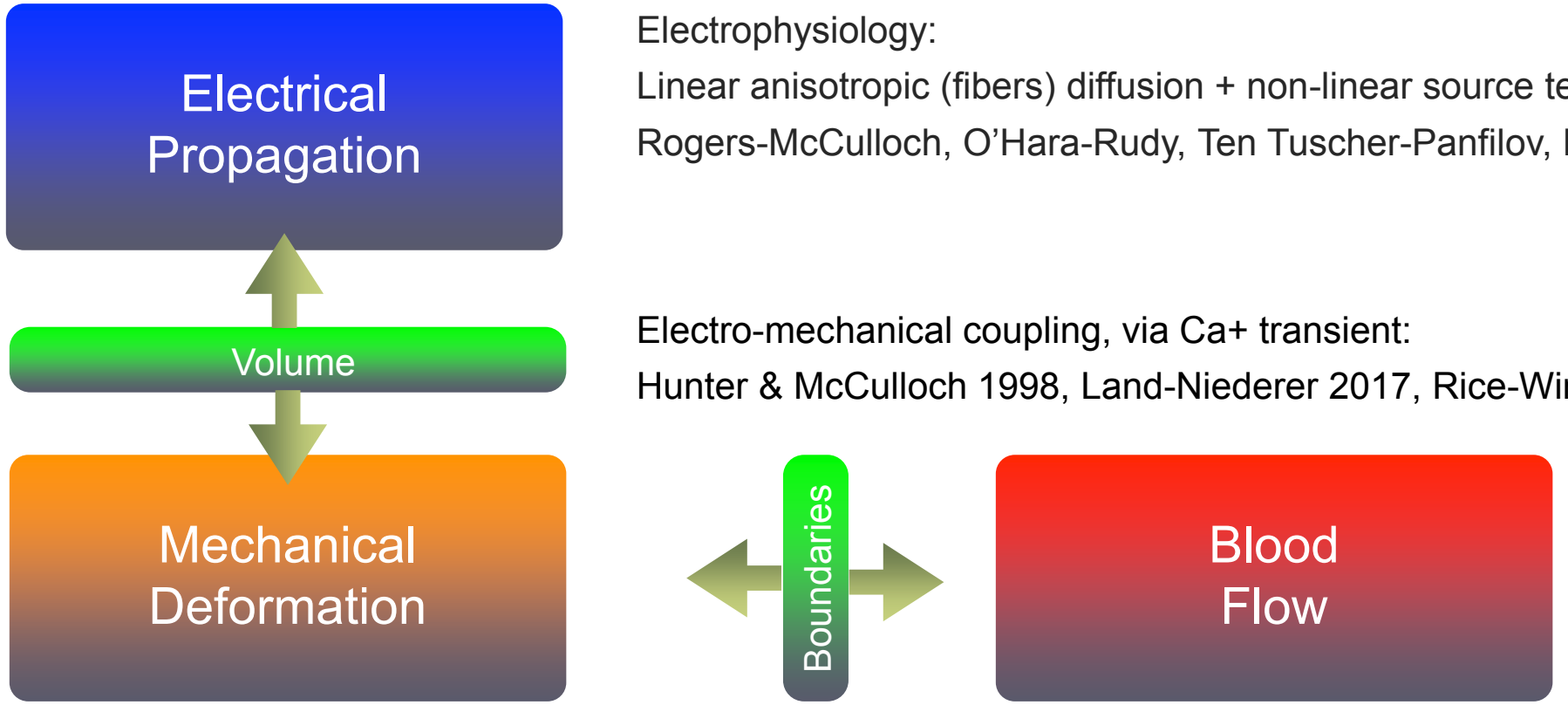
Biomechanics



circulation

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

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

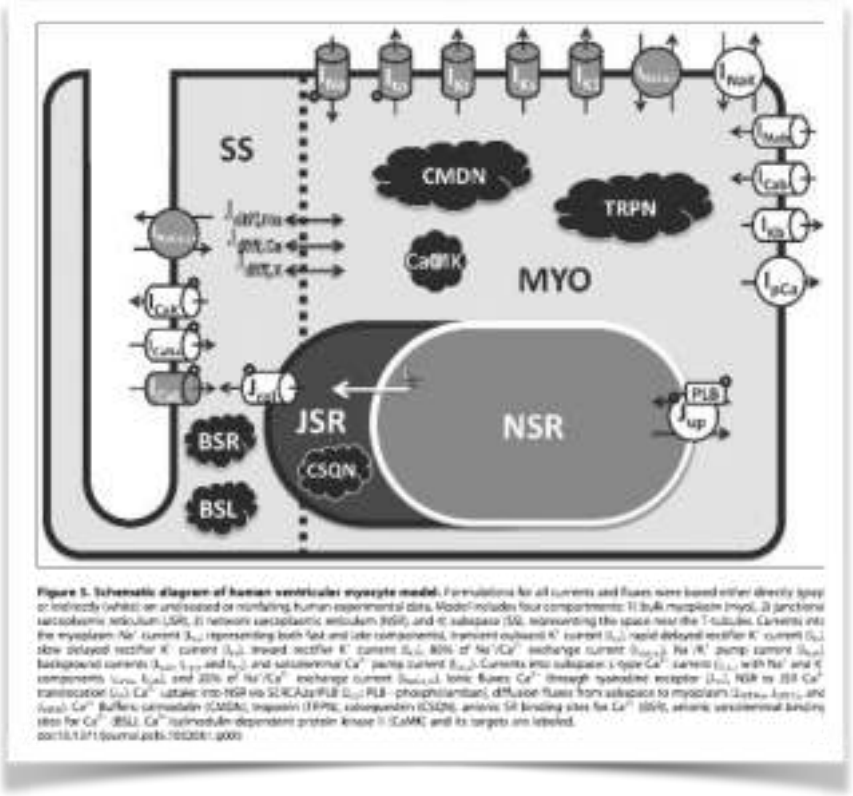
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

SILICOFCM

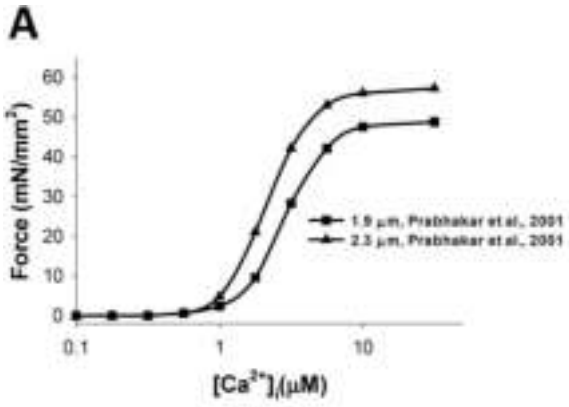
Models

I_{ion}: Human EP model

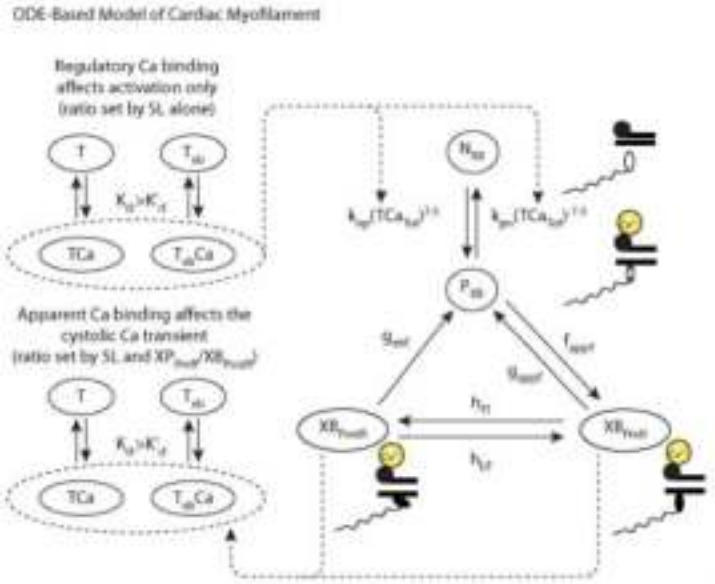
O'Hara- Rudy 2011



ECC: Hunter-McCulloch 1998



ECC: Rice et al. 2008



ECC: Land-Niederer 2017

$$\frac{d\mathrm{CaTRPN}}{dt} = k_{trpn}\left(\left(\frac{[Ca^{2+}]_i}{[Ca^{2+}]_{50}}\right)^{n_{TRPN}}(1-\mathrm{CaTRPN}) - \mathrm{CaTRPN}\right)$$

$$\frac{dB}{dt} = k_b \cdot \mathrm{CaTRPN}^{-n_{TM}/2} \cdot U - k_u \cdot \mathrm{CaTRPN}^{n_{TM}/2} \cdot B$$

$$\frac{dW}{dt} = k_{uw}U - k_{wu}W - k_{ws}W - \gamma_{wz}W$$

$$\frac{dS}{dt} = k_{ws}W - k_{su}S - \gamma_{sz}S$$

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

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

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

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

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

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

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

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

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

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

$$k_b = k_u\mathrm{CaTRPN}^{n_{TM}}/(1 - r_s - (1-r_s)r_w)$$

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

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

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

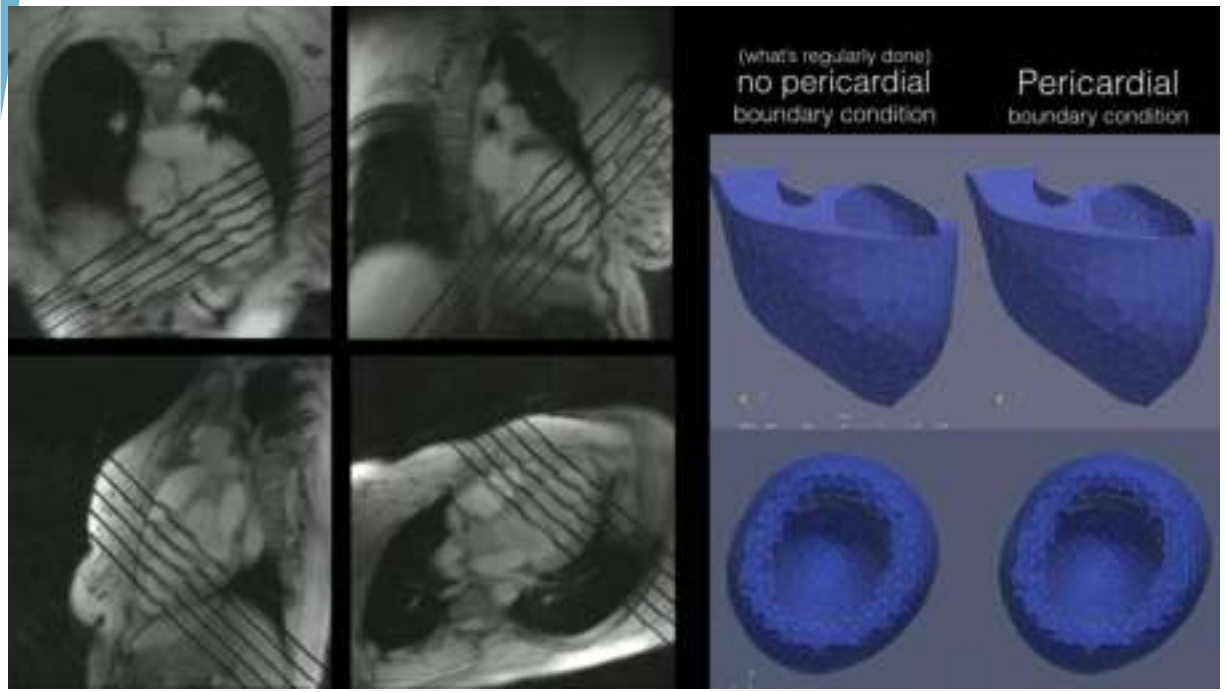
Fully Coupled Electro-Mechanic-Fluid simulation

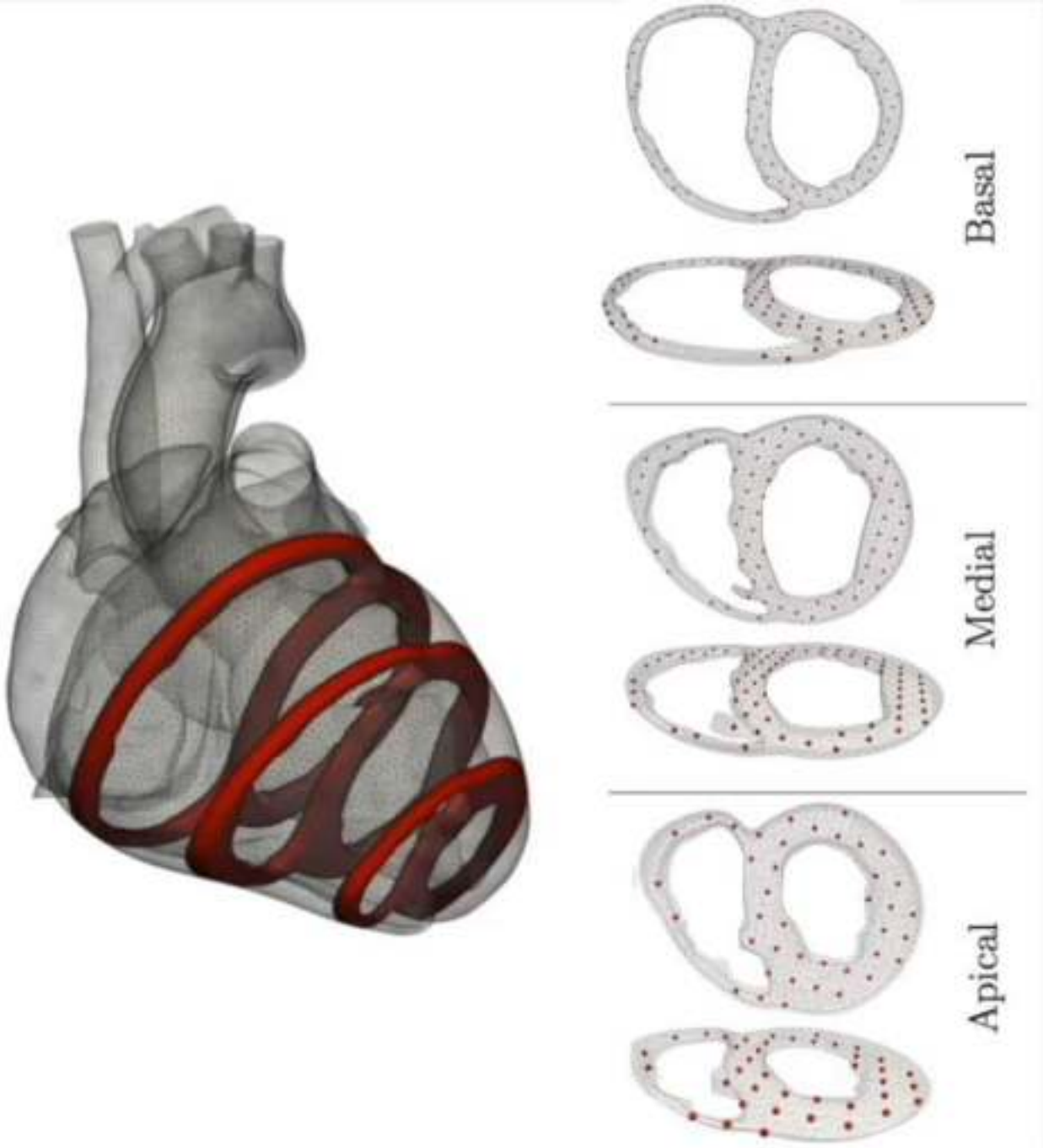
Number of elements:
4M total
240 cores, 12 hrs, 400 ms

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

SILICOFCM

Boundary Conditions and Physiological motion





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

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 mm² cross-section

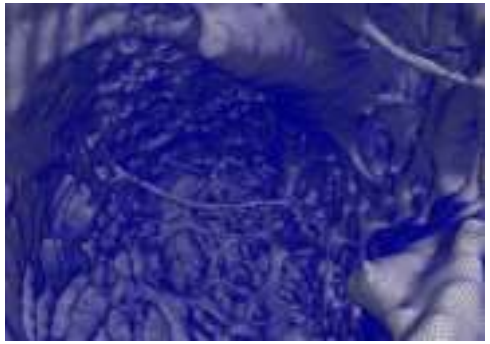
AUTODESK MESHMIXER

Seg3D

ReMESH

Biventricular Detailed Octree Volumetric Meshes

MAXIMUM ELEMENT SIDE LENGTH: 0.4 mm



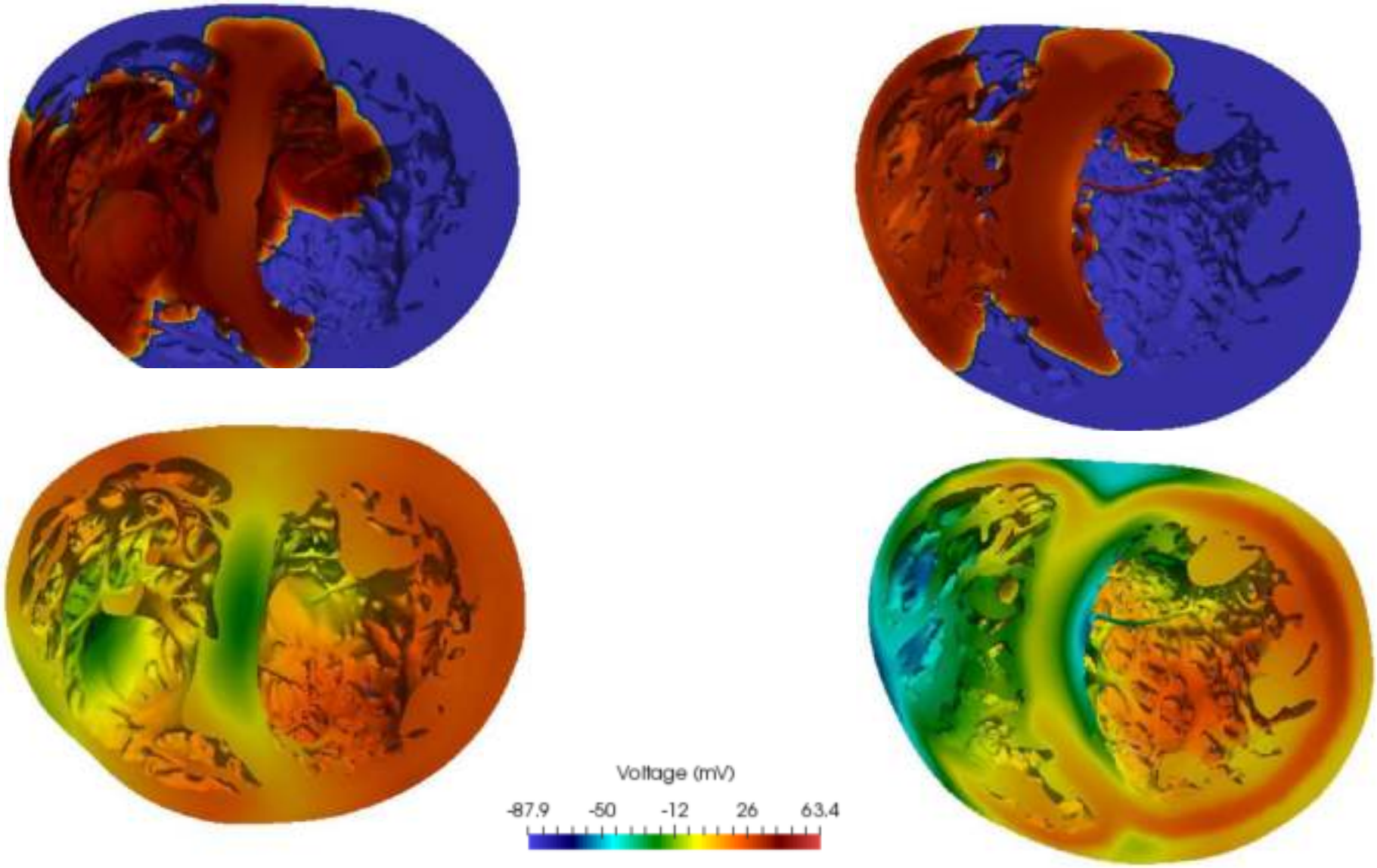
n° elements: 86.318.429
Volume: 394.2 cm^3
n° points: 14.994.563

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

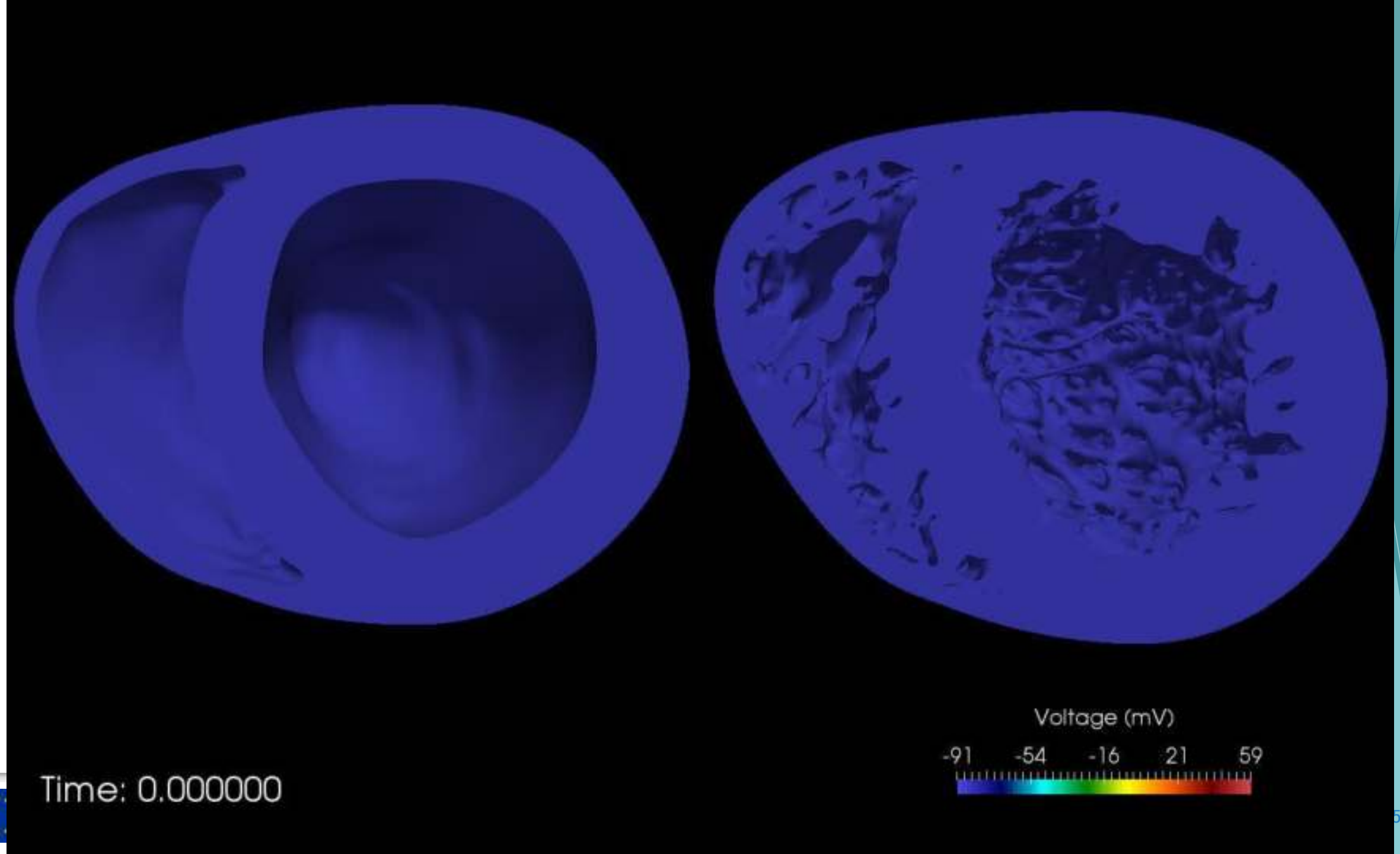
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

Female Phenotype

Male Phenotype



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


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

Virtual Drug Testing

Molecular data

Signaling Pathway selection

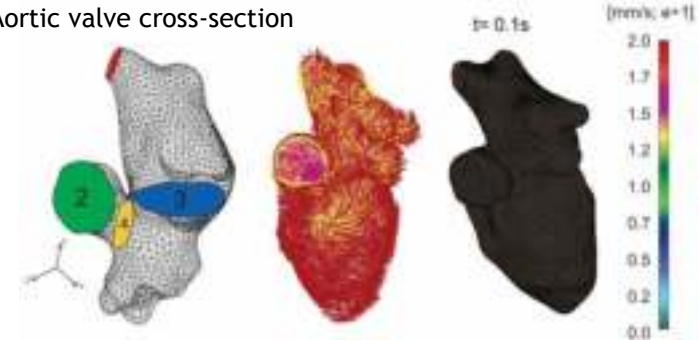
Drug selection

- Drug Database
- Minerva
- Drug/Protein Interactions
- Data Collection

SILICOFCM MUSICO Model

SILICOFCM Finite Element Model

1- Inlet cross-section
2- Outlet cross-section
3- Mitral valve cross-section
4- Aortic valve cross-section



Clinical decision for patient therapy

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

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

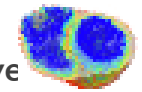
- ✓ Reusable and plausible libraries
- ✓ Geometrical and clinical features
- ✓ Testing of a new drug under different boundary conditions

