SILICOFCM

CompBioMed Conference 2019

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

Prof. Nenad Filipovic

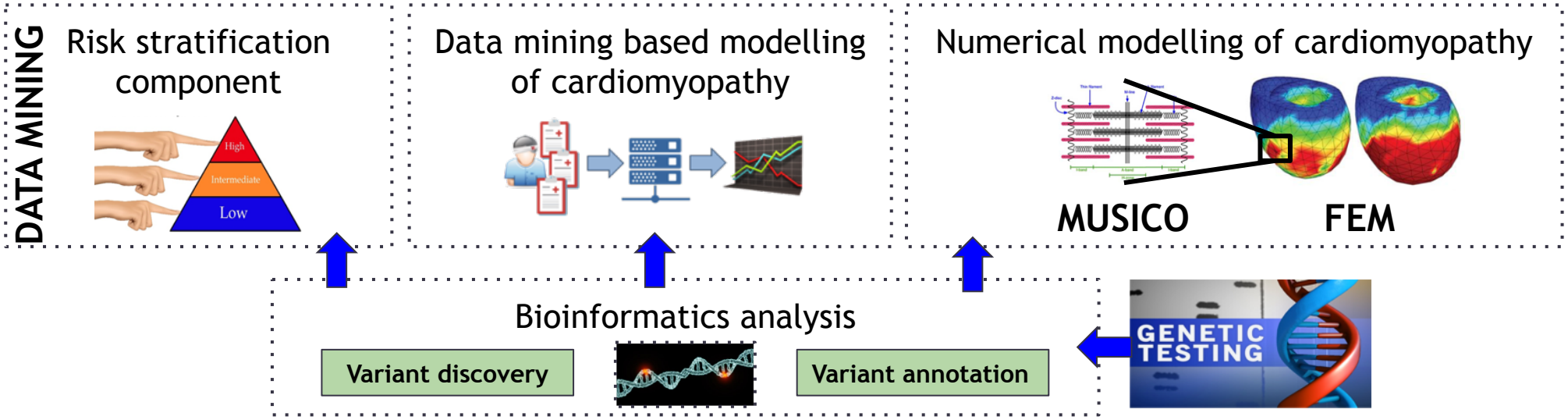
BioIRC Bioengineering Research and Development Center, Kragujevac, Serbia
University of Kragujevac, Serbia

Institute of Engineering and Technology, London: Savoy Place
September 25-27, 2019

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.
- 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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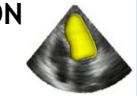
SILICOFCM

SILICOFCM Concept

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

USER 1: Medical doctor

3D IMAGE SEGMENTATION tool

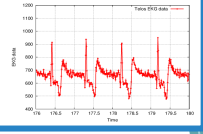


USER 2: Pharmaceutical company

USER 3: Researcher

Virtual experiments database

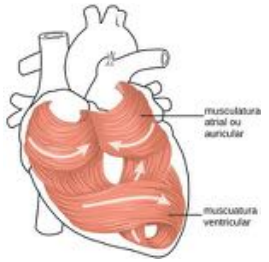
Experiments



Virtual population database

BIOINFORMATICS tool

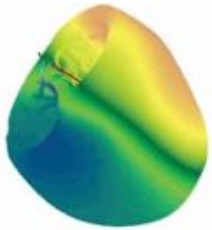
MUSICO tool

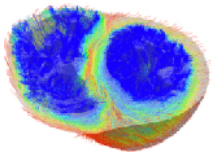


DATA ANALYTICS tool

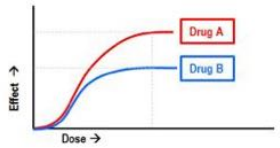
RISK STRATIFICATION

Finite element solver (ALYA, PAK)

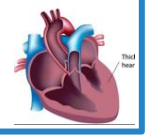




Drug efficacy



Cardiomyopathy disease progression



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Scenario 1

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

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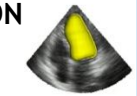

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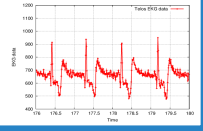

Virtual population database

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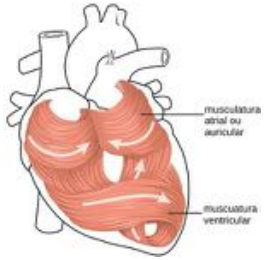
MUSICO tool