DATA ANALYTICS tool

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

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

ALYA Finite element solve



- ✓ Drug distribution, stress distribution and deformations of heart tissue

PAK Finite element solver

- ✓ Identified variants contributing to the disease

BIOINFORMATICS tool

- ✓ Simulation of a wide variety of experimental muscle behavior

MUSICO tool

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

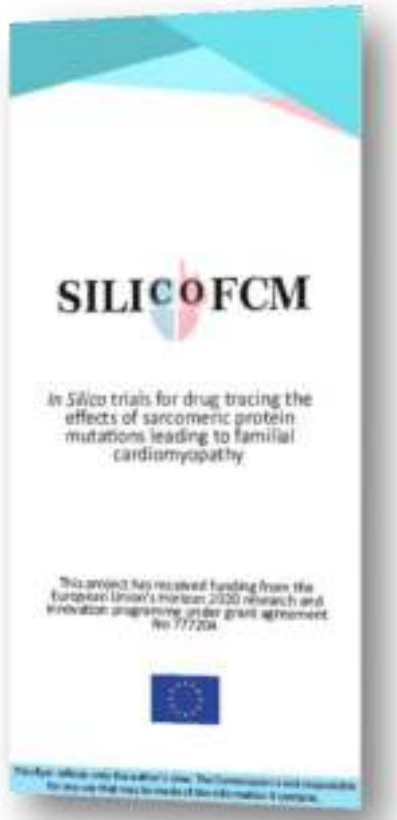
Follow us

Facebook: Silicofcm Project
Twitter: @silicofcm
LinkedIn: SILICOFCM Horizon EU project

Visit our website: www.silicofcm.eu

SILICOFCM DEMO Video
SILICOFCM PROMO Video

Subscribe on our YouTube channel



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

PRECISE4Q

PREDICTIVE MODELLING IN STROKE

Dietmar Frey, Charité

Gunnar Cedersund,

Department of Biomedical Engineering

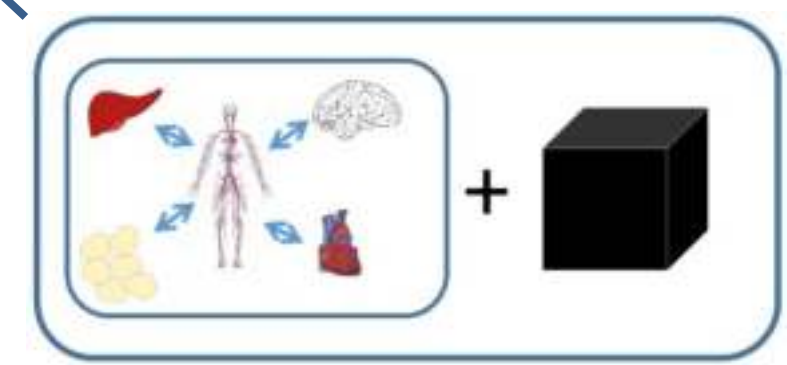
LINKÖPINGS UNIVERSITET

Overview of the project partners and roles

PRECISE4Q
PREDICTIVE MODELLING IN STROKE

P1 Charité (acute, prevention)
P6: Guttman (recovery)
P7: Linköping (prevention)

P2: Empirica, health economy
P4: Zürich – Ethical implications



P1 Charité,
P7: Linköping,
P3 Dublin:

P8: Graz/Muria & P9: DFKI
Health informatics

10 LARGE CLINICAL STUDIES

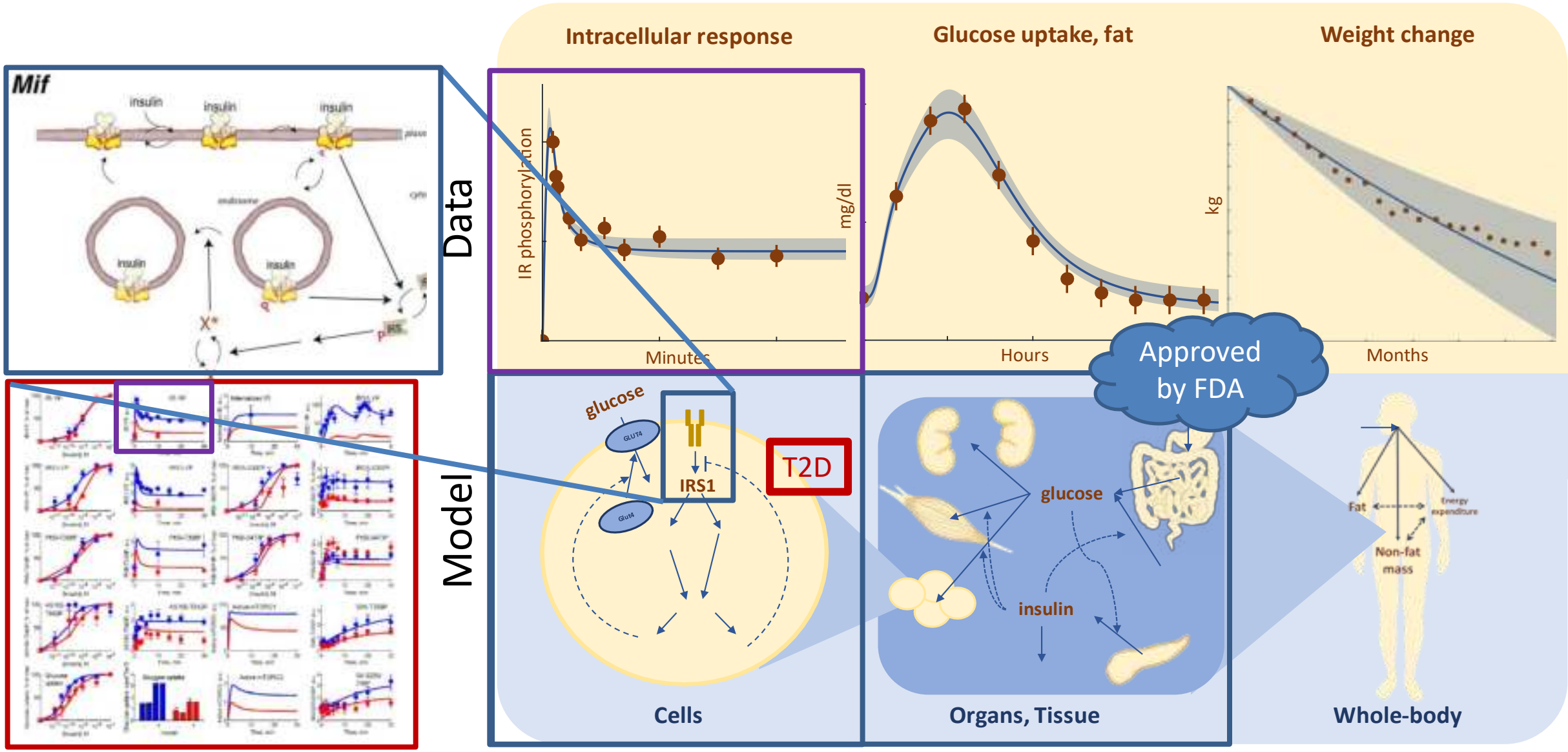
AOK | UKBB | SCAPIS

CARDIPP | Whitehall 2 | Estonian

P11: Qmenta – data warehouse

P3: Dublin - Statistical risk
and imputation models

My own 20 year-long story of multi-level and multi-timescale modelling



Brännmark 2010, JBC

Brännmark 2013, JBC

Nyman 2011, JBC

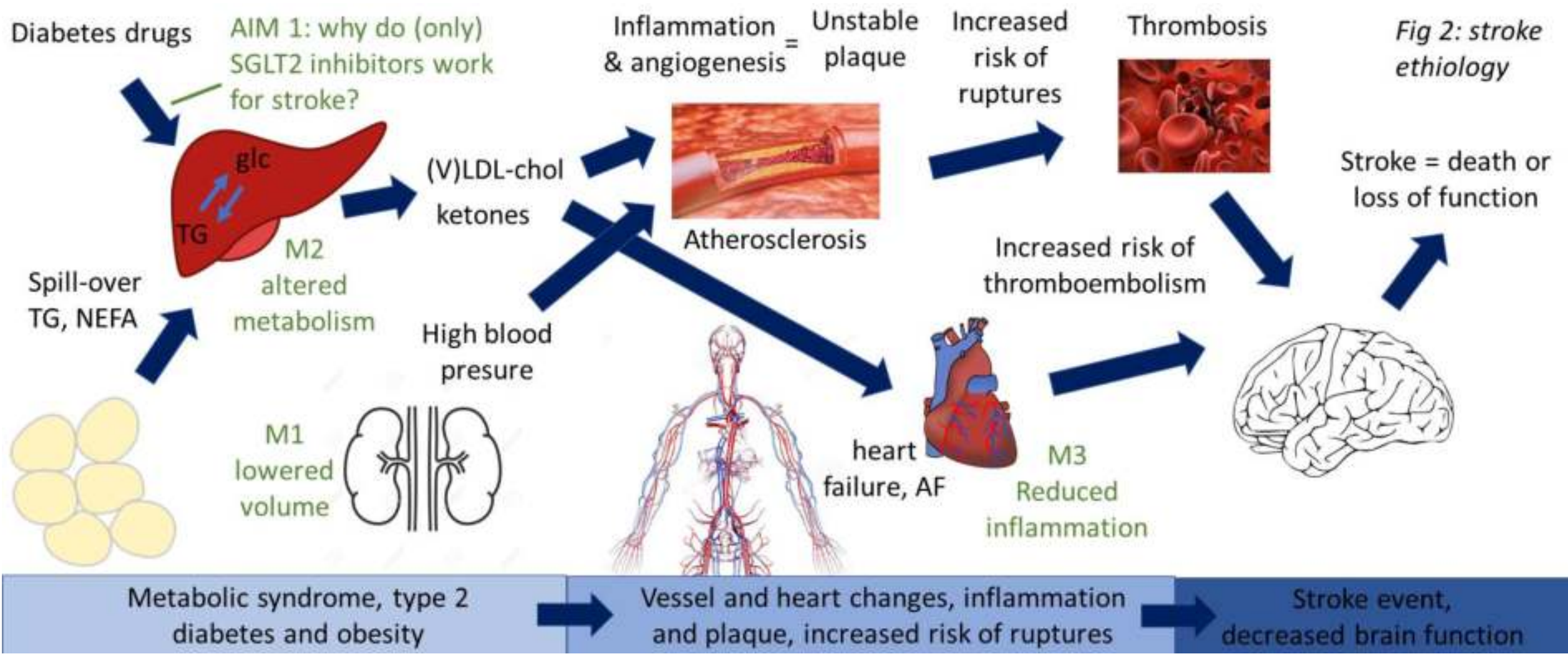
Casas 2017, 2018, Palmér 2014

Lundengård 2016, Sten 2017

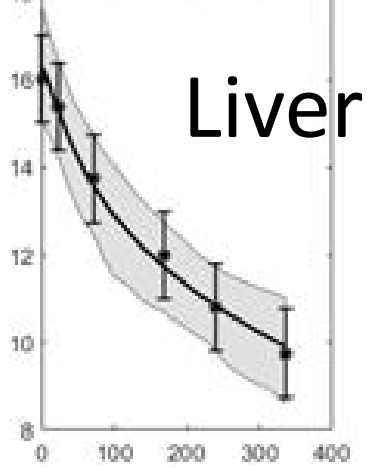
Hall, Lancet, 2011

Nyman and Herrgårdh, *in ms*

Ethiology of an ischemic stroke

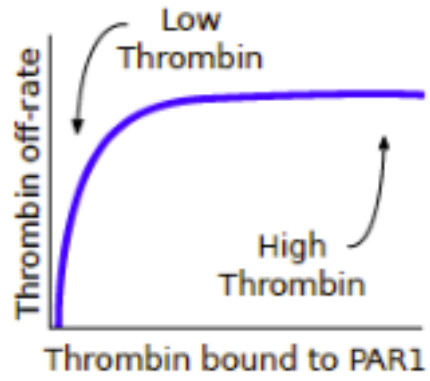


Primary hepatocytes organs-on-a-chip

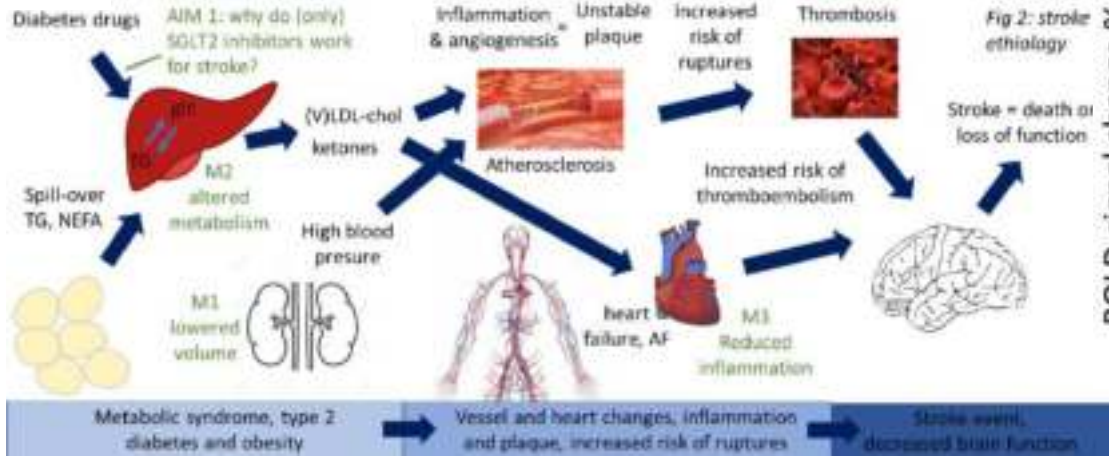


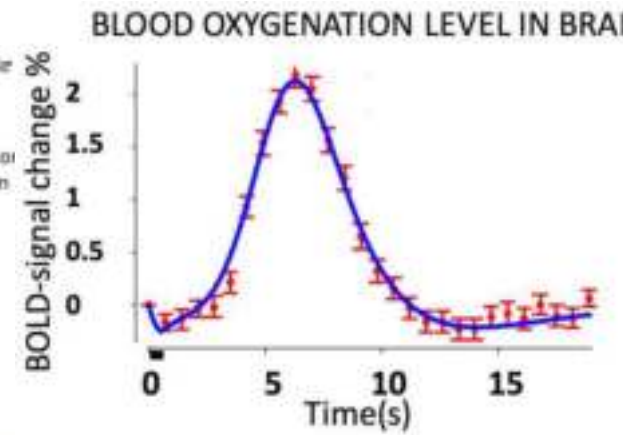
Liver fat

Plaque biopsies, MRI Flow-chamber

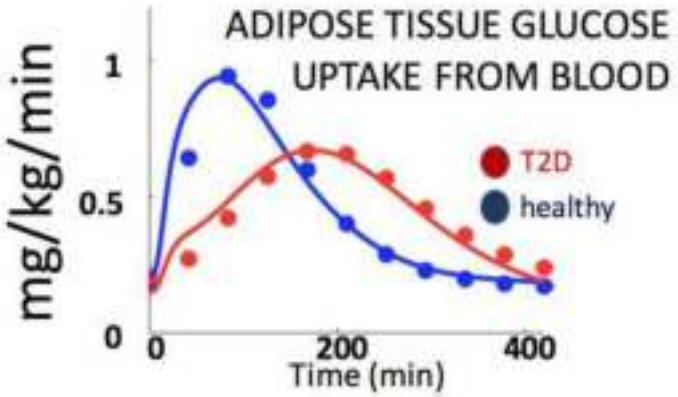


Neuronal models

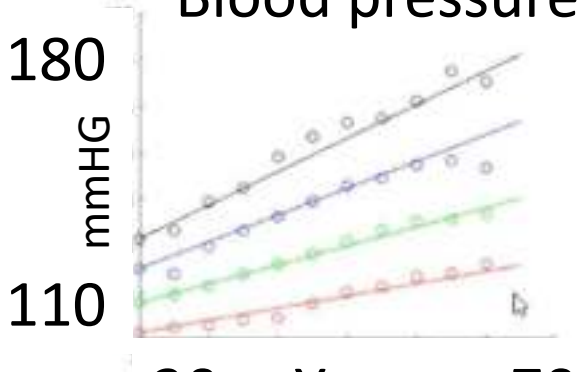




Primary adipocytes, arteriovenous difference data

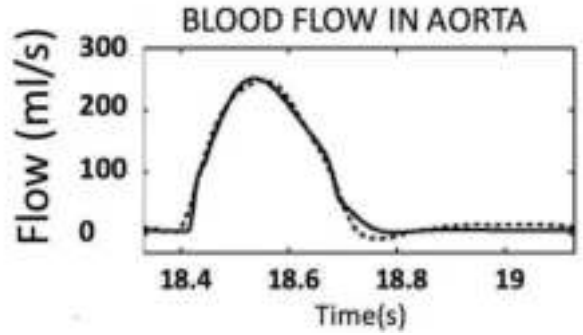


Blood pressure



30 Years 70

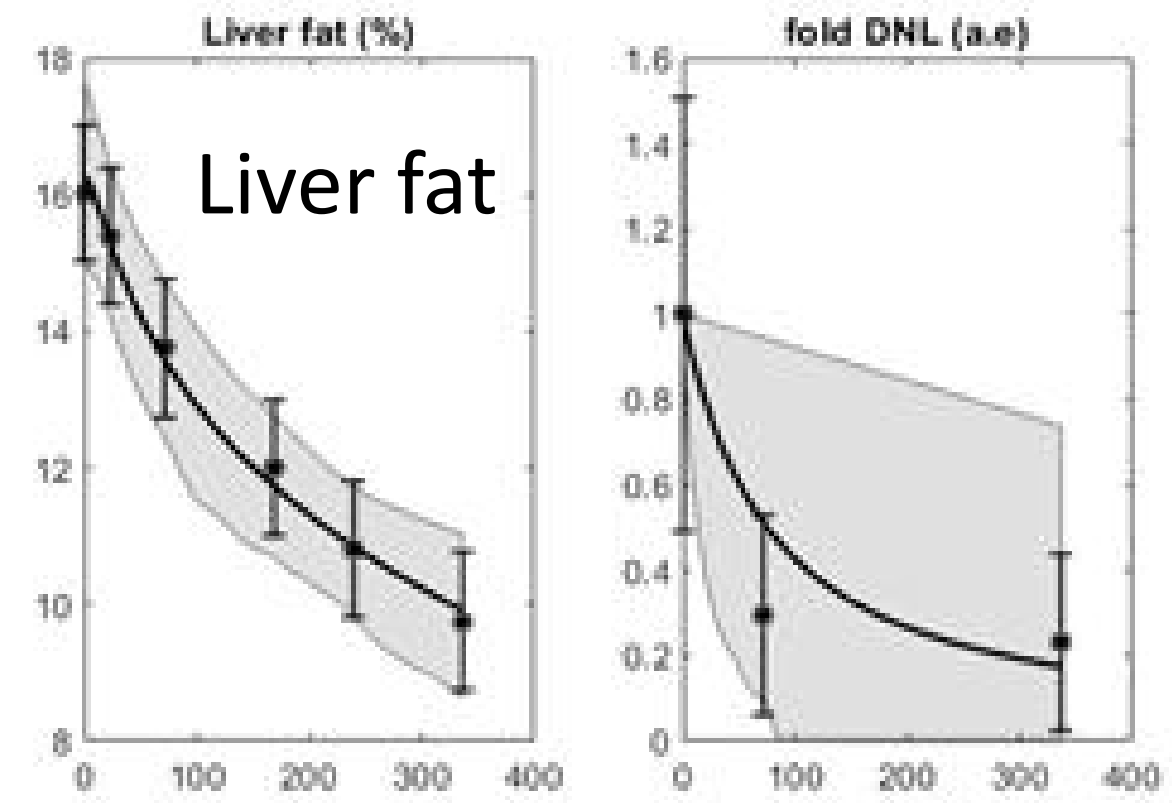
Pre-stroke & post-stroke



4D flow data, organs-on-a-chip

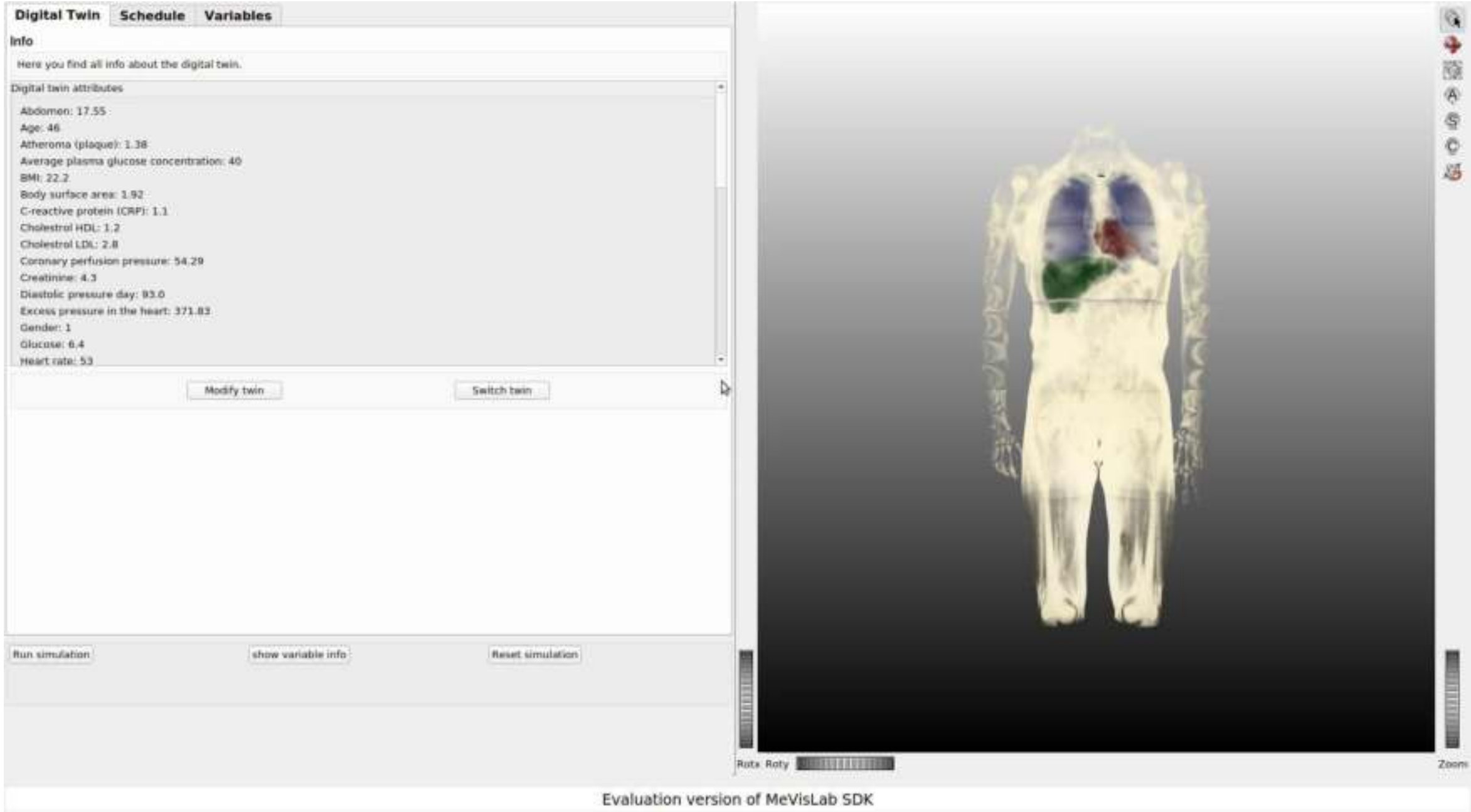
From motivation and prevention to treatment, rehabiliation, and re-integration

- NAFLD (liver fat) is connected to obesity, diet, dyslipidemia, etc, and is a risk factor for liver complications, stroke, etc
- By simulating different scenarios, we can show how the liver fat is getting worse or better depending on the persons diet, exercise, etc.
- Health conversation already lowers the risk of a cardiac event with 30%. ***We want to magnify this effect!***
- Wearable sensors => home monitoring
- Bring the twin to cardiologist, hepatologist, stroke surgery, re-hab, etc



Mardinoglu Cell Metab 2018, Cedersund, *submitted*

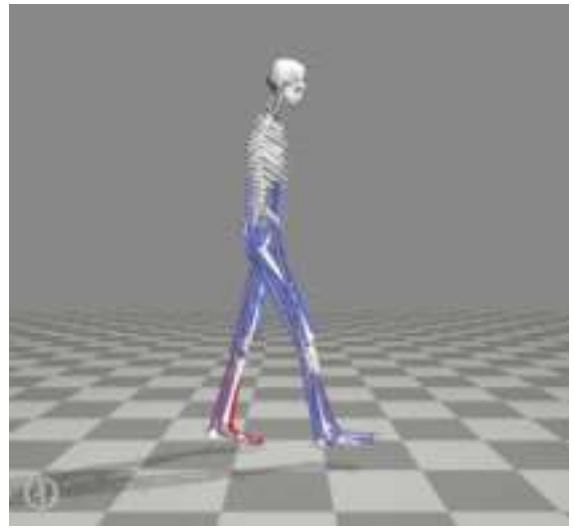
Our digital twin software prototype



Biomechanics and exercise modelling

Biomechanics

Motion-capture

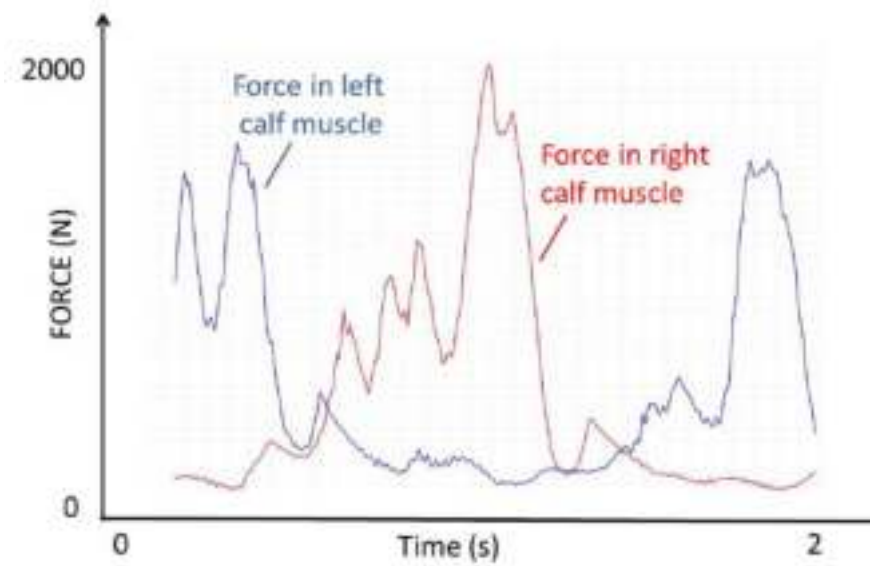


Artificial Intelligence

Deep fake and GAN

Benefits with our approach

- Nicer images in the end
- Connection to medical benefits



Hybrid modelling – basic principle

Gender	1
High bloodpressure	0
Hereditary	0
Length	179
Weight	71,5
Stressed	0
Smoking	0
Hemoglobin	158
Leukocytes	6,4
Thrombocytes	284
Glucose	6,4
Creatinine	4,3
Triiodothyronine	
Cholesterol HDL	
Cholesterol LDL	2,8

Measured/known

unknown

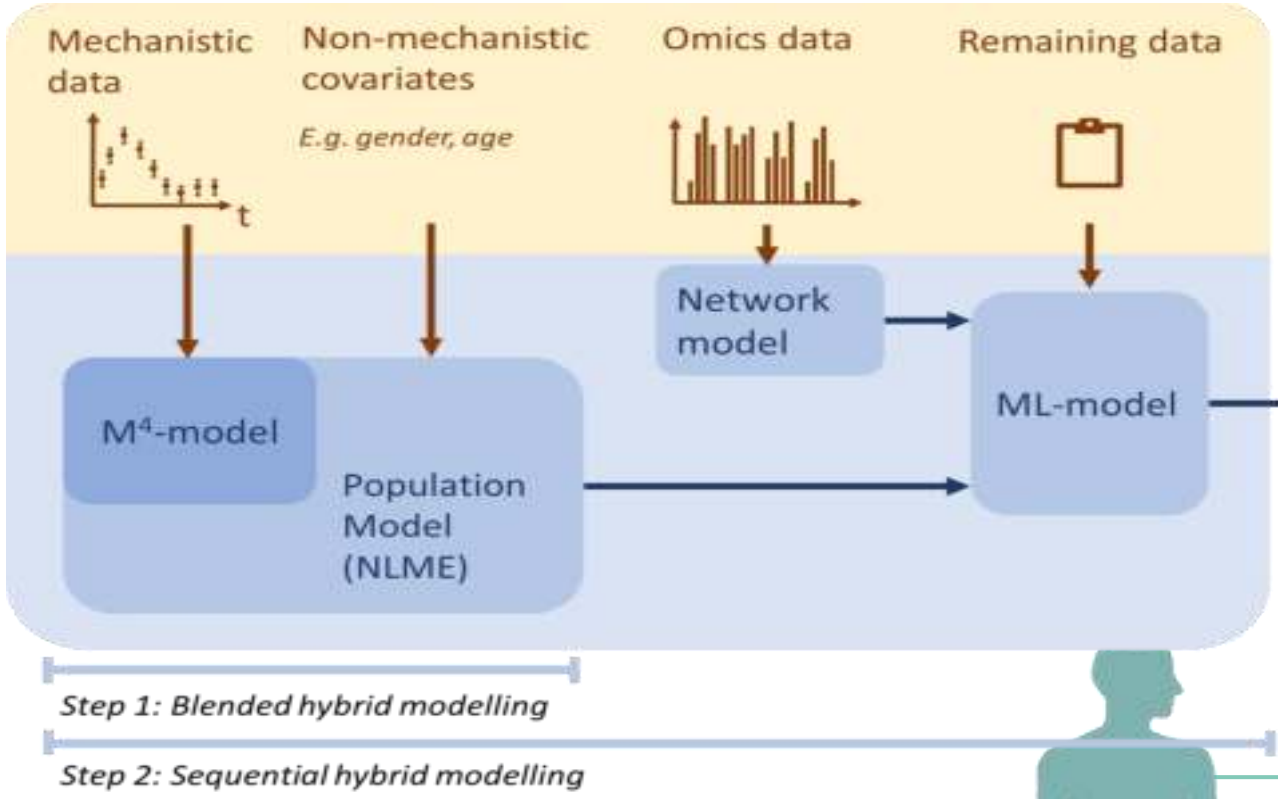
LOAD SCHEDULE

SAVE SCHEDULE

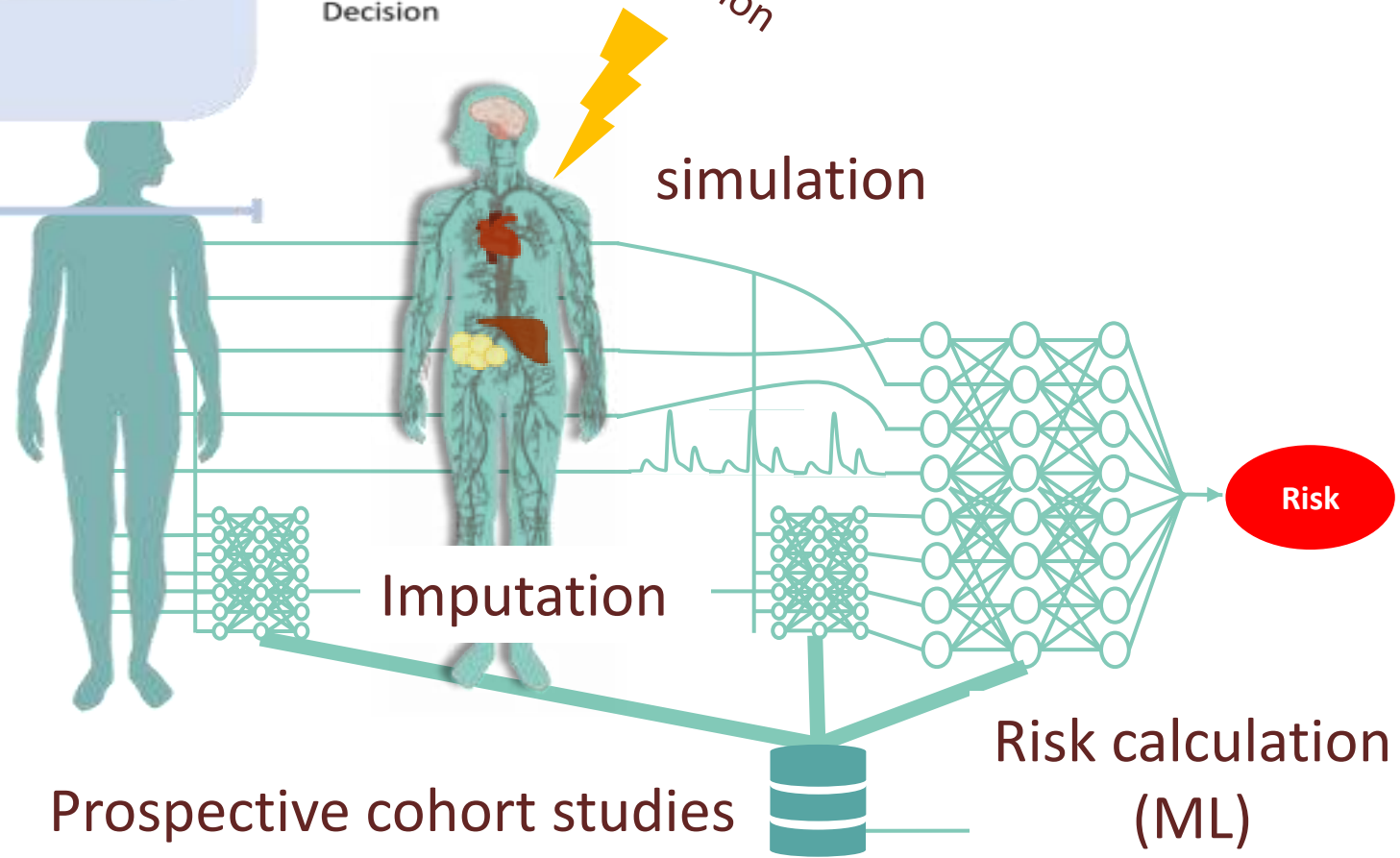
SHOW RISK FACTORS

IMPUTE VALUES

CALCULATE RISK



*And another approach for **simulation** of such hybrid models*



*One hybrid approach for **risk calculation** – combining bioinformatics, mechanistic multi-level population models, and machine learning*

Herrgårdh et al, submitted

Summary and long-term vision: *a personalized patient-centered interconnected healthcare system*

birth

First donation of cells

New cells when needed

first data

Experiments on your own cells in a little ”mini-you”

Translation of results to your own digital twin

Digital twin

Addition of new data

Usage throughout your Patient Journey

Music, arts, gaming, etc

Cedersund, *submitted*

AstraZeneca

A European standardization framework for data integration and data-driven *in-silico* models for personalised medicine

OActive workshop
26 March 2021

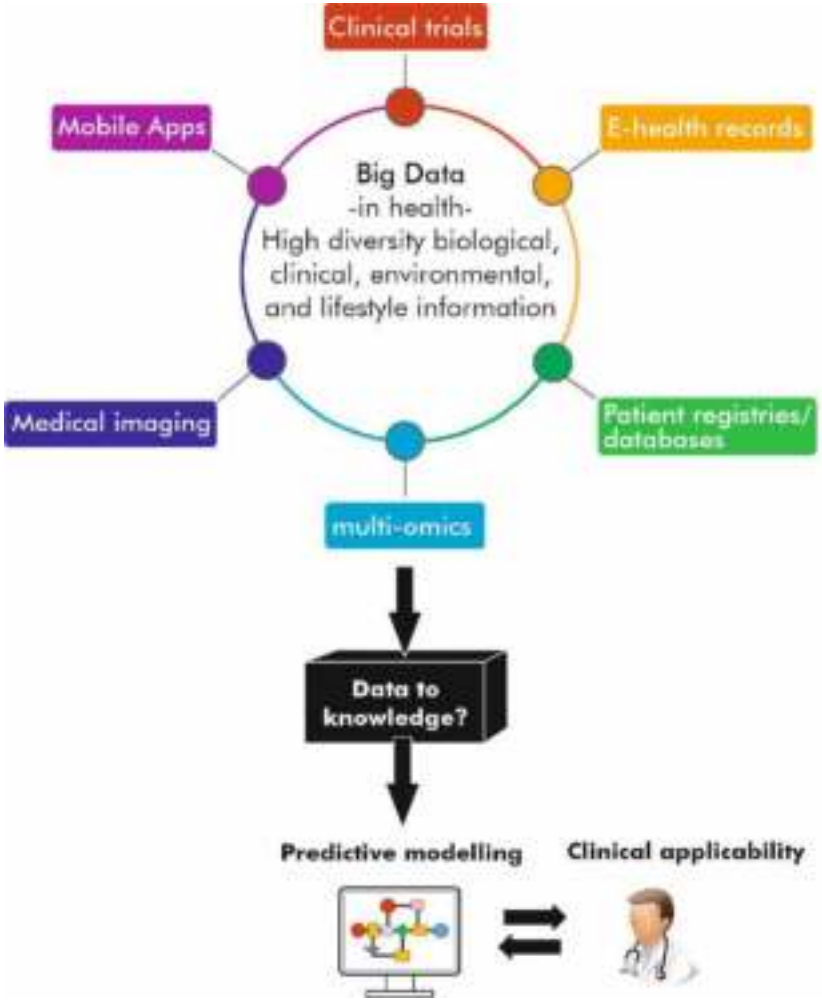
Marc Kirschner, coordinator on behalf of the EU-STANDS4PM consortium

m.kirschner@fz-juelich.de

At a glance

- **Type:** Coordination and support action
- **EC H2020 Work Programme 2018-2020:** Health, demographic change and wellbeing
- **Budget:** 2.0 Mio €
- **Project duration:** 3 years (2019-2021)
- **Consortium:** 16 partners, 8 countries
- **Coordinator:** Forschungszentrum Jülich GmbH, Project Management Jülich

From data to knowledge through *in silico* modelling

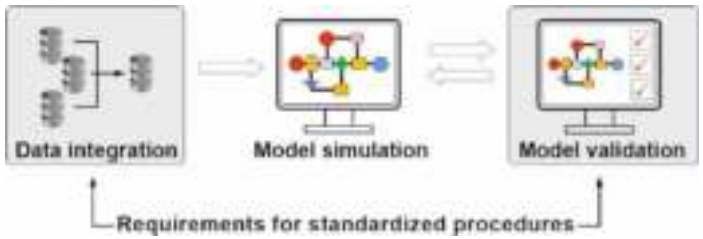


Guidance for

- ⇨ Data harmonization and integration
- ⇨ Model validation
- ⇨ Legal and ethical challenges
- ⇨ Data governance

Development of

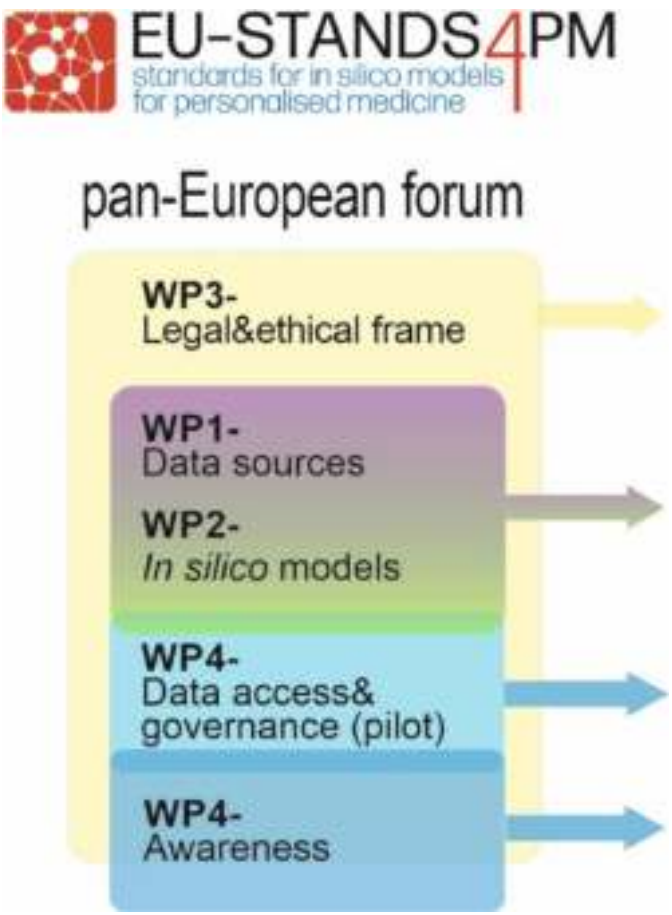
- ⇨ Recommendations and guidelines



Target communities

- ⇨ European collaborative research, Funding organizations, Regulatory bodies

Project structure and output



Project outputs

- **Assessments**
- **State of the art**
- **Reviews**
- **Recommendations**
- **Dissemination**

Selected project outputs, period Jan 2019 – Mar 2021

WP1 – Data sources and models in personalised medicine across Europe

Featuring

- EU-wide mapping of data sources relevant for personalized medicine.
- Online survey with 92 questions regarding
  - datasources and standards
  - modeling methods and standards
  - data access consent

Work in progress

- EU/Project report
- Manuscript

Ingrid Kockum
Karolinska Institutet

WP2 - White Paper on *in silico* models

Featuring

- ⇨ State of the art modelling approaches for personalized medicine
- ⇨ Recommendations for data integration and model validation
- ⇨ Collection of use cases

Work in progress

- ⇨ Manuscript for a review article

Catherine Collin

UNIVERSITY OF COPENHAGEN

First article with guidelines published

Workshop

Søren Brunak, Catherine Bjerre Collin, EU-STANDS4PM Consortium, Katharina Eva Ó Cathaoir, Martin Golebiewski, Marc Kirschner*, Ingrid Kockum, Heike Moser and Dagmar Waltemath

Towards standardization guidelines for *in silico* approaches in personalized medicine

https://doi.org/10.1515/jib-2020-0056
Received: February 18, 2020; Accepted: April 25, 2020

Abstract: Despite the ever progressing technological advances in producing data in health and clinical research, the generation of new knowledge for medical benefits through advanced analytics still lags behind its full potential. Reasons for this obstacle are the inherent heterogeneity of data sources and the lack of broadly accepted standards. Further hurdles are associated with legal and ethical issues surrounding the use of personal/patient data across disciplines and borders. Consequently, there is a need for broadly applicable standards compliant with legal and ethical regulations that allow interpretation of heterogeneous health data through in silico methodologies to advance personalized medicine. To tackle these standardization challenges, the Horizon2020 Coordinating and Support Action EU-STANDS4PM initiated an EU-wide mapping process to evaluate strategies for data integration and data driven in silico modelling approaches to develop standards, recommendations and guidelines for personalized medicine. A first step towards this goal is a broad stakeholder consultation process initiated by an EU-STANDS4PM workshop at the annual COMBINE meeting (COMBINE 2019 workshop report in same issue). This forum analysed the status quo of data and model standards and reflected on possibilities as well as challenges for cross-domain data integration to facilitate in silico modelling approaches for personalized medicine.

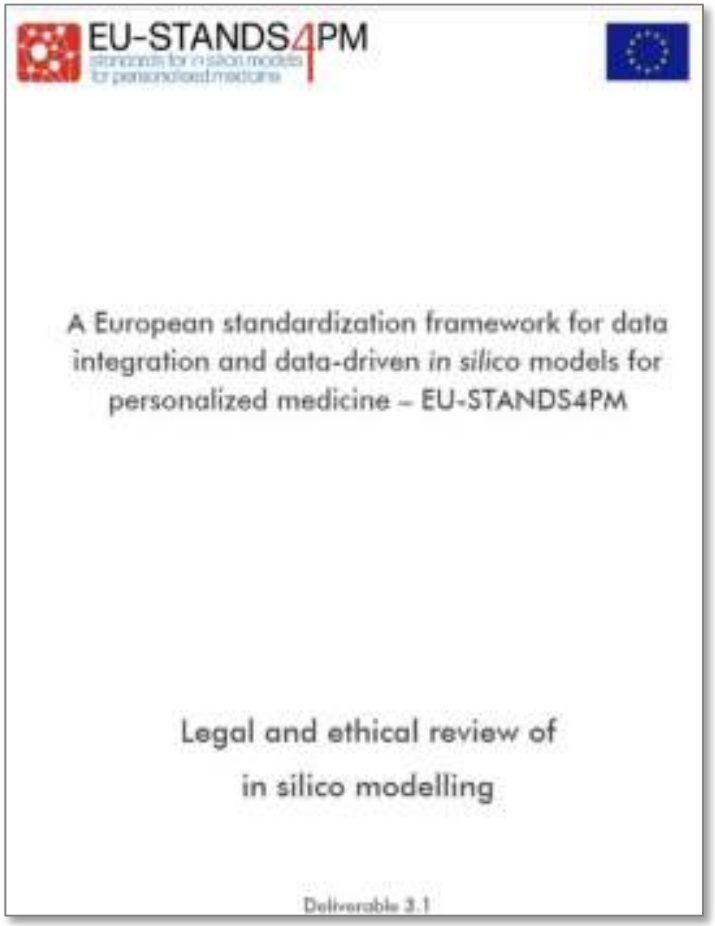
Keywords: data integration; in silico modelling; personalized medicine; reproducibility; standards.

Online in the *Journal of Integrative Bioinformatics*

Contains first set of recommendations addressing

- ⇨ Funders, including the EU-Commission
- ⇨ Health care providers purchasing and developing electronic health care systems
- ⇨ Journals
- ⇨ Research groups
- ⇨ National and regional health data providers
- ⇨ Policy makers

WP 3 - Legal and ethical review of *in silico* modelling



Featuring

- ⇨ Consent, GDPR and Patient´s rights
- ⇨ Compact and comprehensive version available
- ⇨ www.eu-stands4pm.eu
- ⇨ Manuscript accepted in *Computer Law & Security Review: The International Journal of Technology Law and Practice (2021)*

Mette Hartlev

UNIVERSITY OF COPENHAGEN

WP4 - New harmonized Data Access Agreement

Featuring

- ⇨ Better data flexibility across collaborative projects
- ⇨ Fully GDPR compliable
- ⇨ On European Genome-Phenome Archive website as a default template
- ⇨ More: EU-CORDIS news release

www.eu-stands4pm.eu

Work in progress

- ⇨ Manuscript in preparation

Stamatina Liosi
Stephan Beck
UCL

Work with ISO

ISO liaisons

- ISO/TC276 Biotechnology, WG5 Data Processing and Integration (established)
- ISO/TC 215 Health Informatics, SG 1 Genomics Informatics (established)

Work in progress

- ISO Technical Report (ISO/TC276/WG5)

Requirements for in silico-models for personalized medicine — Guidelines for verifying and validating predictive computational models in EU collaborative research

Some interactions with relevant projects

- ⇨ Invitation to project-specific events
- ⇨ Review of reports and documents (hDAA, legal/ethical report)
- ⇨ Co-authorship of reports, white papers, publications
- ⇨ Recruitment of experts

The players and their key tasks

H2020 core projects/ data governance pilot

UCL

UNIVERSITÀ DI PARMA
BD2DECIDE

QIAGEN
SPIDIA4P

CAU
SYSCID

LifeCycle

Karolinska Institutet
MultipleMS

Standardization

DIN

HITS
QIAGEN

Data and models

elixir
UNIVERSITY OF COPENHAGEN
BAYER

Universität Rostock

Legal/ethical frame

UNIVERSITY OF COPENHAGEN

UNIVERSITY OF OXFORD

Regulatory support

famhp

Coordination

JÜLICH FORSCHUNGSZENTRUM

ptj Projektträger Jülich Forschungszentrum Jülich

Acknowledgements

EU-STANDS4PM is funded by the European Union Horizon2020 framework programme of the European Commission, Directorate-General for Research and Innovation under Grant Agreement # 825843.

Back-UP Project

Personalised Prognostic Models to Improve Well-being and Return to Work After Neck and Low Back Pain

http://backup-project.eu/

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777090

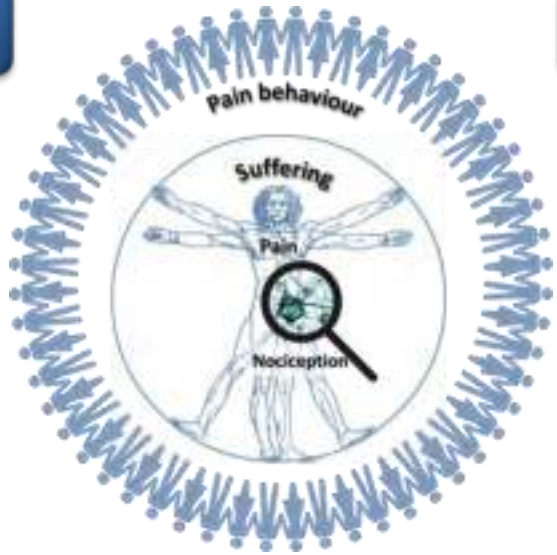
Dimensions of neck and low back pain studied in Back-UP