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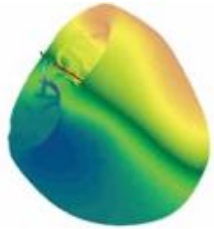

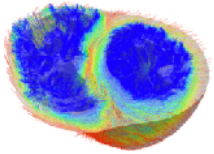

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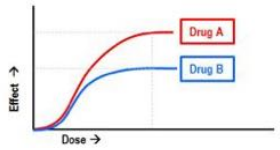
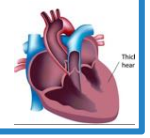


Cardiomyopathy disease progression



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Scenario 2

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

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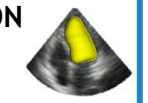

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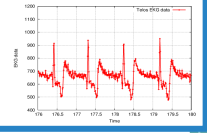
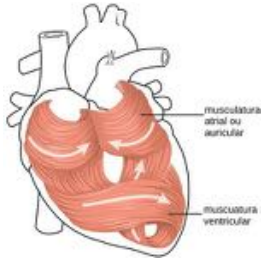


Virtual population database

BIOINFORMATICS tool

MUSICO tool



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RISK STRATIFICATION

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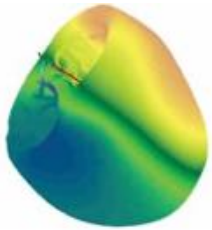

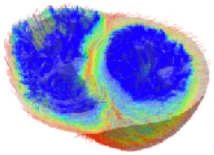

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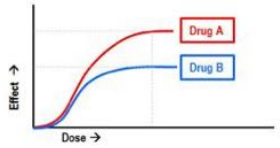
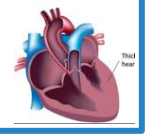


Cardiomyopathy disease progression



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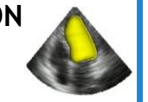
Scenario 3

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

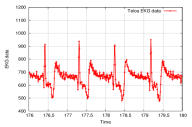
3D IMAGE SEGMENTATION tool



USER 3: Researcher

Virtual experiments database

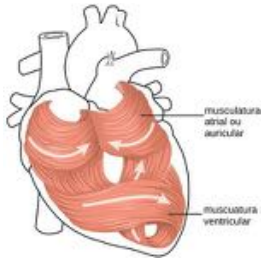
Experiments



Virtual population database

BIOINFORMATICS tool

MUSICO tool



DATA ANALYTICS tool

RISK STRATIFICATION

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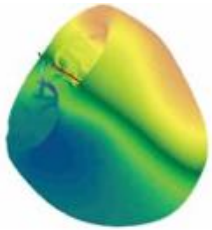

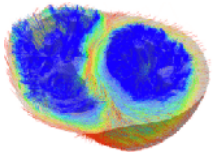

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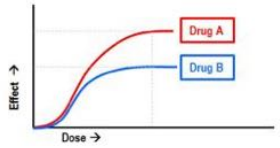

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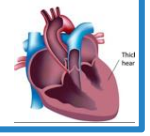