Mind

- Self-efficacy
- Fear
- Beliefs

Workplace

- Conditions
- Interventions



Life style

- Physical activity

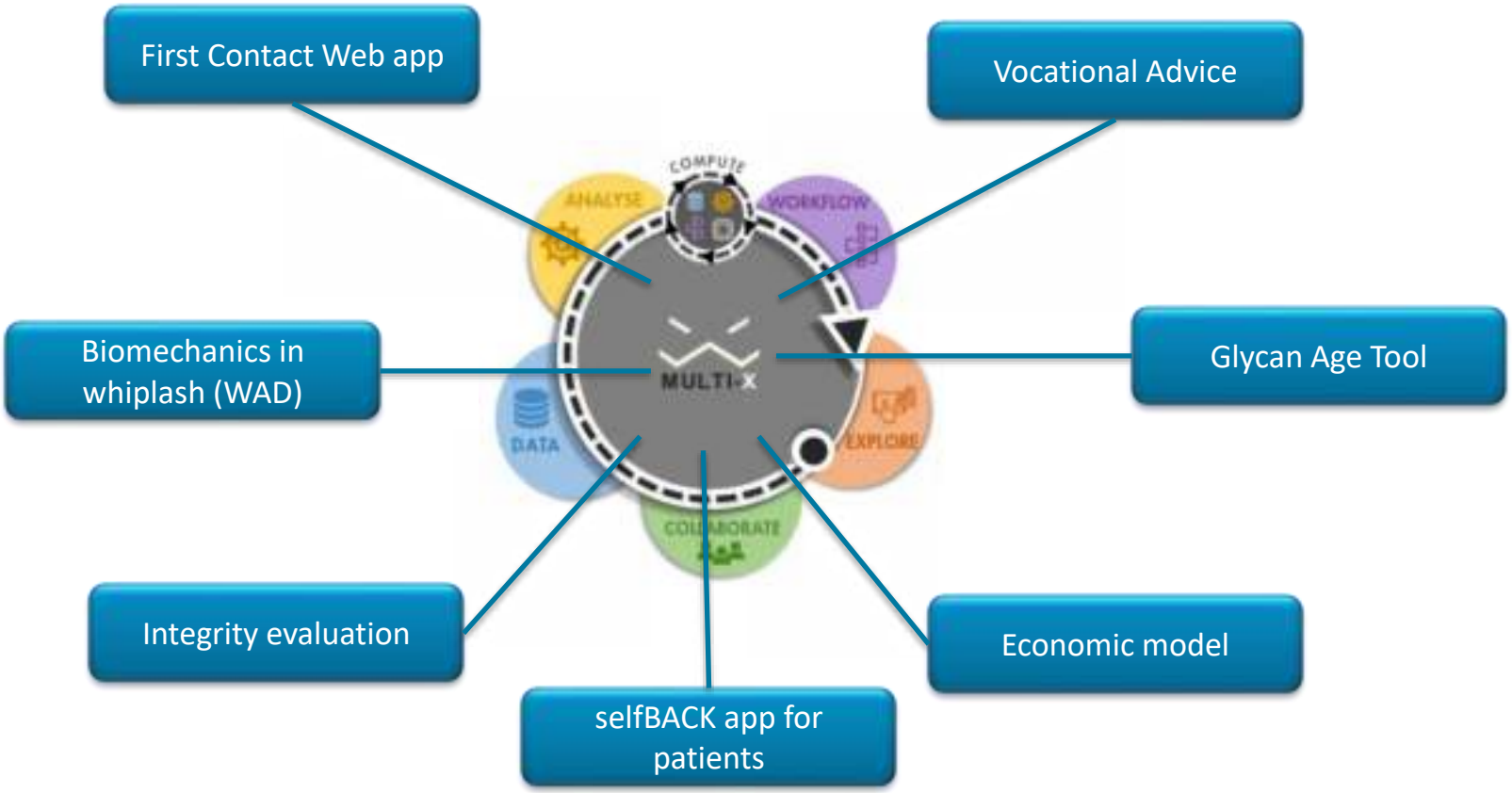
Body

- Biomechanics

Cells

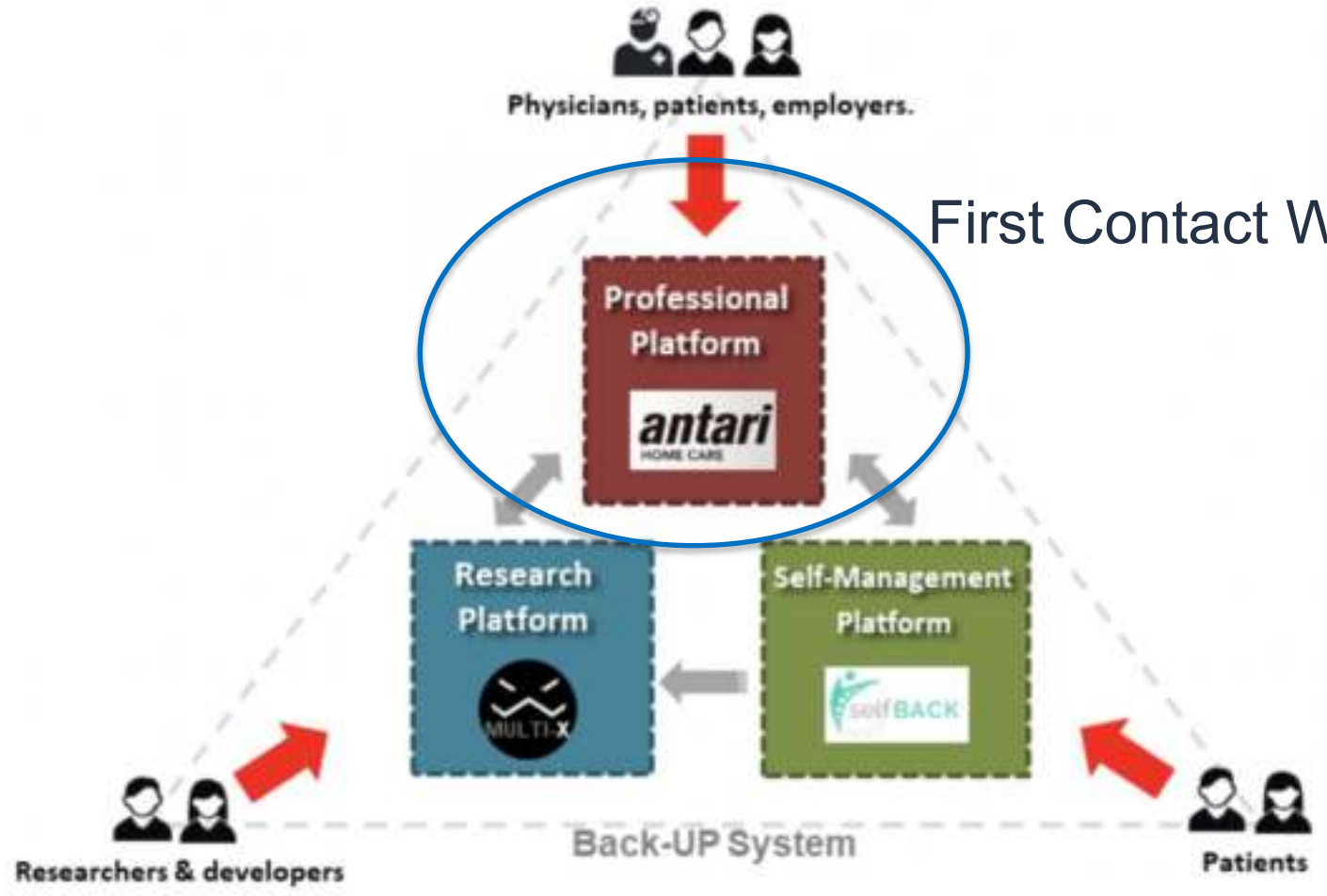
- Glycans

Platform Demonstrators



Back-UP First Contact Web App

Use cases and information flow



First Contact Web App

Diagram displaying the main users of each platform integrating the Back-UP System.

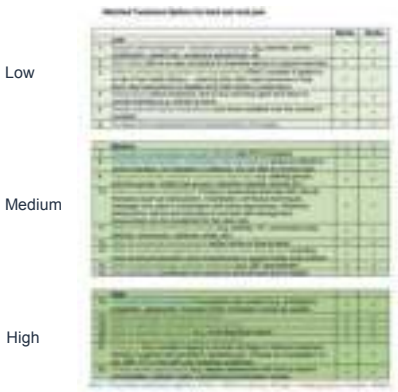
Key web app components/functions:

Users are first contact clinicians across the EU (e.g. GPs, OH, PTs, OS).

1. Prognostic stratification Using STarT MSK Tool

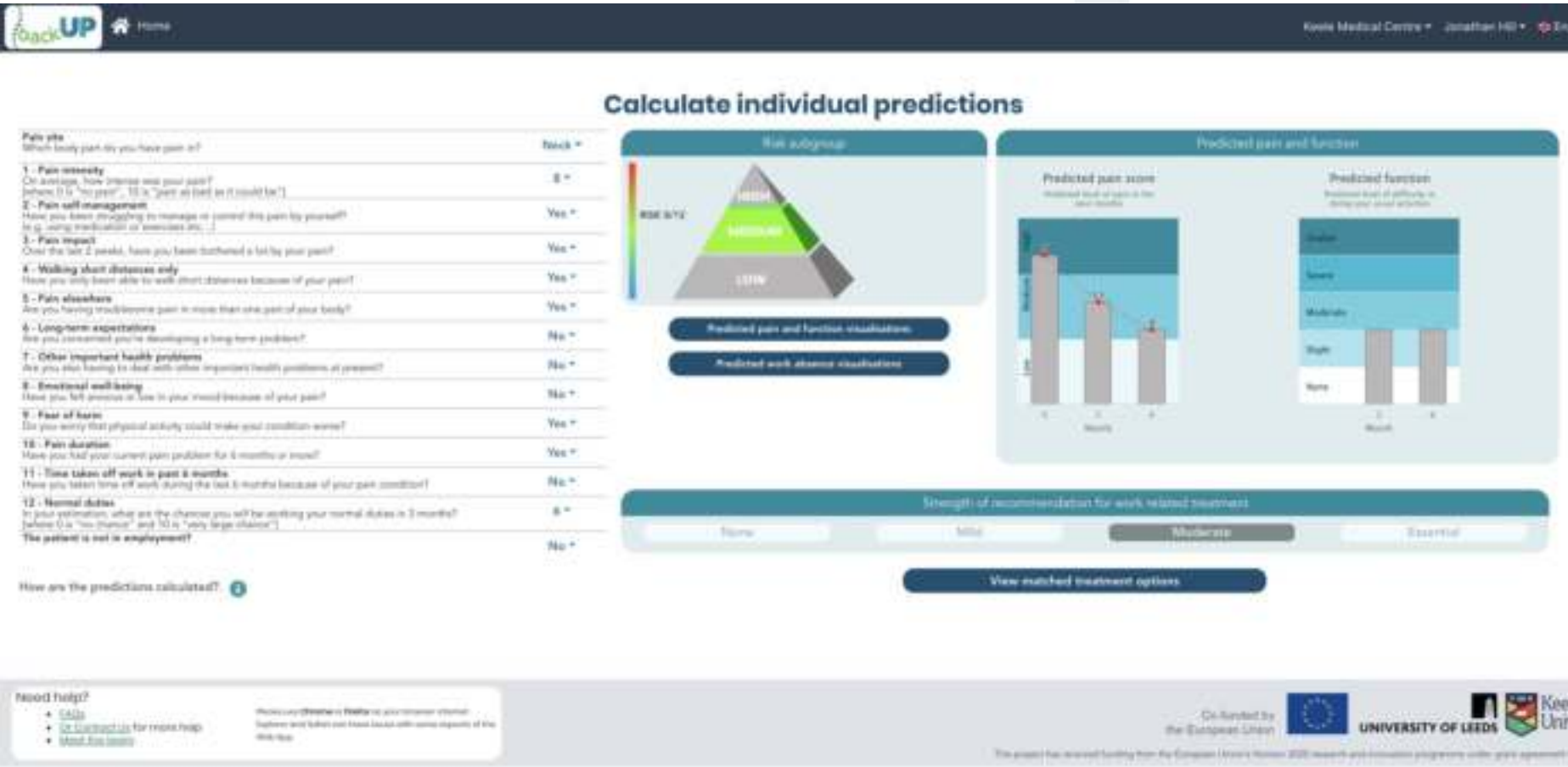
2. Individualised prediction graphs

3. Treatment selection tool & self-management



4. Personalised care plan - -populated by prognostic information and treatment choices made

Screenshots: Individual risk predictions

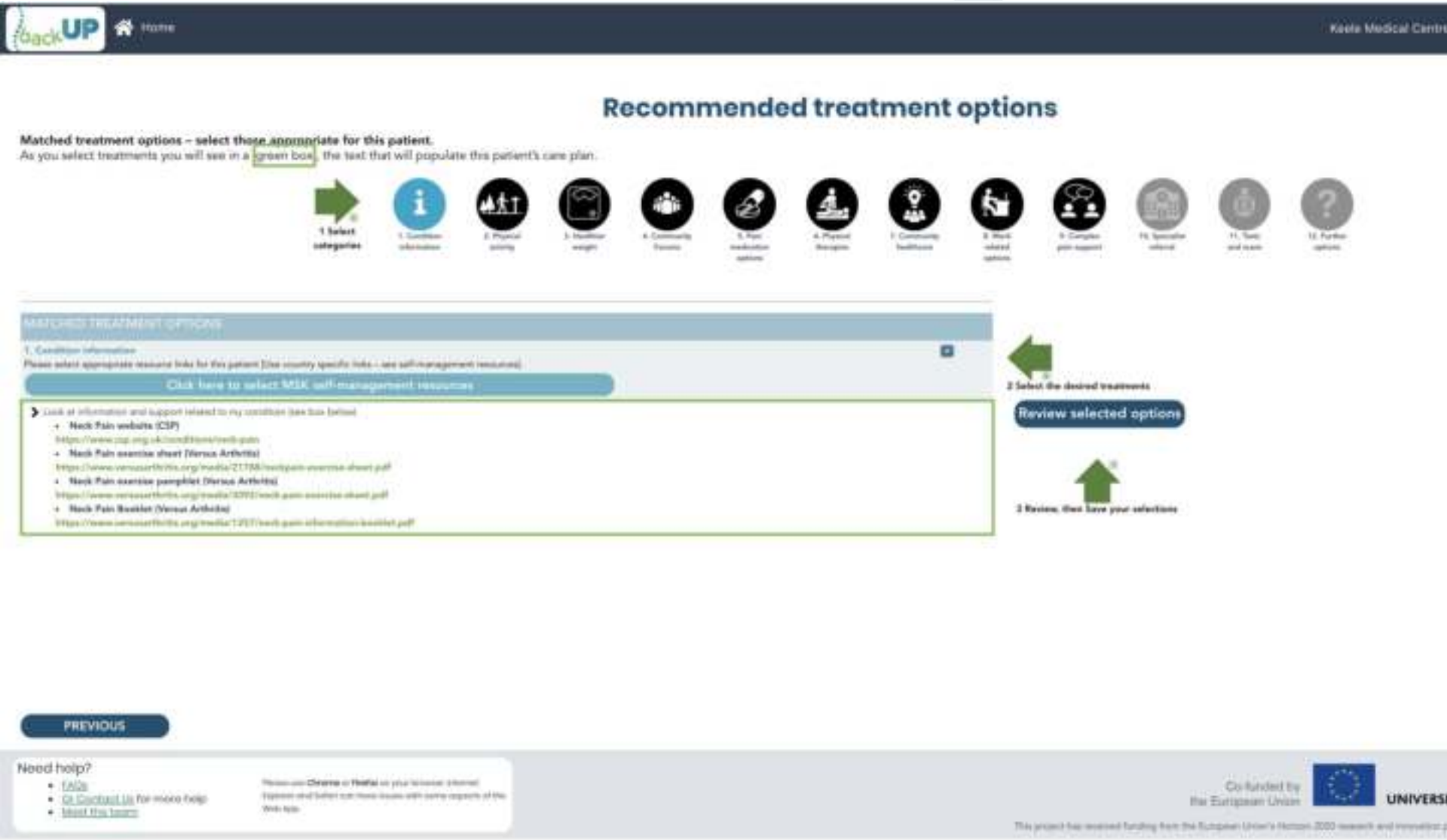


It's the Keele difference.

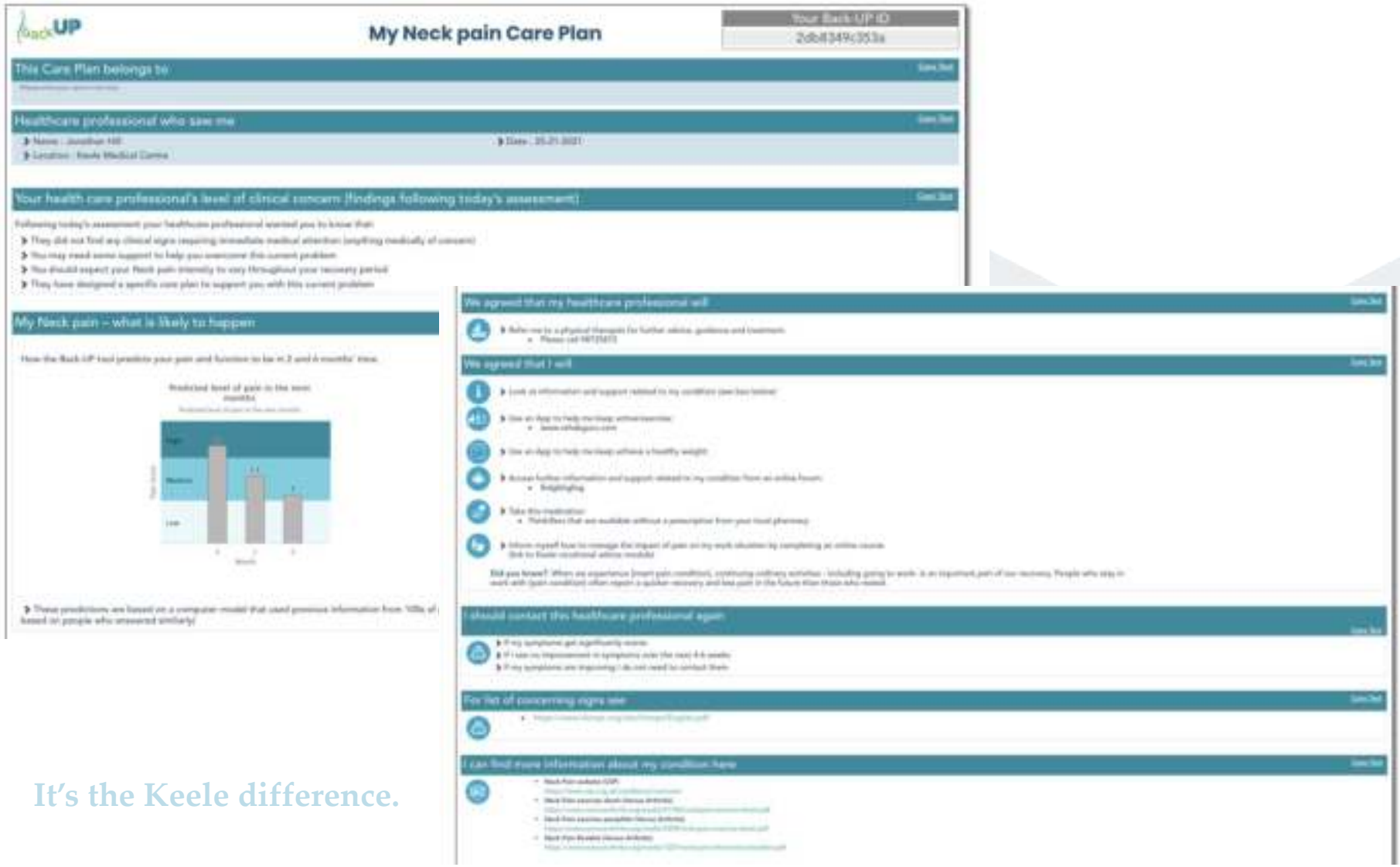
Keele UNIVERSITY

https://back-upv1.multi-x.org/

Recommended treatment options



Personalised care plan



Implications for OActive

- Think about possibilities for
  - Validating our predictions models in OA patients
  - Ensure prediction models work at the point-of-consultation
  - Consider adding shared decision-making tools and personalised care planning within the platform to add value

Thank you to everyone

Jonathan Hill (j.hill@keele.ac.uk)

Research Institute for Primary Care and Health Sciences
Primary Care Centre Versus Arthritis
David Weatherall Building
Keele University
Newcastle-under-Lyme
Staffordshire
ST5 5BG
+44 (0)1782 732000
keele.ac.uk/pchs

SUPPORTED BY
NIHR | National Institute for Health Research

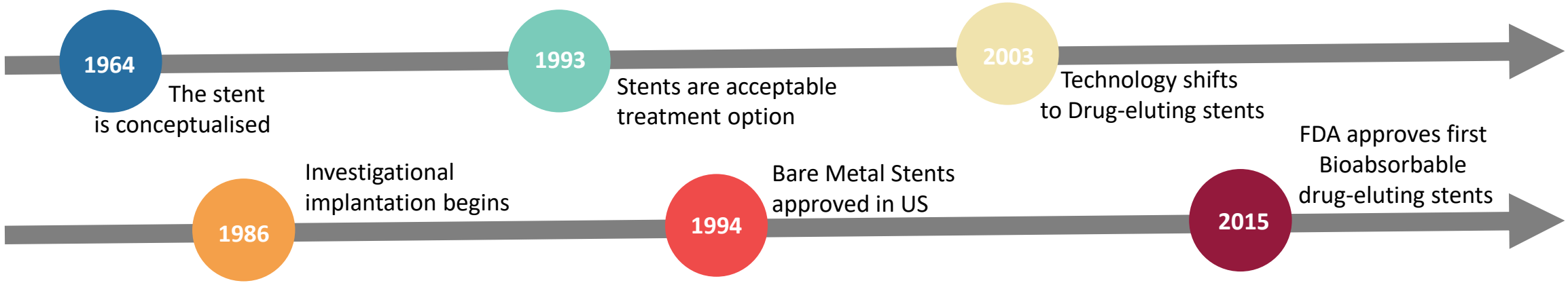
HORIZON 2020
777119

InSilc:

An *in silico* platform for drug-eluting BVS design, development and evaluation

Introduction

- Coronary Artery Disease (CAD) is caused by the build-up of atherosclerotic plaques inside the coronary arteries.
- CAD is the leading cause of mortality worldwide and accounts for over 4 million deaths per year.
- Percutaneous coronary intervention (PCI) with stents is the most widely performed procedure for the treatment of symptomatic CAD.



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

Introduction

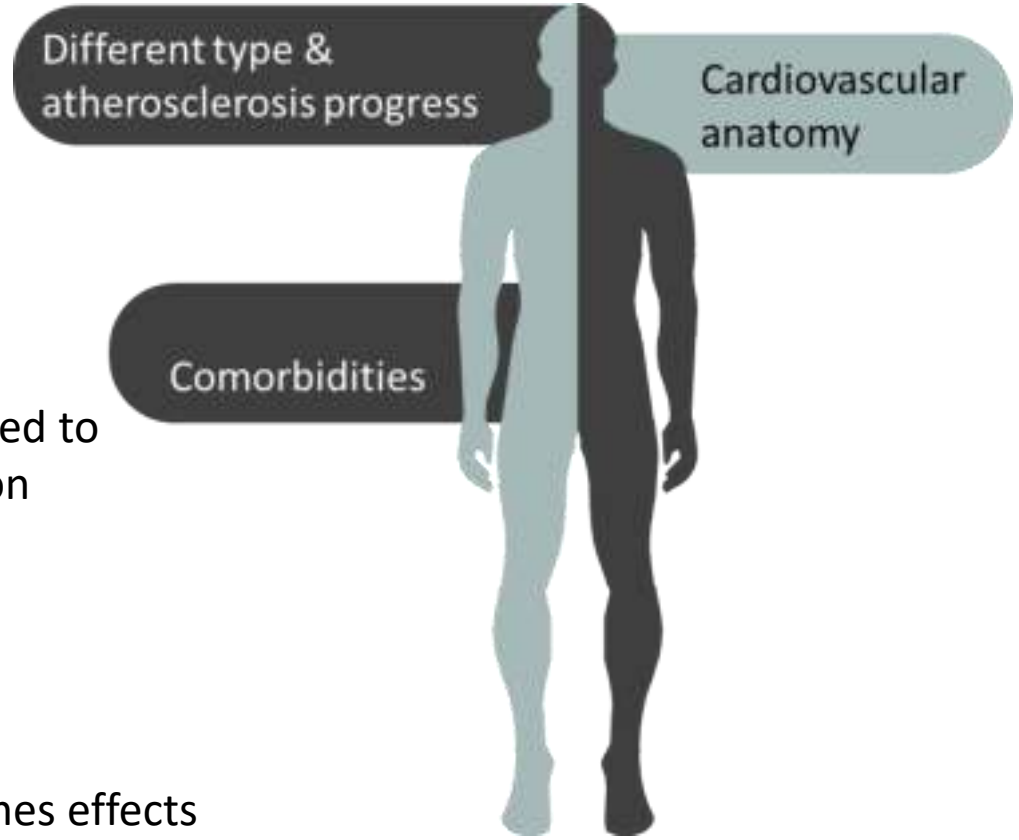
- The advent of **drug-eluting bioresorbable vascular scaffolds (BVS** have emerged as a major breakthrough for treatment of coronary artery lesions.
- The scaffold is expanded to reopen the vessel, releases the drug, completely dissolves by itself within 2 years, restoring normal arterial function, hence preventing late stent blockage and new atherosclerosis formation.

- Currently, to ensure the **safety and efficacy** of a drug-eluting BVS is tested
  - in the laboratory (in vitro - ISO standard)
  - on animals (in vivo)
  - on humans (clinical evaluation/trial).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

Limitations of pipeline to design a new BVS

- ISO standard mechanical testing is slow and expensive
- Animal testing is idealized (and ethical issues)
- Clinical testing is expensive, unpredictable (e.g. ABSORB), not set up for precision medicine.



Some patients are expected to improve after implantation

Clinical studies are based upon a "one-size-fits-all' approach

Some patients present adverse outcomes effects (In stent restenosis, Stent thrombosis) or even die.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

InSilc consortium

- Interventional cardiologists
- Technical partners with extensive expertise in the field of computer modelling and simulation: (i) biomedical imaging (ii) coronary fluid dynamics, (iii) mechanical modelling and biomechanics
- Experts in the field of *in vitro* mechanical testing and animal studies
- Biology experts
- CRO with significant experience in providing services for regulatory authorizations and clinical trials for biomedical products
- Cloud experts for platforms development and integration
- Stent Biomedical Industry.

Outside the Consortium Stent Industry

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

The Project

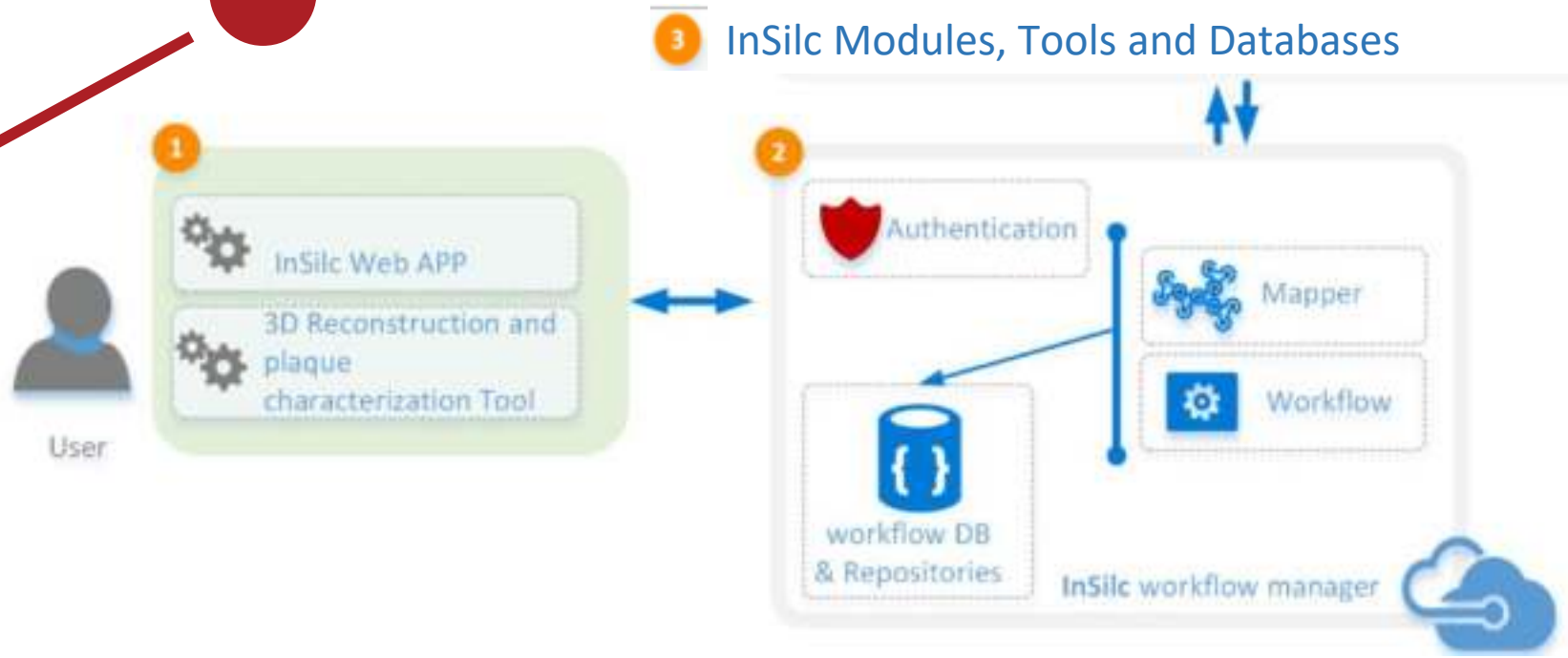
InSilc project aimed to create an **in silico trial platform** for designing, developing **BVS,** based on comprehensive biological and biomedical knowledge and advanced modelling approaches.

The Platform

InSilc platform includes multidisciplinary and multiscale models simulating the drug-eluting BVS in the acute/short & medium/long term.

The Users

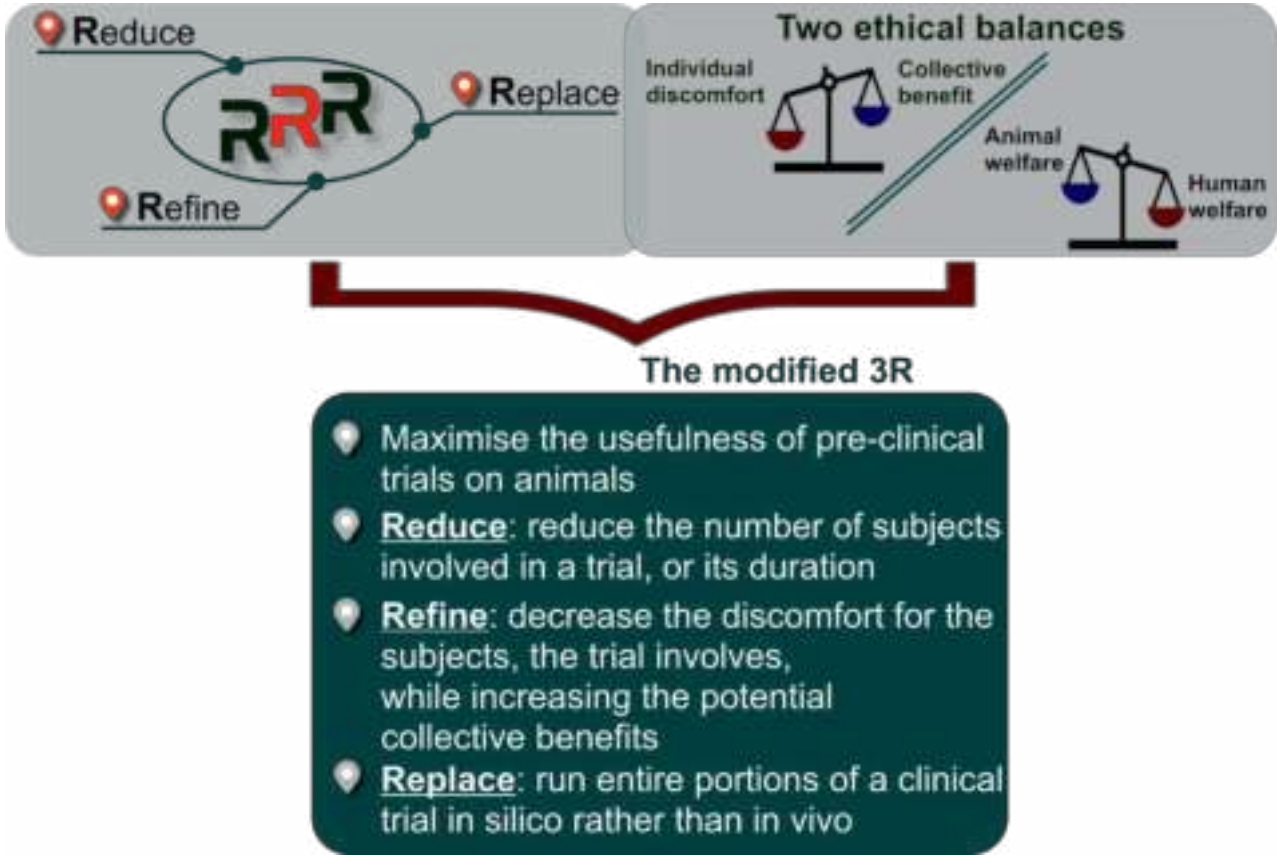
Stent Industry
Interventional Cardiologist
Researchers
Contract Research Organization



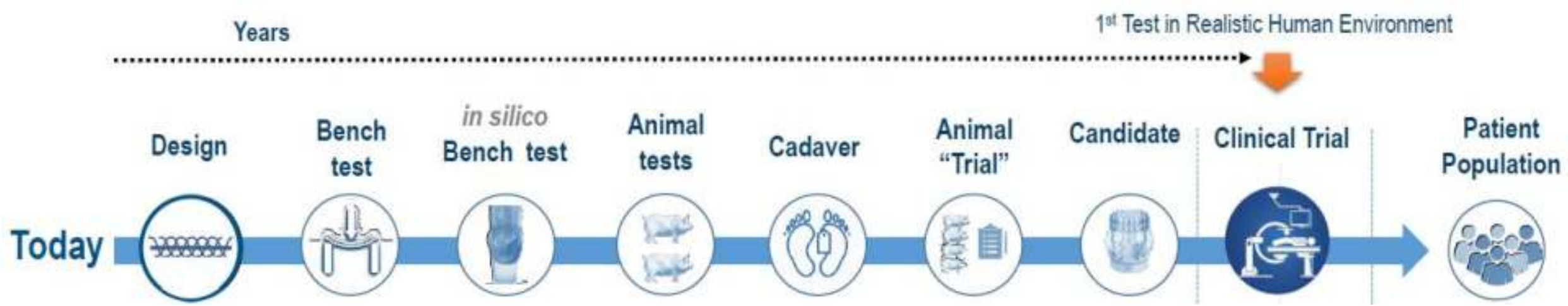
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

InSilc Vision and Value Proposition

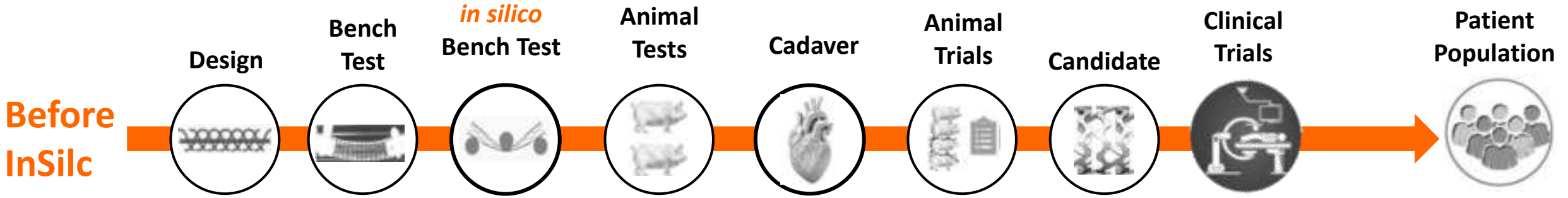
- Supplement and accelerate ISO standard mechanical testing
- Extrapolate animal testing results to virtual patient vasculature geometries
- Supplement clinical studies with virtual patients



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119



Scheme taken from T. Morrison (FDA) presentation, Advancing in silico Medicine at the FDA: Perspectives on Simulation in Medical Devices", July 23, 2019



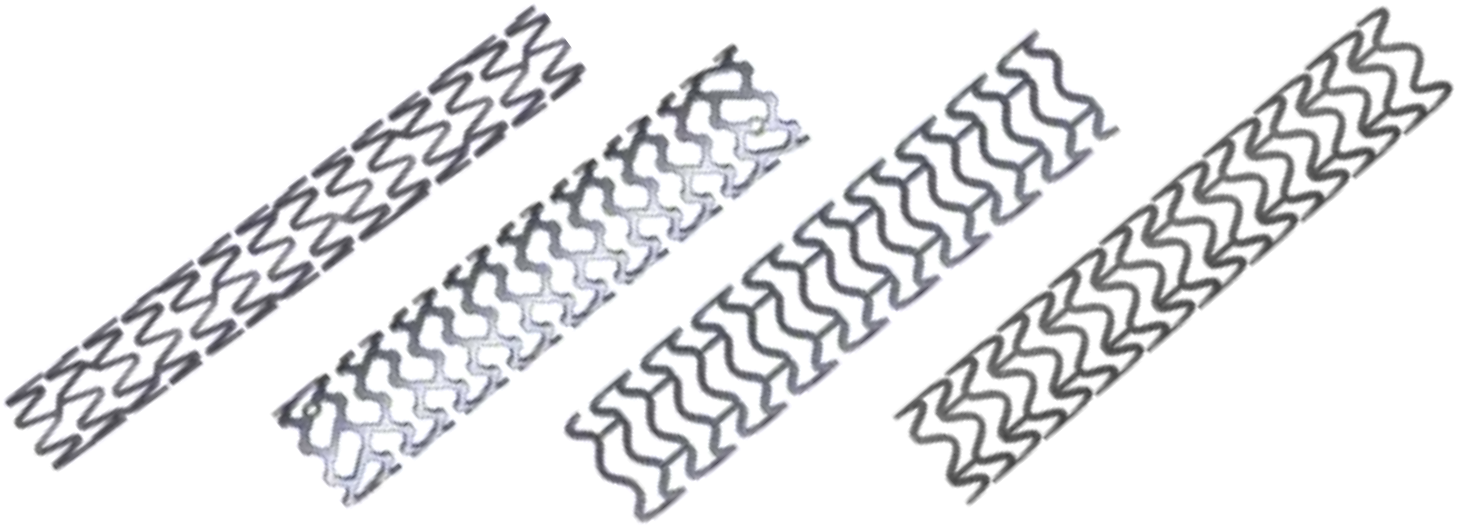
The same scheme applied to BVS design

Patient Population

Design

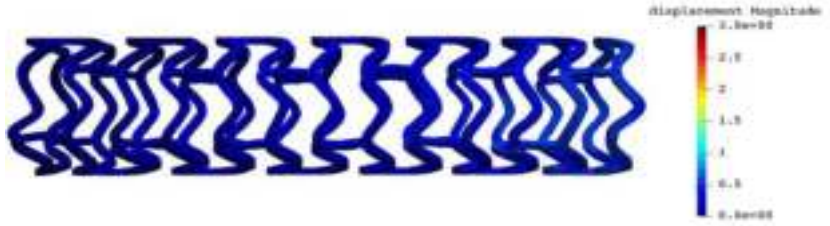
After InSilc

Virtual devices

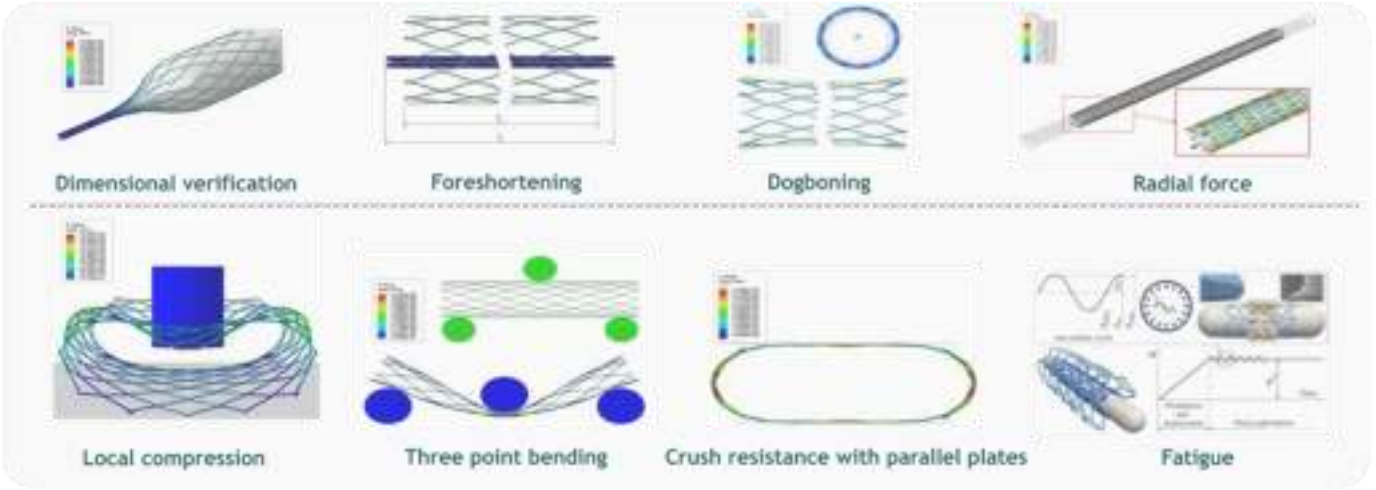


Validated «digital twins» of the various designing solutions

Video



REPLACE the bench tests



After InSilc

in silico

Design

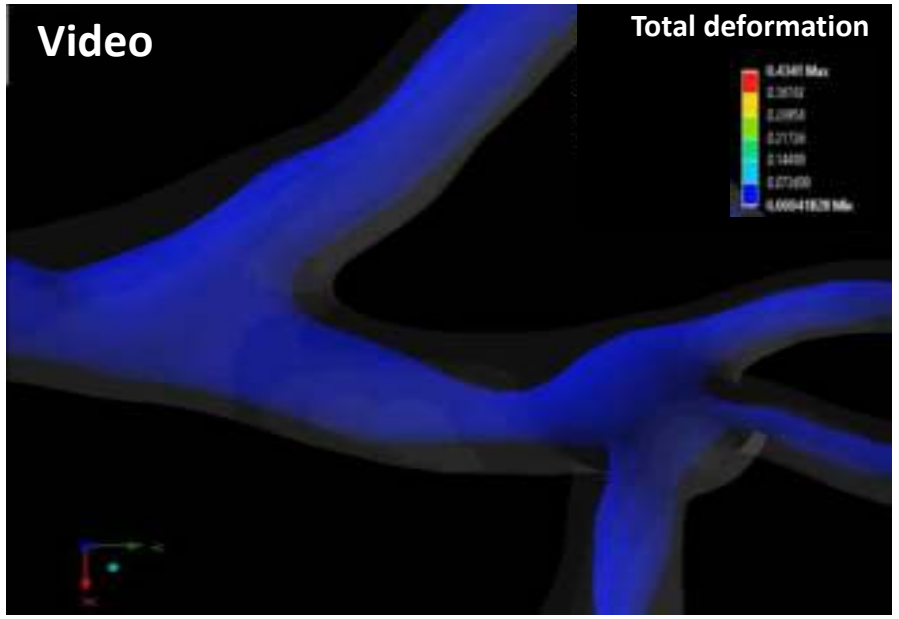
Bench Test

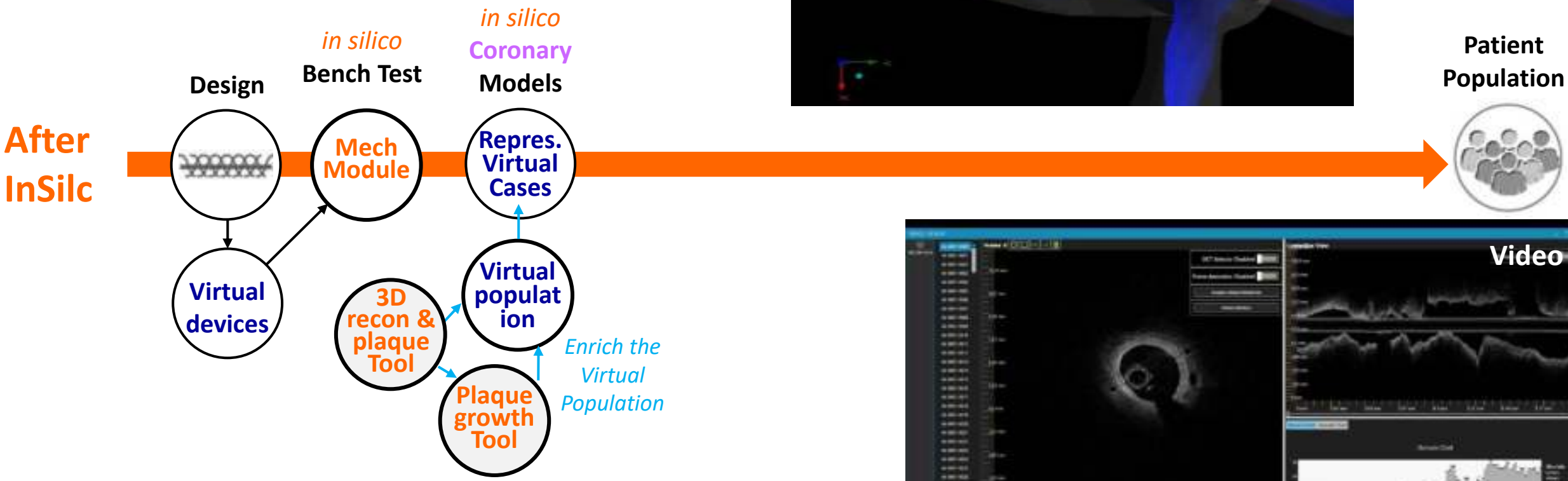
Mech Module

Virtual devices

Patient Population

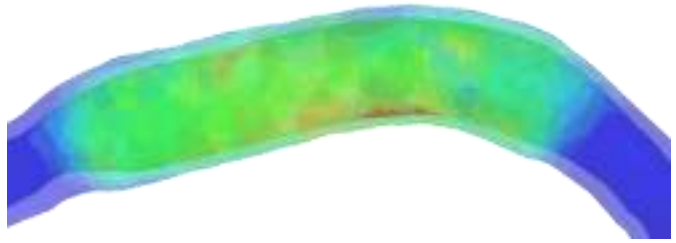
Enrichment of virtual population
creating virtual patients with different characteristics
(morphological and clinical)

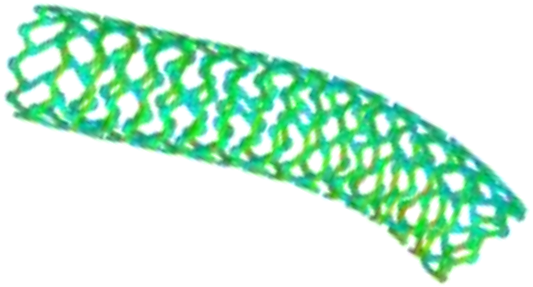




Creation of virtual population &
selection of HUMAN representative cases
used in preliminary screening of the various BVS designs

REFINE data in ACUTE conditions (risk of arterial wall or stent damage)





in silico **Animal & Human Tests**

After InSilc

Design

Bench Test *in silico*

Mech Module

Virtual devices

Coronary Models *in silico*

Repres. Virtual Cases

ACUTE

Deploy ment Module

3D recon & plaque Tool

Virtual populat ion

Plaque growth Tool

Enrich the Virtual Population

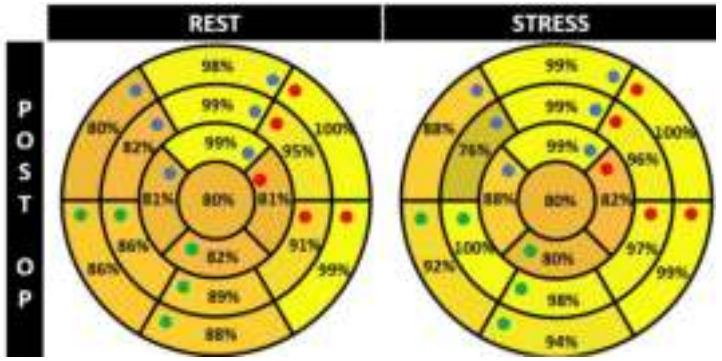
Video

Patient Population

Provide inputs for subsequent modules

Predict ACUTE endpoints related with Clinical trials Objective Performance criteria (lumen gain, strut malapposition)

REFINE data in SHORT term (myocardial perfusion under stress)



in silico **Animal & Human Tests**

After InSilc

Design

Virtual devices

in silico **Bench Test**

Mech Module

in silico **Coronary Models**

Repres. Virtual Cases

3D recon & plaque Tool

Virtual populat ion

Plaque growth Tool

Enrich the Virtual Population

ACUTE

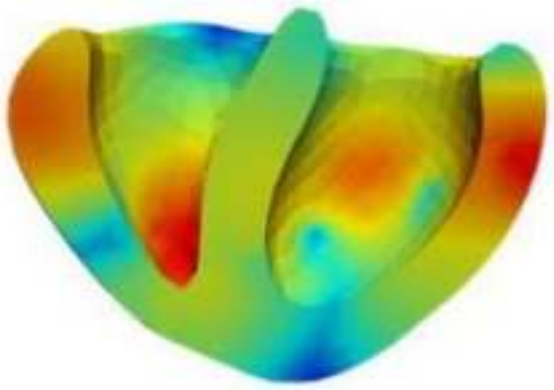
Deploy ment Module

SHORT

Myocar. Perfusion Module

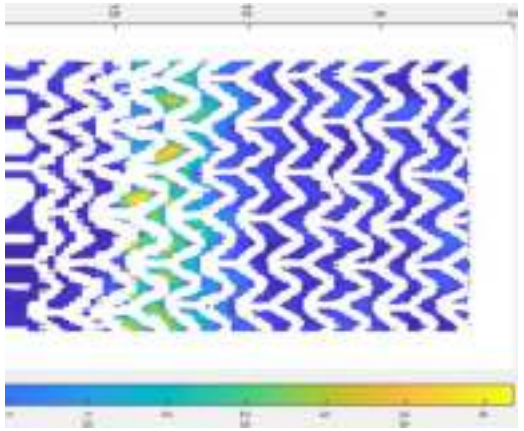
Patient Population

Predict how myocardial perfusion improves after BVS implantation (SHORT)