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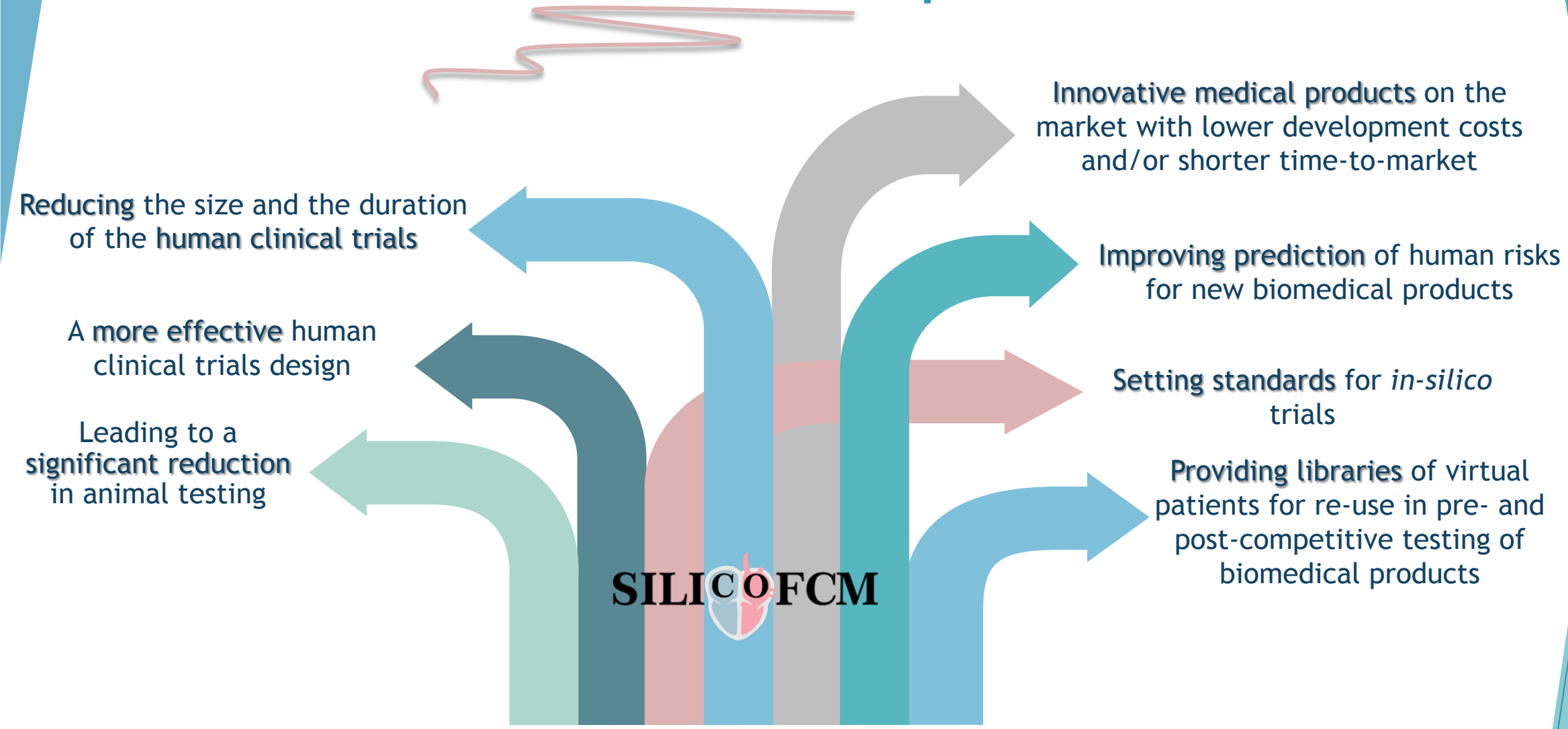
SILICOFCM Impact