Provide flow rate BCs to the Fluid Dynamics module

WSS maps as possible additional clinical marker for in-stent restenosis



in silico **Animal & Human Tests**

After InSilc

Design

Virtual devices

in silico **Bench Test**

Mech Module

in silico **Coronary Models**

Repres. Virtual Cases

3D recon & plaque Tool

Virtual populat ion

Plaque growth Tool

Enrich the Virtual Population

ACUTE

Deploy ment Module

SHORT

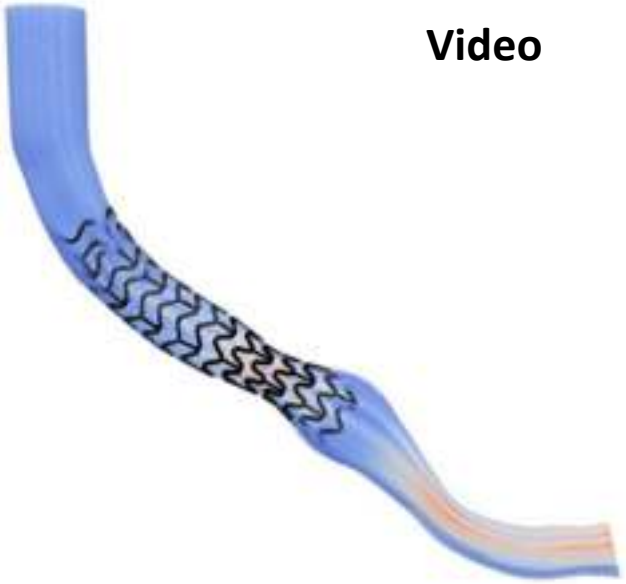
Myocar. Perfusion Module

Fluid-dynamic Module

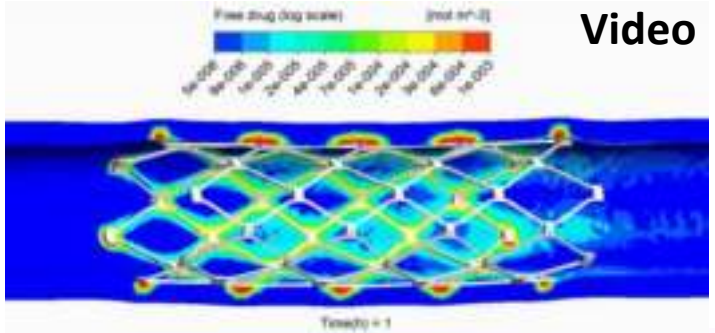
Patient Population

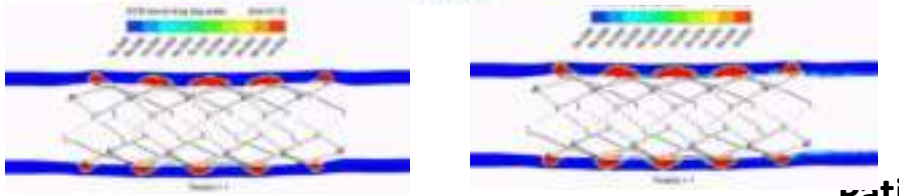
Video

Predict how the stent presence affects the local hemodynamics



Wall drug content as possible additional clinical marker for suboptimal tissue healing and excessive SMC proliferation





in silico **Animal & `Human Tests**

SHORT

in silico **Bench Test**

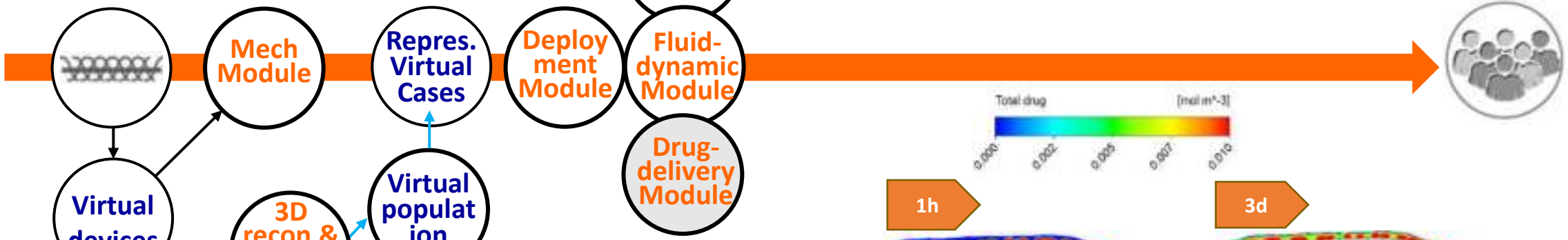
in silico **Coronary Models**

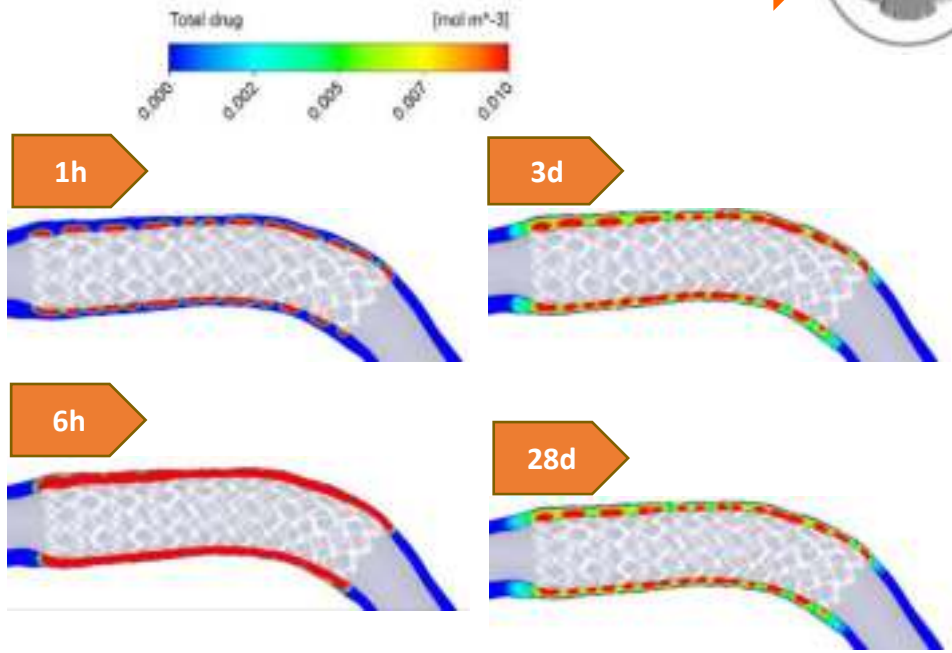
ACUTE

Design

Patient Population

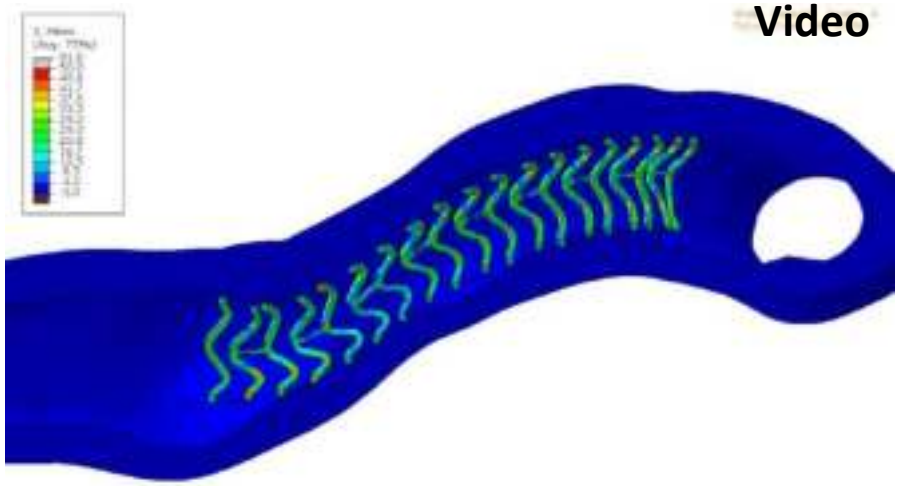
After InSilc





Predict how drug is released to the wall (in time & space)

Video



in silico **Animal & Human Tests**

SHORT

MEDIUM-LONG

in silico Coronary Models

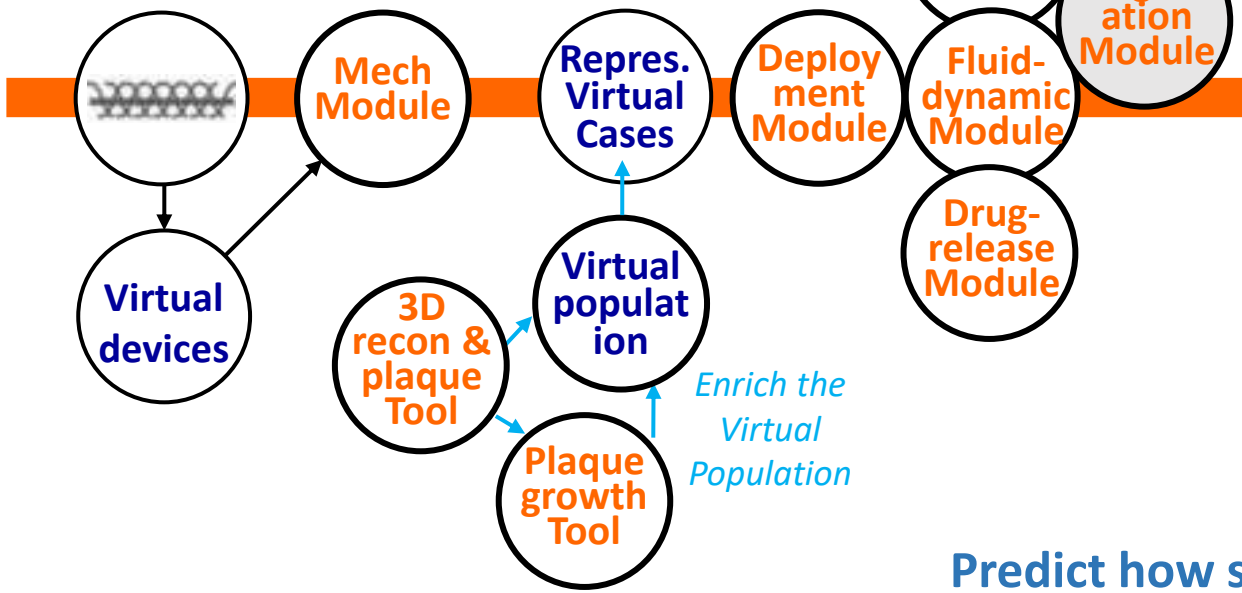
in silico Bench Test

ACUTE

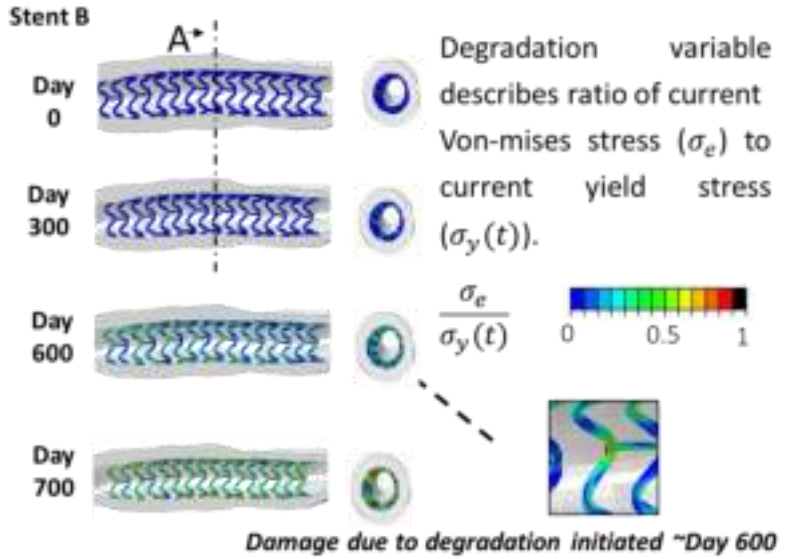
Design

Population

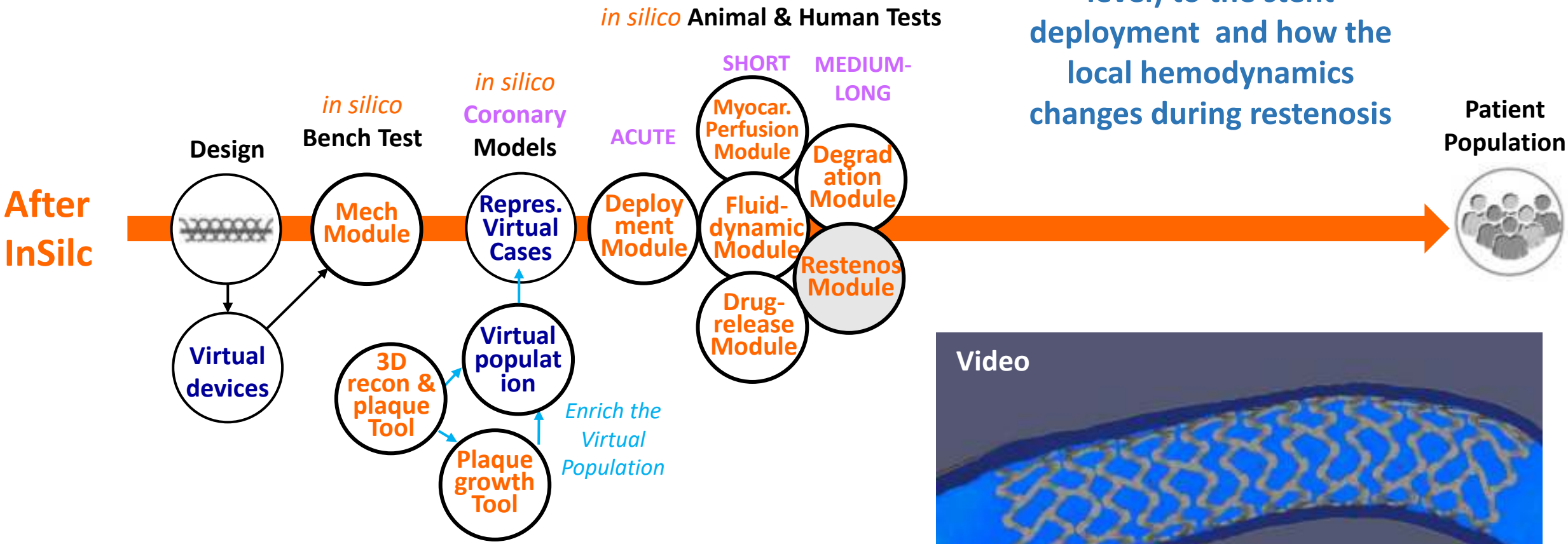
After InSilc

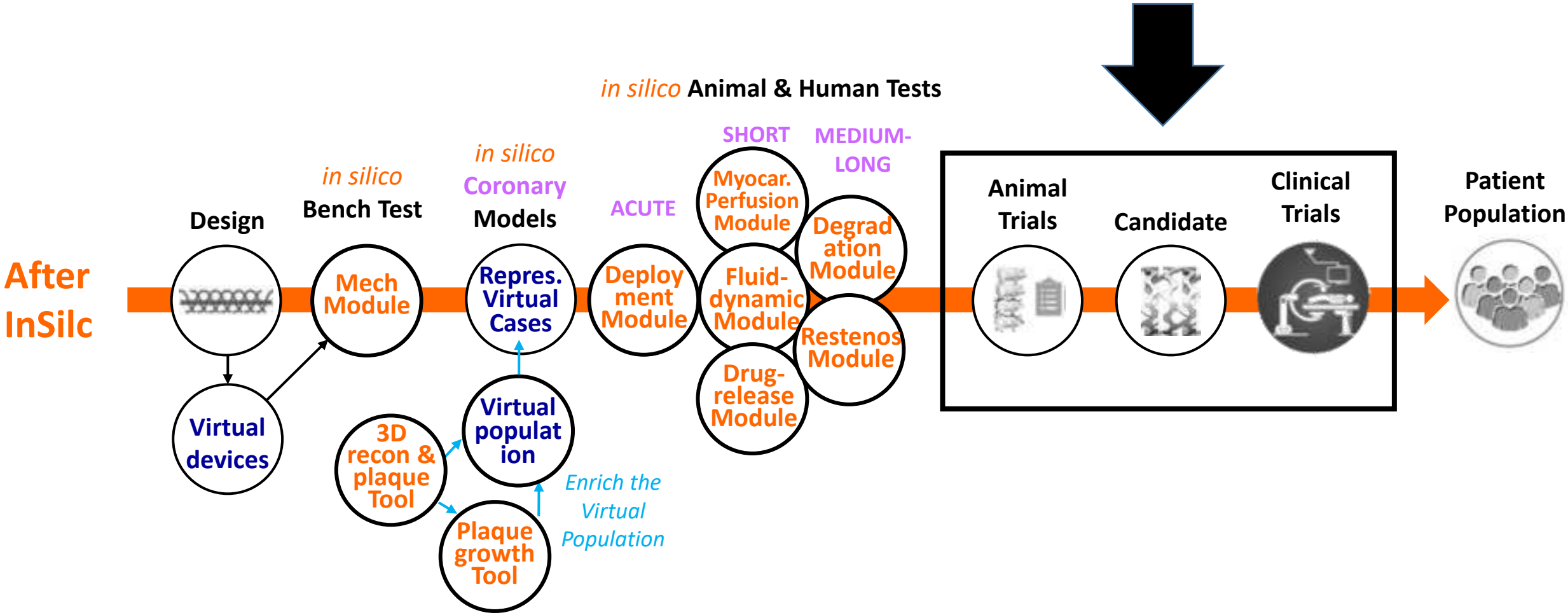


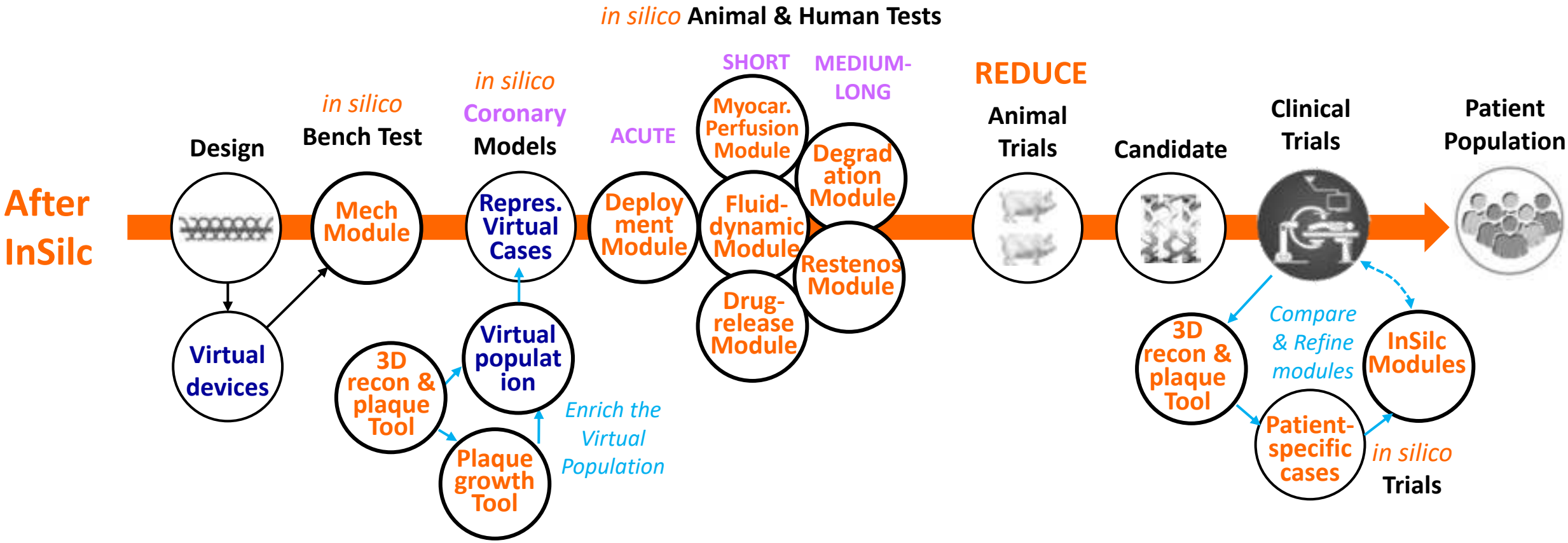
Predict how stent degrades and how this affects the wall scaffolding

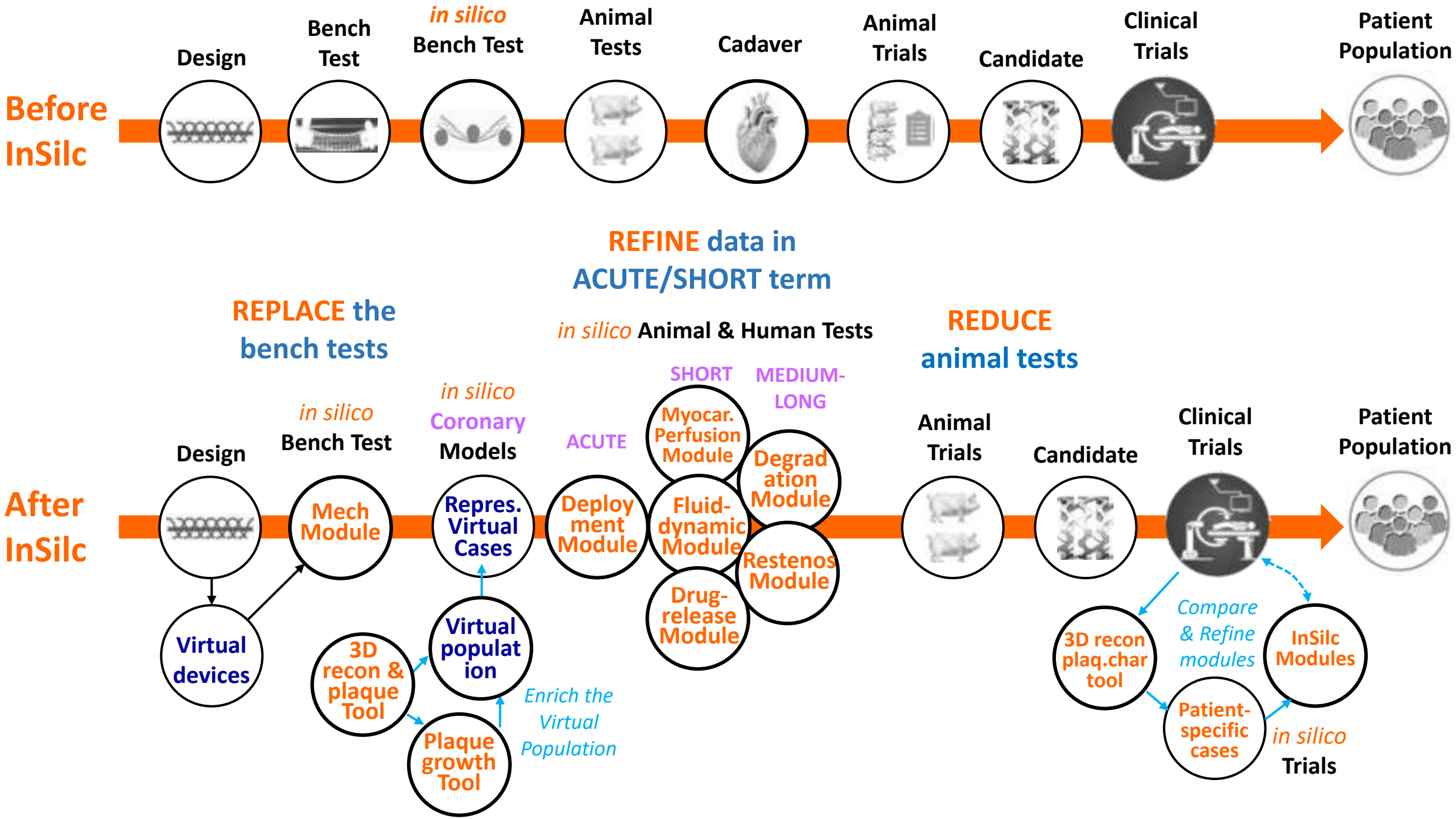


Predict how the coronary wall responds (cellular level) to the stent deployment and how the local hemodynamics changes during restenosis




After InSilc
Design
in silico Bench Test
in silico Coronary Models
in silico Animal & Human Tests
ACUTE
SHORT
MEDIUM-LONG
Mech Module
Repres. Virtual Cases
Deployment Module
Myocar. Perfusion Module
Fluid-dynamic Module
Drug-release Module
Degradation Module
Restenosis Module
Virtual devices
3D recon & plaque Tool
Virtual population
Plaque growth Tool
Enrich the Virtual Population
Animal Trials
Candidate
Clinical Trials
Patient Population


in silico Animal & Human Tests
After InSilc
Design
in silico Bench Test
in silico Coronary Models
ACUTE
SHORT
MEDIUM-LONG
REDUCE
Animal Trials
Candidate
Clinical Trials
Patient Population
Mech Module
Repres. Virtual Cases
Deployment Module
Myocar. Perfusion Module
Fluid-dynamic Module
Drug-release Module
Degradation Module
Restenosis Module
Virtual devices
3D recon & plaque Tool
Virtual population
Plaque growth Tool
Enrich the Virtual Population
Compare & Refine modules
3D recon & plaque Tool
InSilc Modules
Patient-specific cases
in silico Trials


Before InSilc
Design
Bench Test
in silico Bench Test
Animal Tests
Cadaver
Animal Trials
Candidate
Clinical Trials
Patient Population
REFINE data in ACUTE/SHORT term
REPLACE the bench tests
in silico Animal & Human Tests
REDUCE animal tests
After InSilc
Design
in silico Bench Test
in silico Coronary Models
ACUTE
SHORT
MEDIUM-LONG
Animal Trials
Candidate
Clinical Trials
Patient Population
Virtual devices
Mech Module
Repres. Virtual Cases
Deployment Module
Myocar. Perfusion Module
Fluid-dynamic Module
Drug-release Module
Degradation Module
Restenos Module
3D recon & plaque Tool
Virtual population
Plaque growth Tool
Enrich the Virtual Population
3D recon plaq.char tool
Compare & Refine modules
InSilc Modules
Patient-specific cases
in silico Trials

Platform → InSilc scenarios of use

01

Compare existing stents

For the selected virtual anatomy the stenting outcomes are predicted for two stents (BRS and partially degradable stent, already available in the Virtual stent database) and suitably compared.

02

Compare anatomy configurations and patient conditions

For a specific stent, the stenting outcomes are predicted considering different virtual anatomies & patient conditions.

05

Pre-clinical testing assessment

To perform in silico all the standard mechanical stent testing according to ISO.

03

Compare different clinical procedures

For a selected virtual anatomy and the considered stent, the stenting outcome when different implantation procedures are simulated is predicted.

04

Design new stents

For the selected virtual anatomy the stenting outcomes are predicted, when parameters such as design or material are changed in a specific stent.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

Scenario No1 - Compare existing stents

Deployment Module

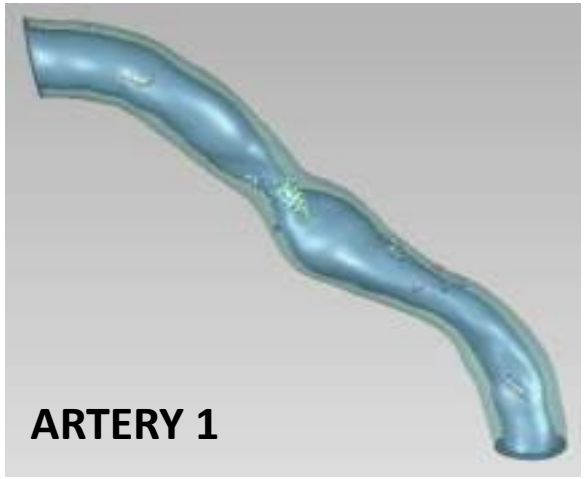
Degradation Module

3D reconstruction and plaque characterization tool

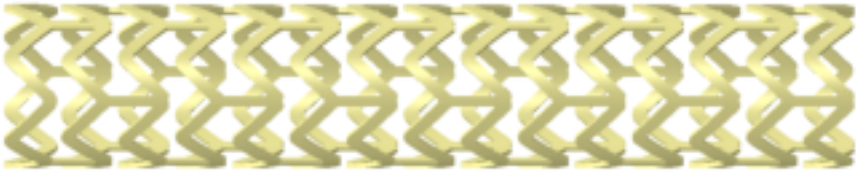
Fluid Dynamics Module

BVS 1

In the same stenotic artery…



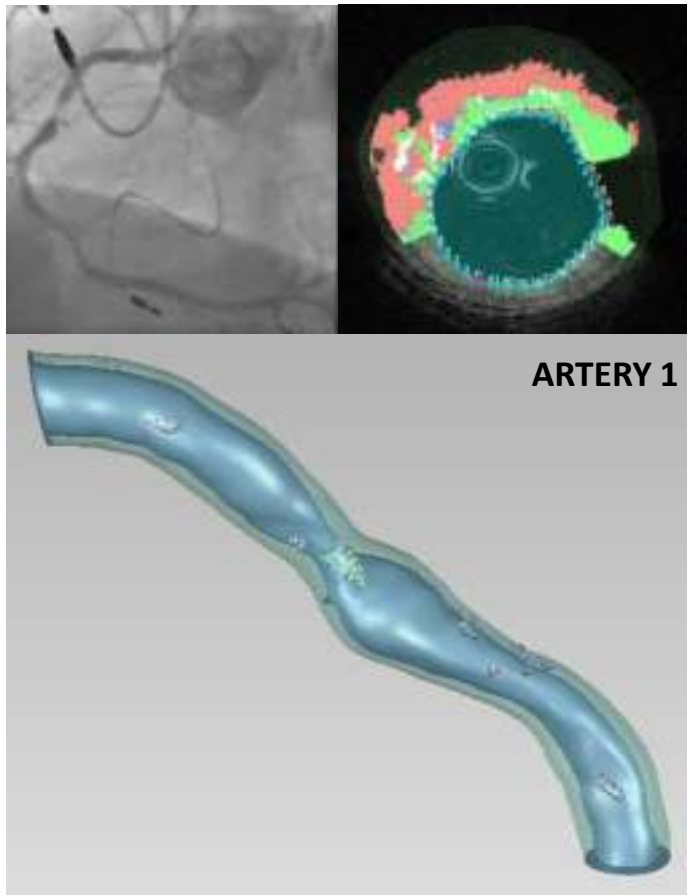
BVS 2



In vivo you can’t!

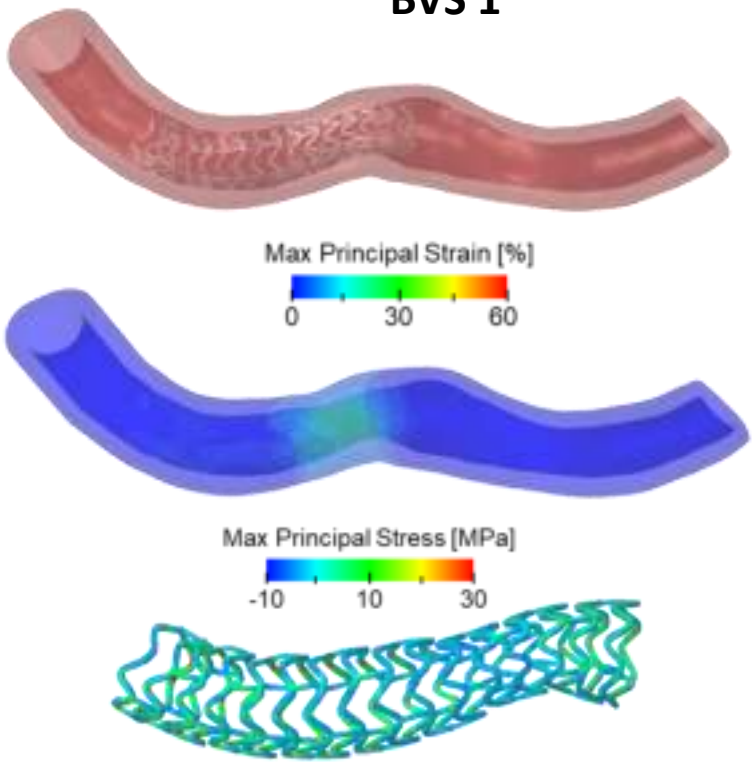
This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 777119

3D reconstruction & plaque characterization Tool



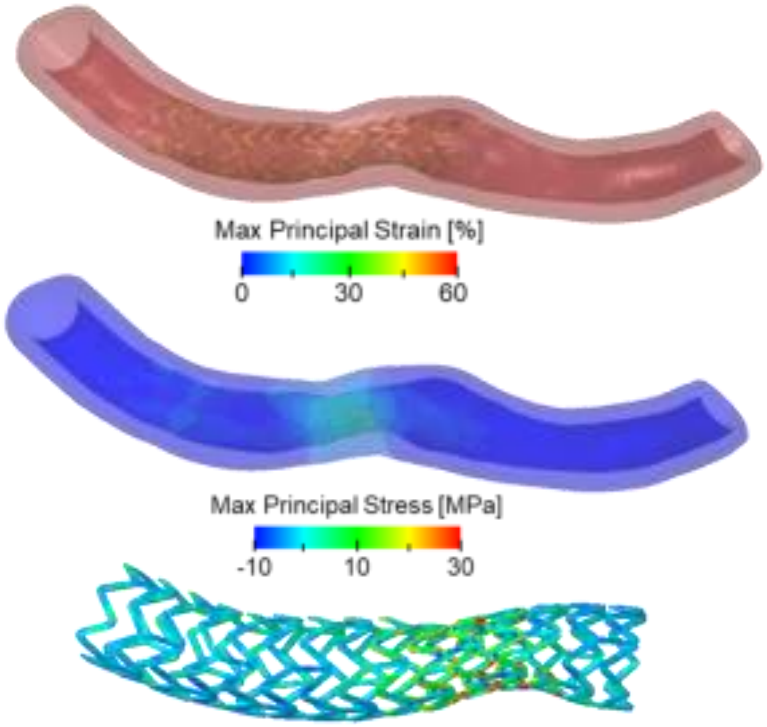
Deployment Module

BVS 1



Lumen Gain: 54%
Malapposition: proximal and distal

BVS 2



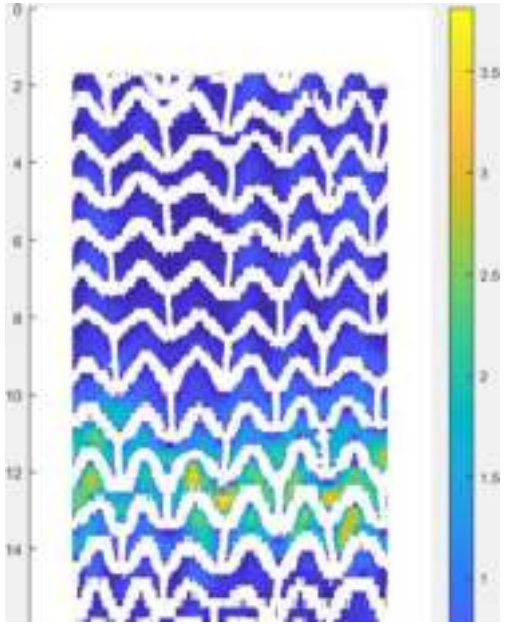
Lumen Gain: 40%
Malapposition: proximal and distal

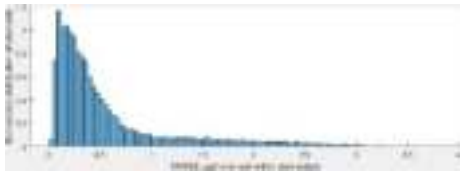
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

Fluid dynamics Module

BVS 1

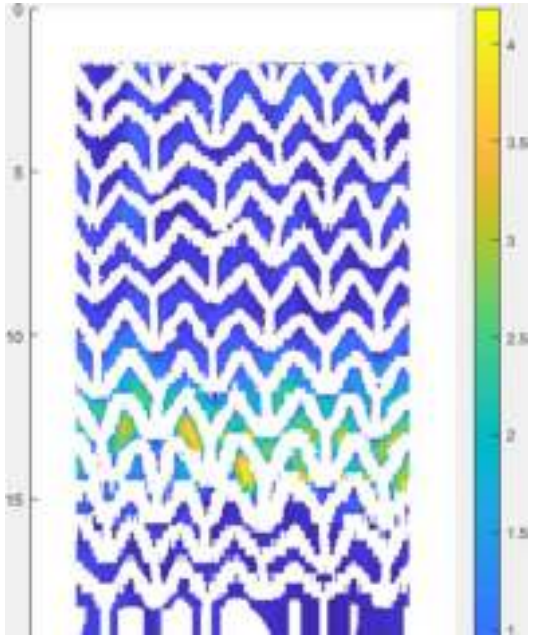
TAWSS

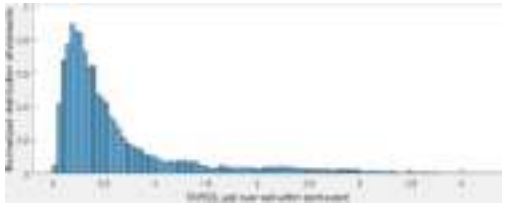




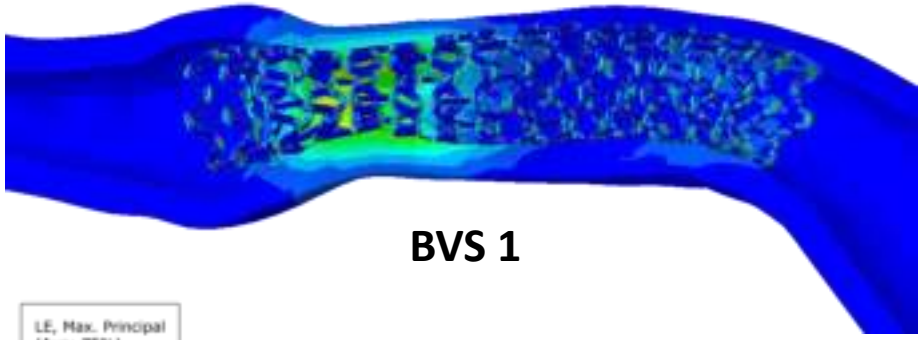
BVS 2

TAWSS

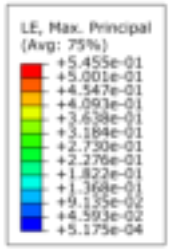


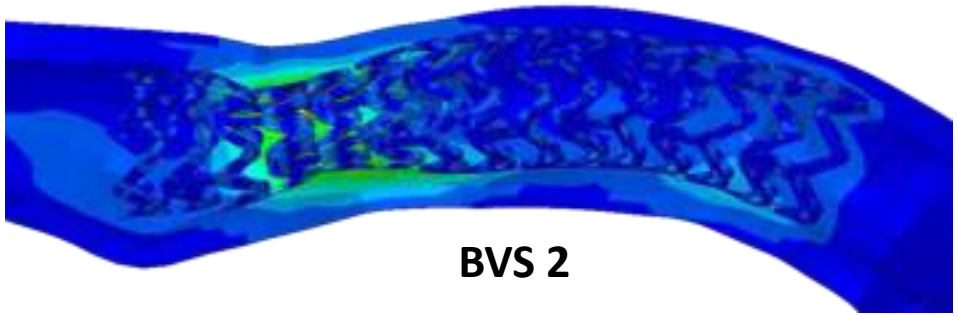


Degradation Module



BVS 1





BVS 2

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

Validation strategy

Task	status
Modules validation	Validation ongoing according to “V&V40 - Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices”. Ending on April 2021.
Metrics used in validation	Modules outputs correlation with real Clinical Trials Objective Performance Criteria
Data used for validation and virtual patient geometries creation	Experimental data (in vitro validation) Retrospective data (550 patients) Prospective data (100 patients; 2 clinical centers in ERASMUS-Netherlands, UOI – Greece).

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 777119

InSilc Business strategy

- InSilc is **a service oriented** in silico cloud platform
- The pricing strategy depends on:
  - Type of user
  - Number of virtual patients employed in the in silico trial
  - Modules employed in the in silico trial

- The computational time depends on:
  - Complexity of cases (e.g. number of procedural steps, stent length,…)
  - Modules employed in the in silico trial

  Just to give an idea, the full pipeline required **10 days** for the presented Scenario n.1

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

Possible intended use of InSilc platform

1 Simulations as decision-support system for Stent companies

2 As a tool for training/research

- No regulatory constraints
- Need proper validation and robust simulation results

3 Computer simulation results as supporting digital evidence for the regulatory evaluation of BVS

- Need for formally validated simulation results, based on a risk-inform credibility assessment framework
- Formal reporting
- Preliminary consultation with EU regulatory bodies

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

KU LEUVEN

LIÈGE université
GIGA institute

MSCA-ITN CarBon: A Marie Sklodowska Curie training network combining *in silico*, *in vitro* and *in vivo* approaches to study Cartilage and Bone biology and engineering

Liesbet Geris
U.Liège & KU Leuven, Belgium

Car Bon

prometheus

biomech
UNIVERSITY OF LIÈGE RESEARCH UNIT

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Marie Sklodowska-Curie grant agreement No 721432

MSCA-ITN: Training objectives

- train 14 high potential scientists
  - to combine knowledge of cartilage & bone developmental biology, pathobiology and tissue engineering with skills in cell culture, animal models, proteomics, biomaterial development, bioreactors and computational modelling.
- Exchange of knowledge and multidisciplinary collaboration between these fields of research
  - to raise the **next generation of researchers with the skills, multidisciplinary knowledge** and on-the-job training experience necessary to tackle all aspects of bone and cartilage disease and repair

Research Objectives

- understand the **role and interplay of cell secreted factors, extracellular matrix components and mechanical loading** in cartilage and bone formation and repair

- use the combined knowledge and skills of matrix biology and tissue engineering to **develop novel, biologically inspired biomaterials** for the formation of stable cartilage and vascularised bone

- use **knowledge of cell biology, proteomics, mechano- and pathobiology** integrated by computational modelling to identify and to pursue drug targetable components for bone healing and osteoarthritis


Cartilage
Bone

Joint OA

- Disease-modifying drugs
  - Raphaëlle Lesage
- Tissue Engineering strategies
  - Satanik Mukherjee

Joint OA

- Disease-modifying drugs
  - Raphaëlle Lesage
- Tissue Engineering strategies
  - Satanik Mukherjee

Chondrocyte Regu

Knowledge Base *Wnt*

Description

- e.g. Wnt3a; MGI:98955, NCBI gene: 22416
- Wnt is a growth factor which play a vital role in proliferation and hypertrophy of chondrocytes. It is essential for joint health *(Day TF, 2005)* *(Guo X, 2009)* *(Monteagudo S, 2017)* *(Zhang M, 2010)*
- Wnt pathway summary: it is initiated by binding of Wnts to the Wnt receptor (frizzled)/co-receptor (lipoprotein receptor-related protein-LRP-5/6) complex, triggering a conformational change in the downstream molecule complex that consist of Dishevelled, adenomatosis polyposis coli (APC), axin, glycogen synthase kinase 3β (GSK3β), β-catenin, and other proteins. Through sequential changes in interaction and phosphorylation status of these proteins, phosphorylation of the amino-terminal domain of β-catenin is disturbed, leading to stabilization and nuclear translocation of β-catenin. The nuclear-translocated β-catenin stimulates transcription of the target genes with co-transcription factors such as T-cell factor/lymphoid-enhancing factor (TCF/LEF) family *(Usami Y, 2016)*

Regulatory Mechanism Summary

DKK and FRZB are antognists of Wnt, they inhibit it by binding, which subsequently brakes hypertrophic differentiation in articular cartilage *(Lejten JC, 2012)*

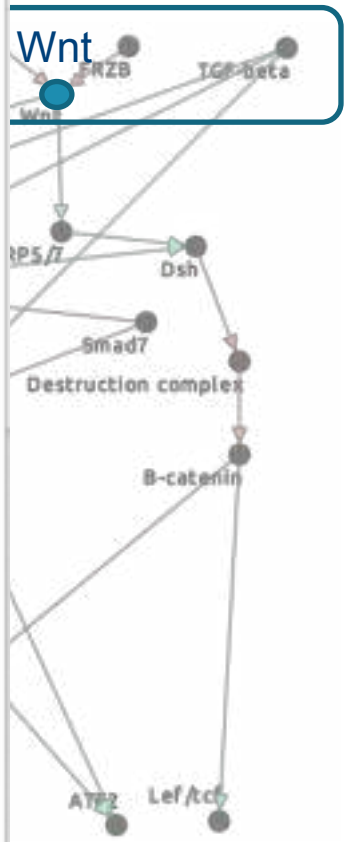
Upstream Regulators

DKK1

FRZB

References

1. Day TF, Guo X, Garrett-Beal L, and Yang Y.*Wnt/beta-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis.*Dev Cell 2005 May8; (5) 739-50.pmid:15866164
2. Guo X, Mak KK, Taketo MM, and Yang Y.*The Wnt/beta-catenin pathway interacts differentially with PTHrP signaling to control chondrocyte hypertrophy and final maturation.*PLoS One 2009 Jun 264; (6) e6067.pmid:19557172
3. Leijten JC, Emons J, Sticht C, van Gool S, Decker E, Uitterlinden A, Rappold G, Hofman A, Rivadeneira F, Scherjon S, Wit JM, van Meurs J, van Blitterswijk CA, and Karperien M.*Gremlin 1, frizzled-related protein, and Dkk-1 are key regulators of human articular cartilage homeostasis.*Arthritis

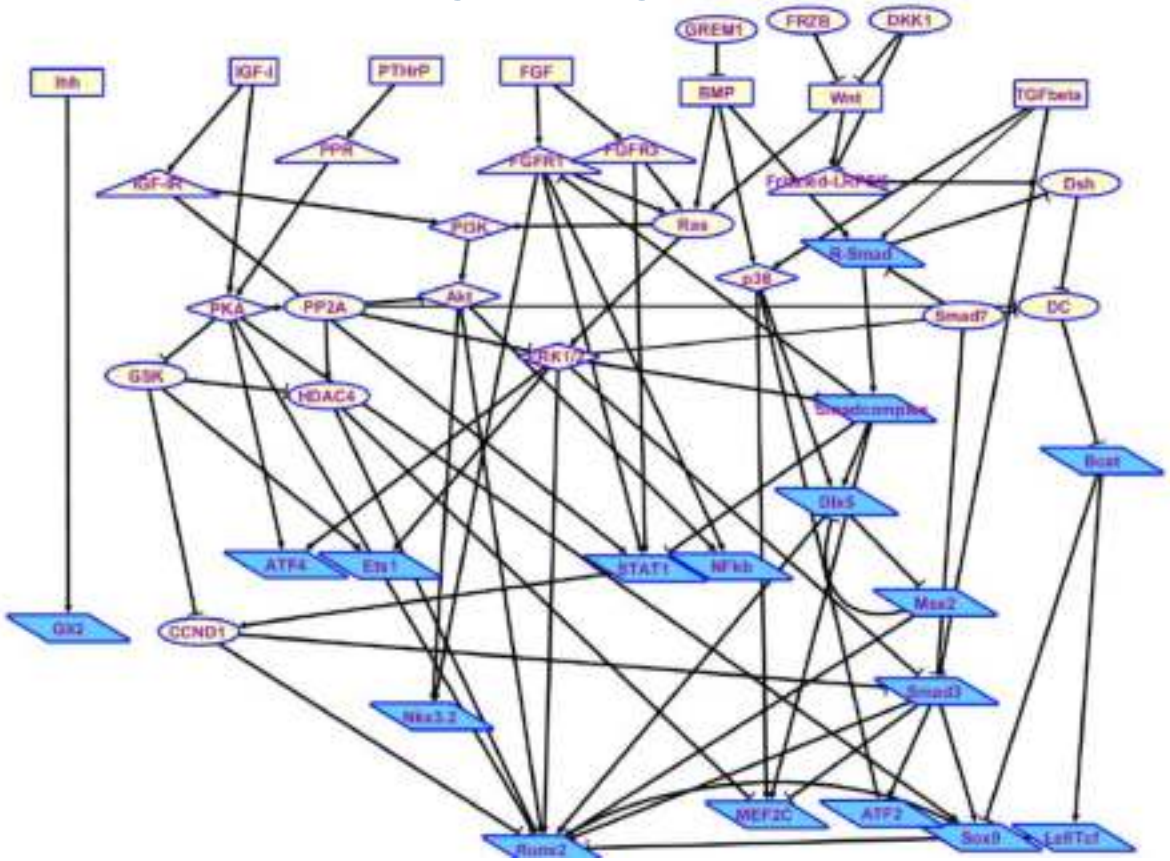


sily shareable

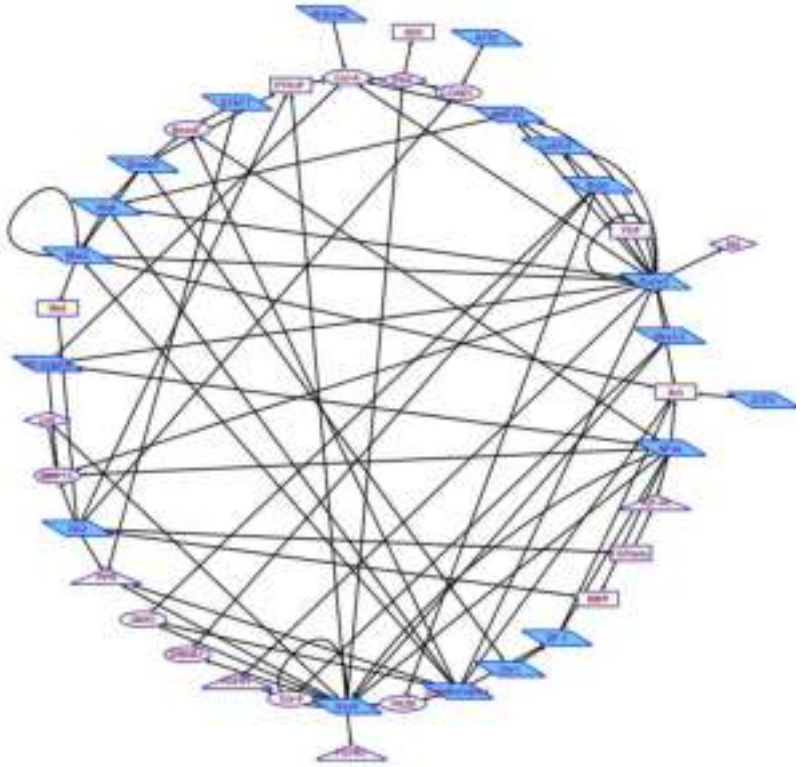
e for modeling

Literature derived networks

Protein signalling network



Gene regulatory network



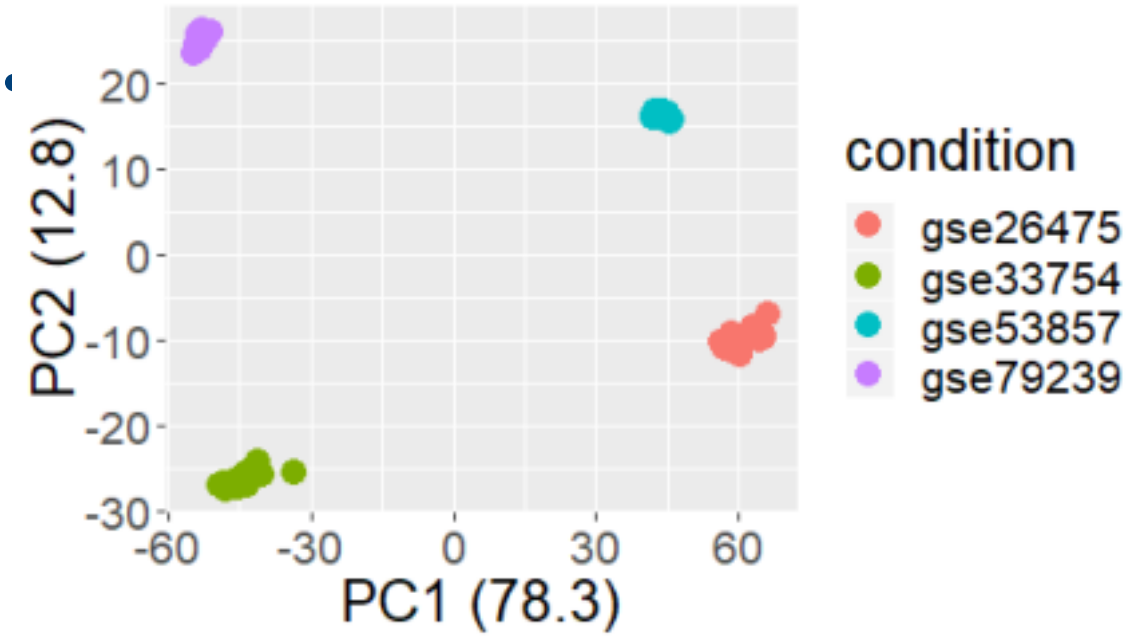
Growth factors, signalling molecules

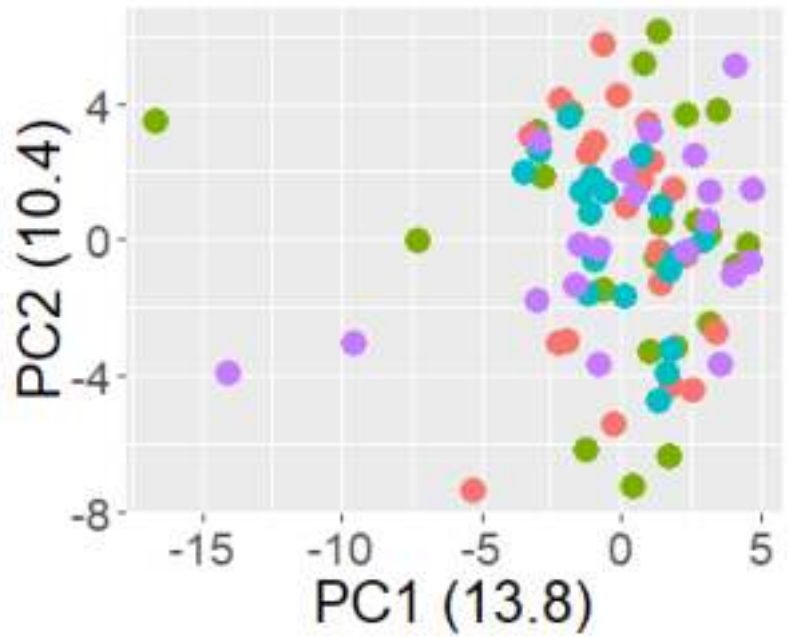
TF Transcription factors

Genes

Network inference approach

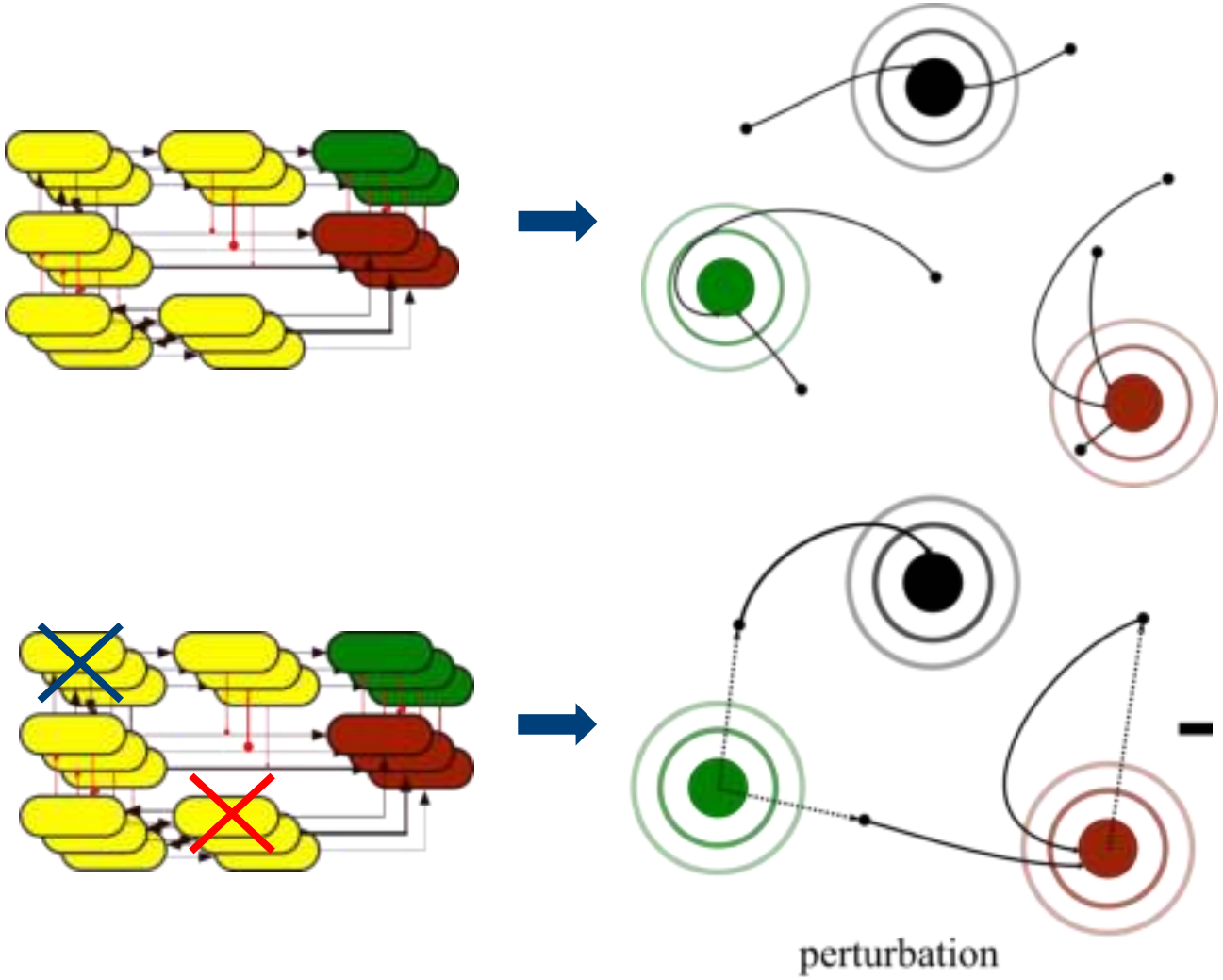
- Micro array studies > cross platform assembly pipeline (Combat)
  - Growth plate (chondrocytes)
  - OA mouse models





Lesage et al., Front Bioeng Biotech, 2018; Lesage et al., in preparation

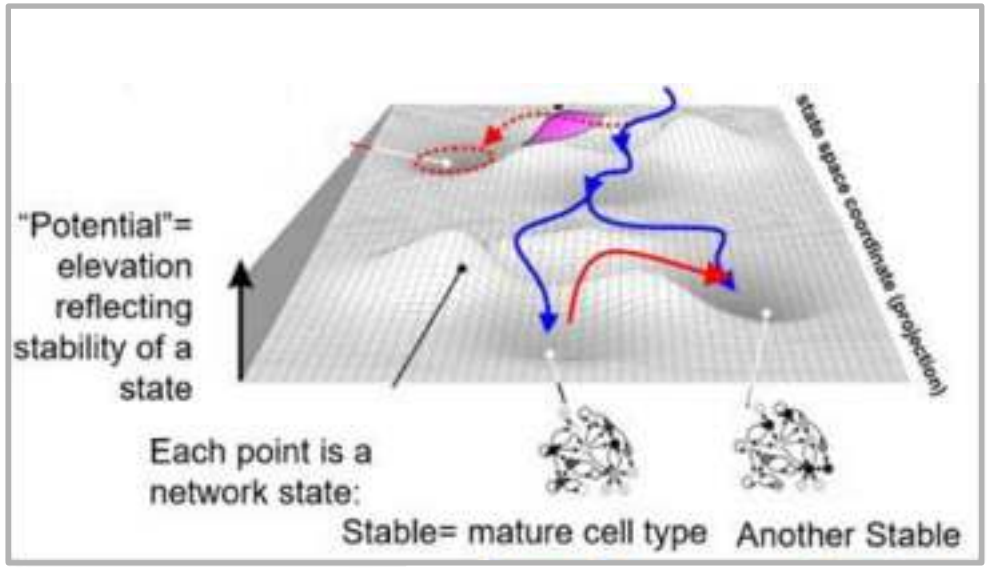
Canalisation and perturbation



Kerkhofs et al., PLoS ONE, 2015

Canalisation

Waddington's landscape:



From S.Huang et al. *Seminar in Cell & Developmental Biology* (2009)

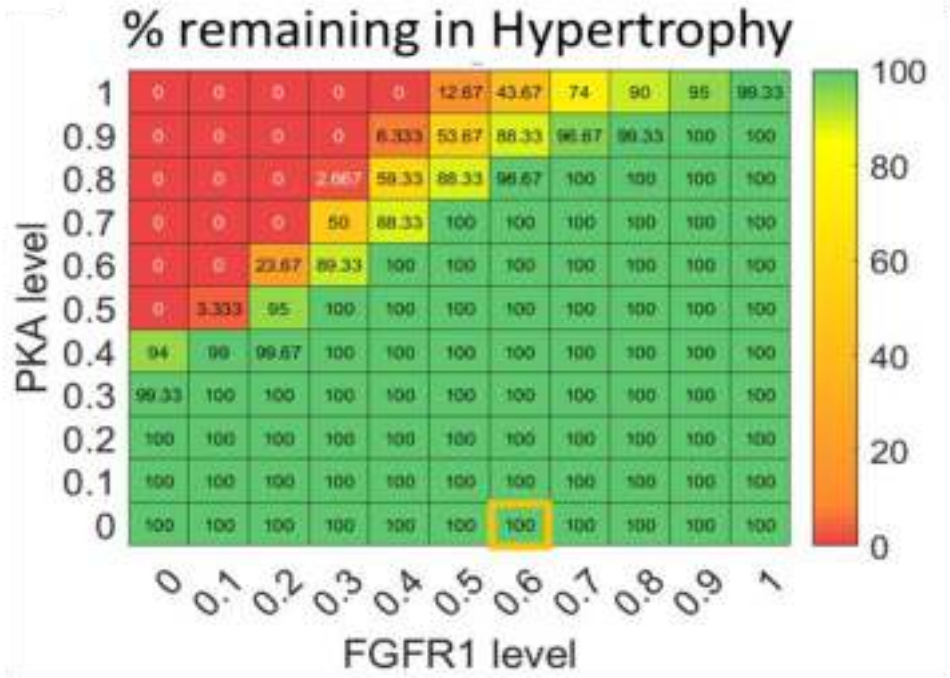
Predicted activity profile:

	Hyp	Healthy	None
WNT	1	0	
BMP	0.9	0	
FGF	1	0	
IHH	1	0,3	
PTHRP	0	1	
IGF	0	1	
TFGB	0	1	
MAPK/ERK	1	0	
Runx2	1	0	
Mmp13	1	0	
Col-X	0.9	0	
Col-II	0	1	
Sox9	0	1	
Nkx3.2	0	1	
Inflammation	0,8	0	
CANALISATION	**2%**	**21%**	**77%**

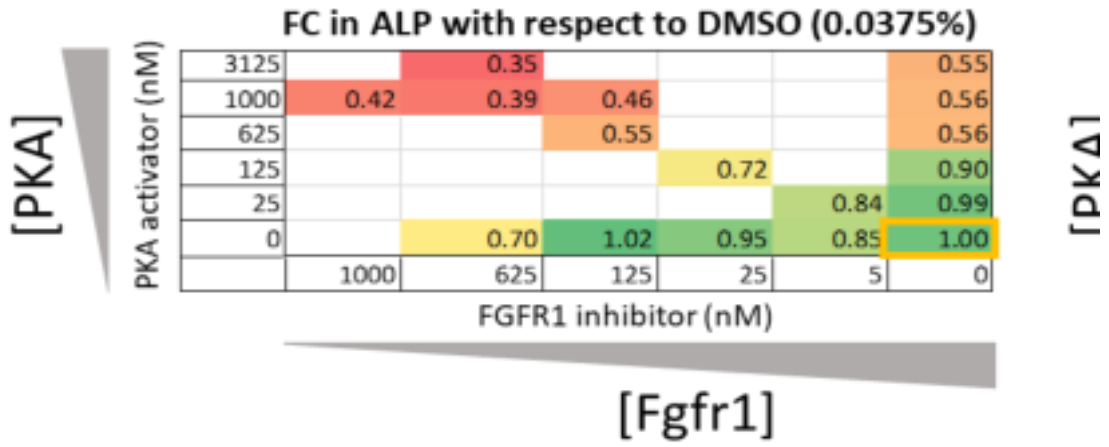
In silico confirmed by in vitro (ATDC5)

PKA activation + FGFR1 inhibition

In silico



In vitro

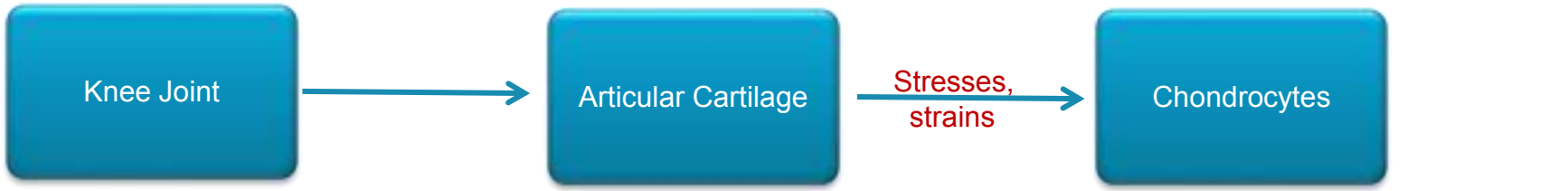


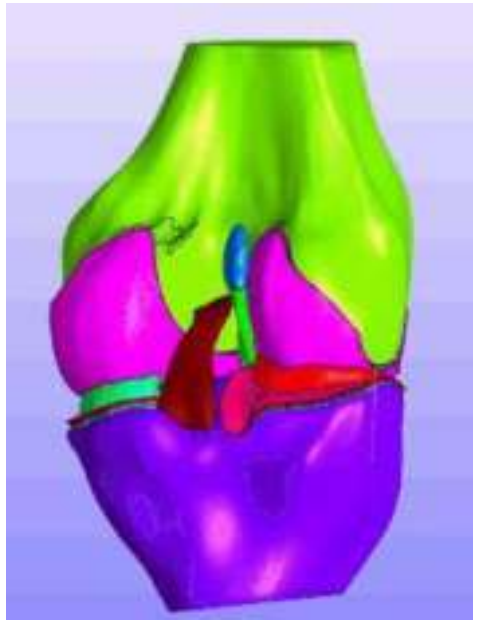
- Minimal amount of PKA required to see any positive effect
- The lower the PKA, the more we need to block FGFR1 to achieve equivalent effect

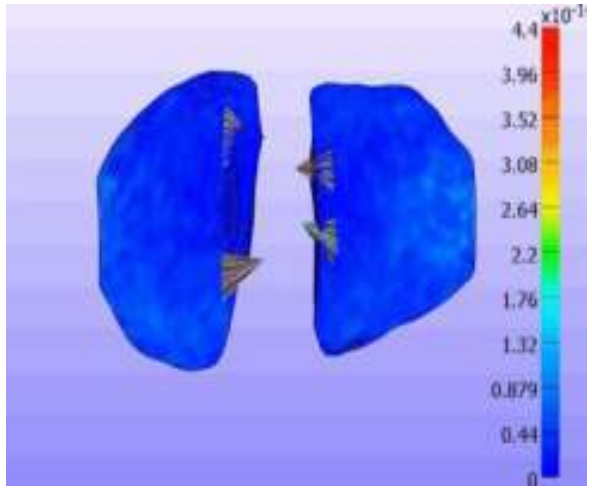
Joint OA

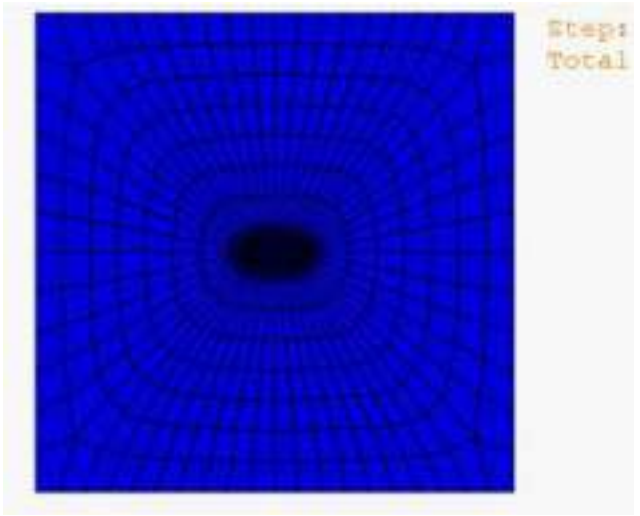
- Disease-modifying drugs
  - Raphaëlle Lesage
- Tissue Engineering strategies
  - Satanik Mukherjee

Next steps: in the human environment



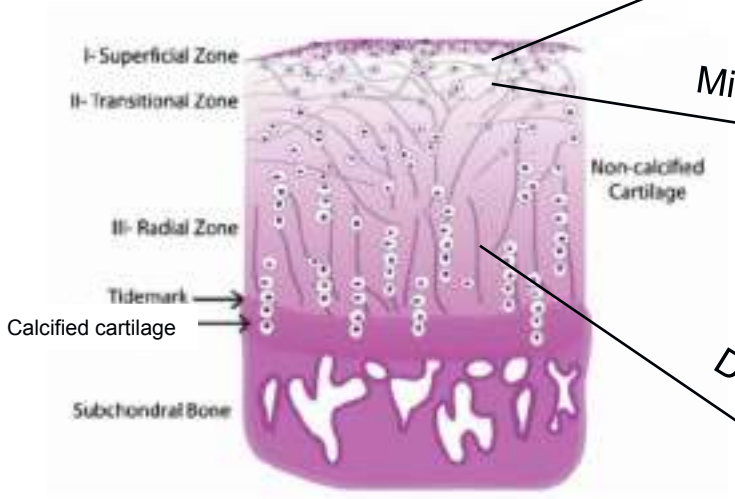




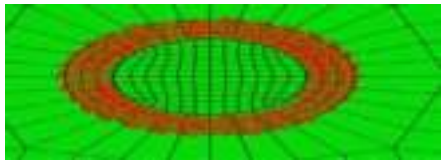


Mukherjee et al., in preparation; Mukherjee & Lesage et al., in preparation

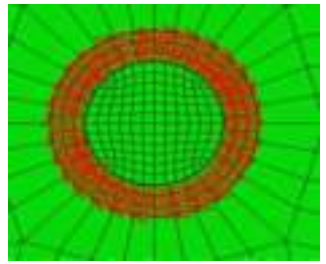
Zonal variation of chondrocyte micro-environment



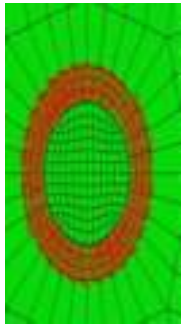
Gadjanski et.al. 2011



Superficial Zone



Middle Zone



Deep Zone

PCM fibril orientation

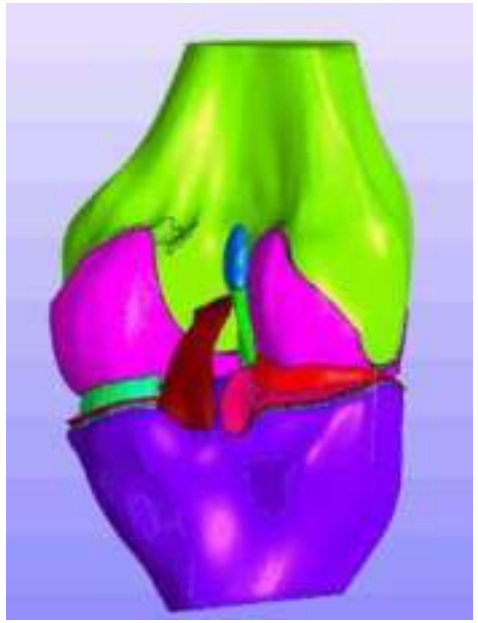
Next steps: in the human environment

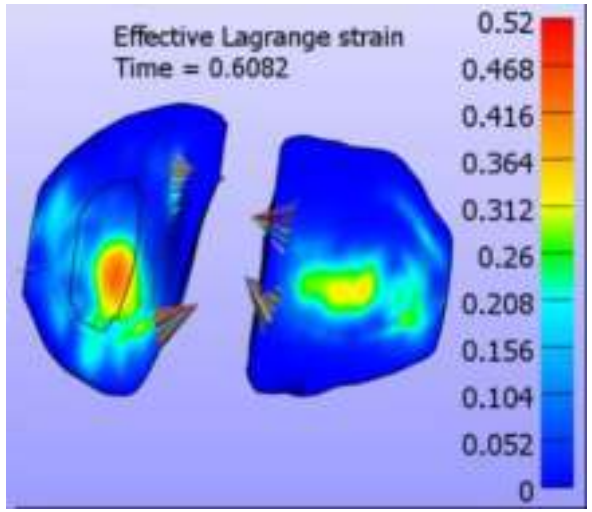
Altered conditions

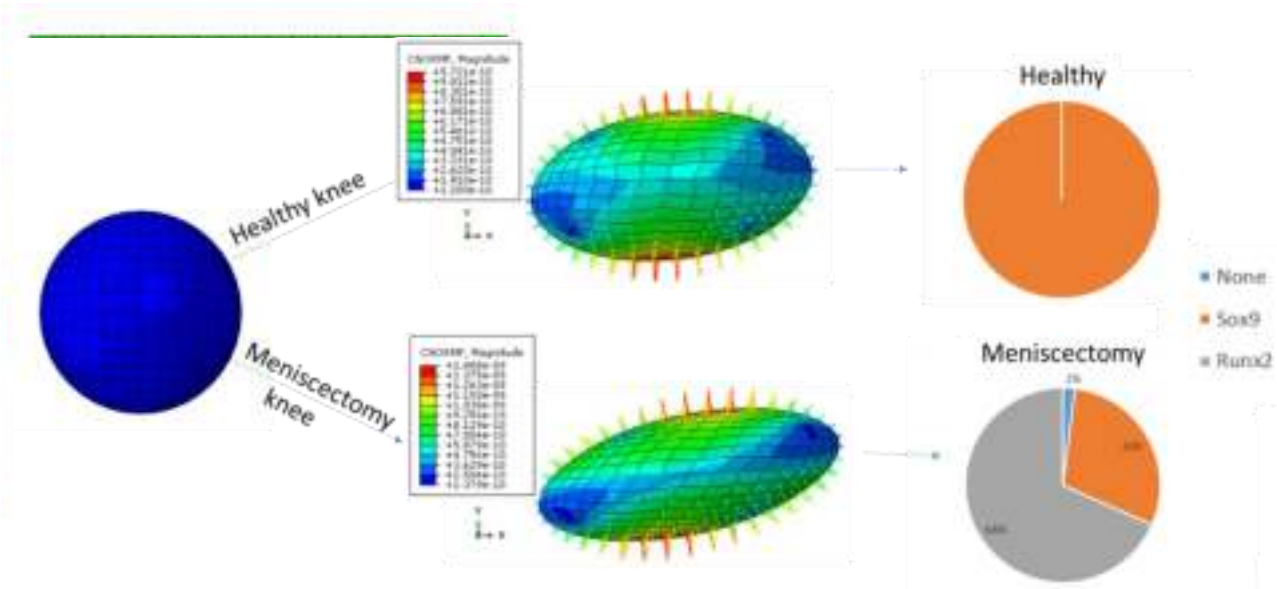
Computational Homogenization

Changes in ECM properties, cellular hypertrophy.

Knee Joint → Articular Cartilage → Stresses, strains → Chondrocytes → Forces on integrins → Intracellular regulatory networks

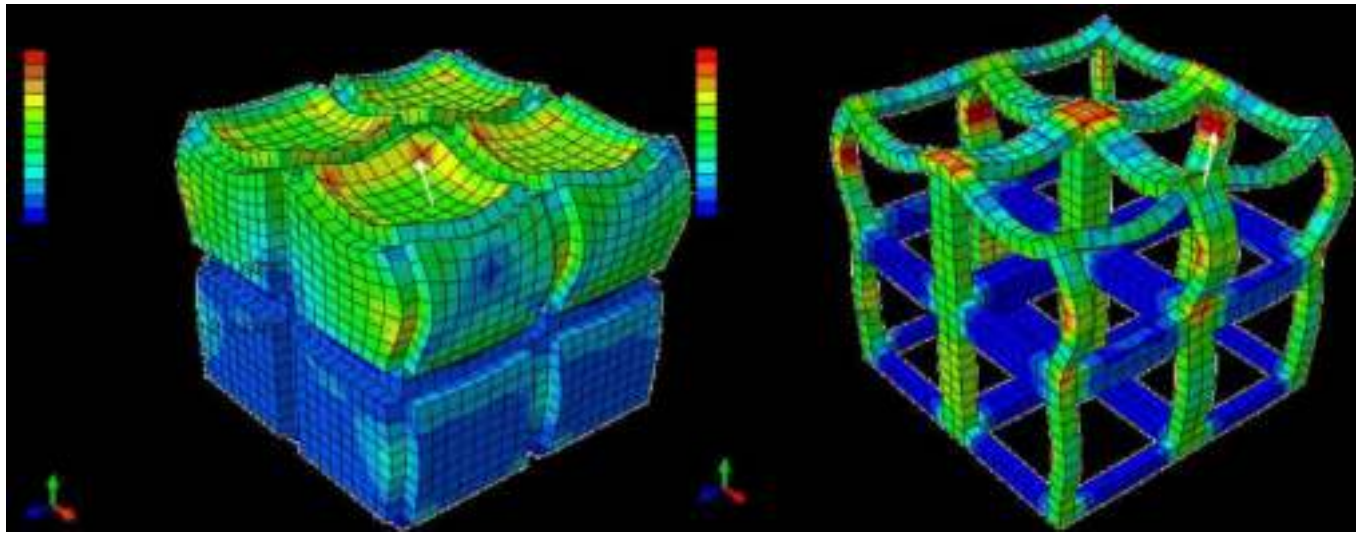


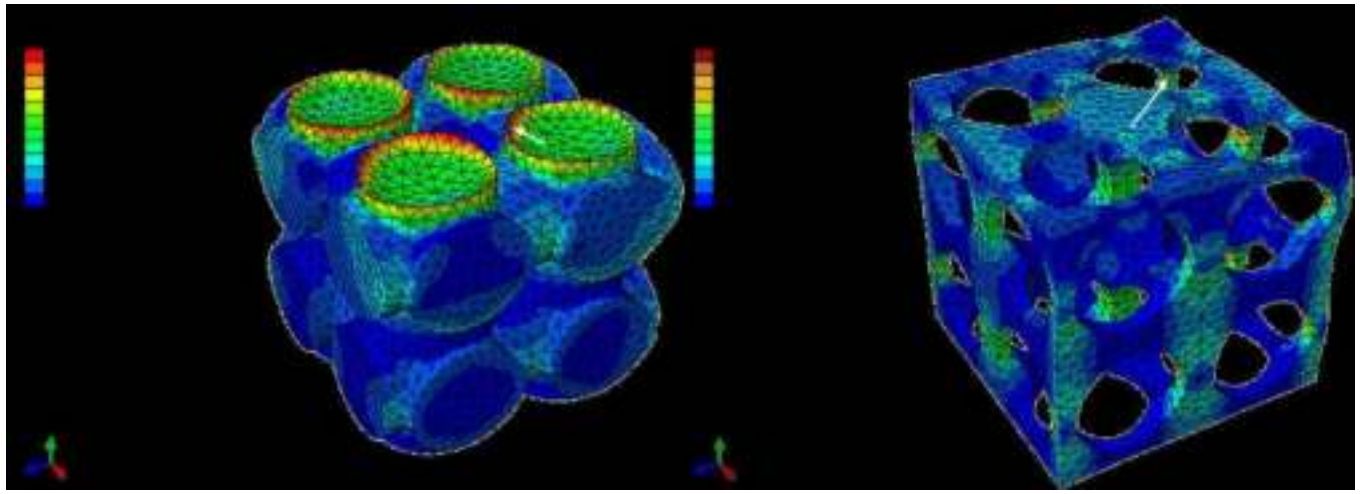




Mukherjee et al., in preparation; Mukherjee & Lesage et al., in preparation

Living implants for OA





Conclusion & Impact

- Very succesful in achieving its goals

  - Highly interdisciplinary training
  - Very natural establishment of across-group collaborations for all ESRs
  - Good science
  - Exploitable results

https://www.carbonresearch.eu/

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Marie Sklodowska-Curie grant agreement No 721432