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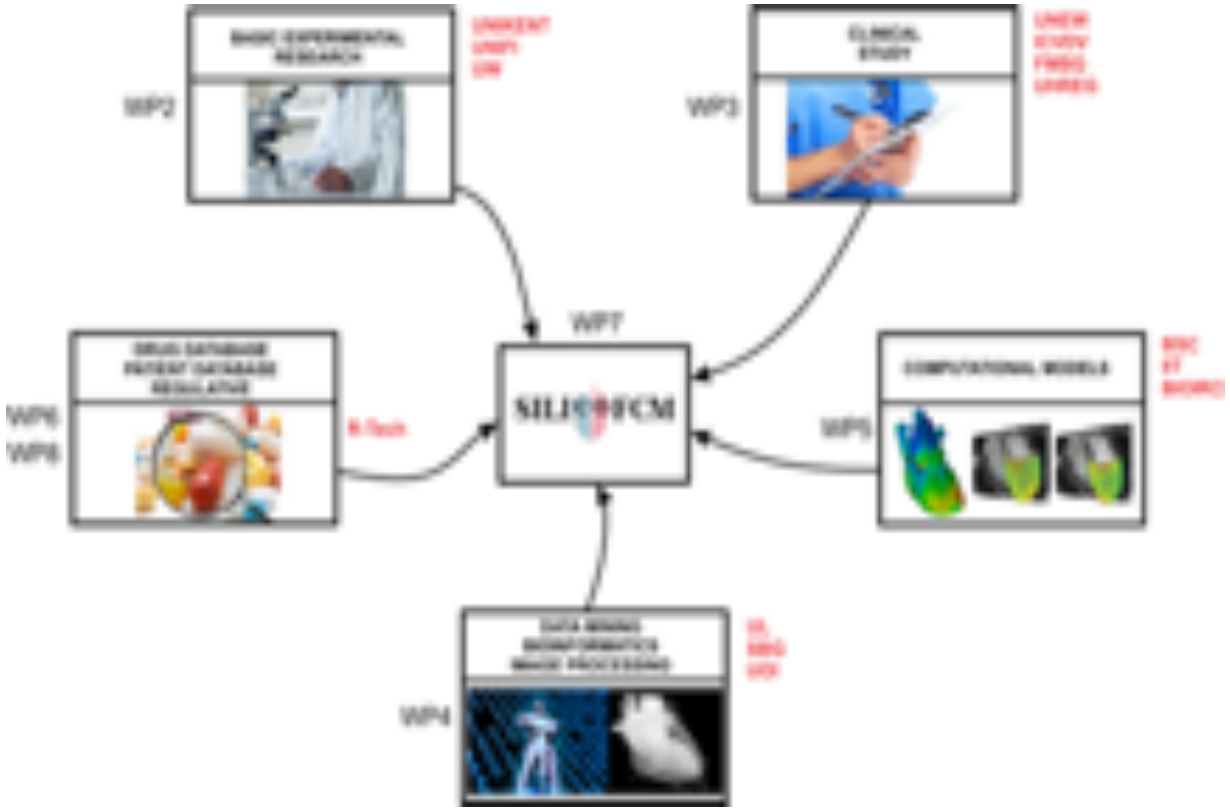
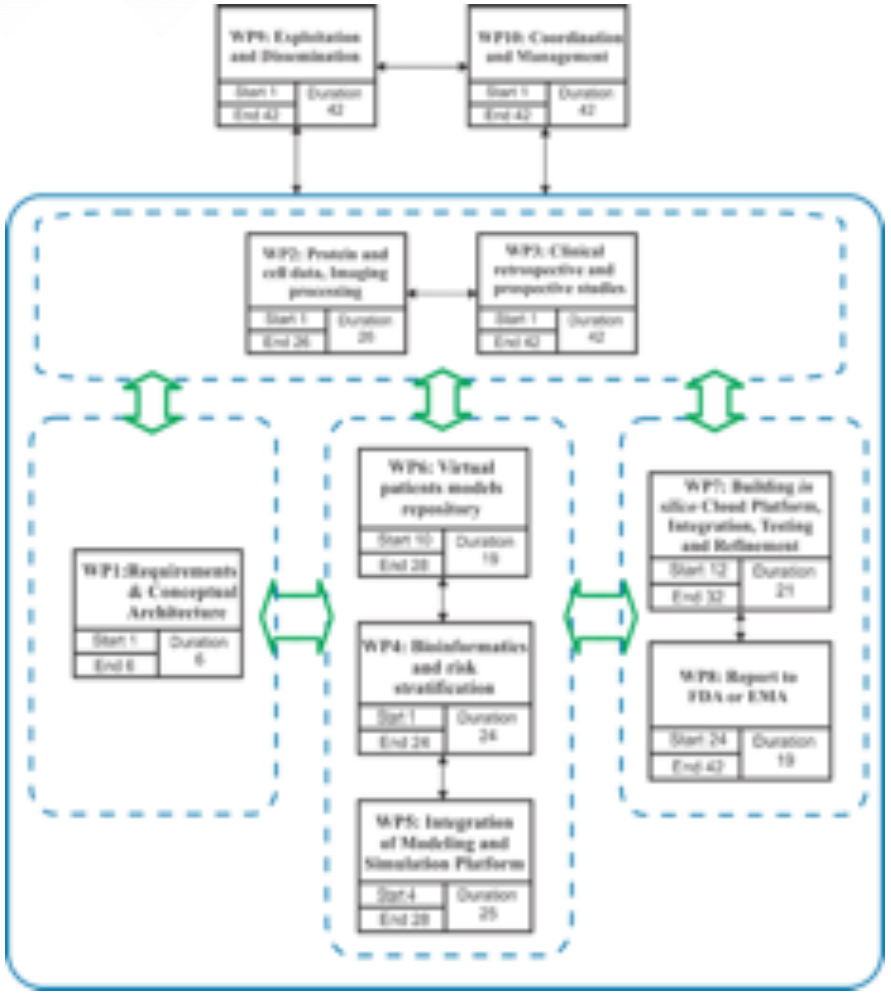
WPs Interaction





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SILICOFCM

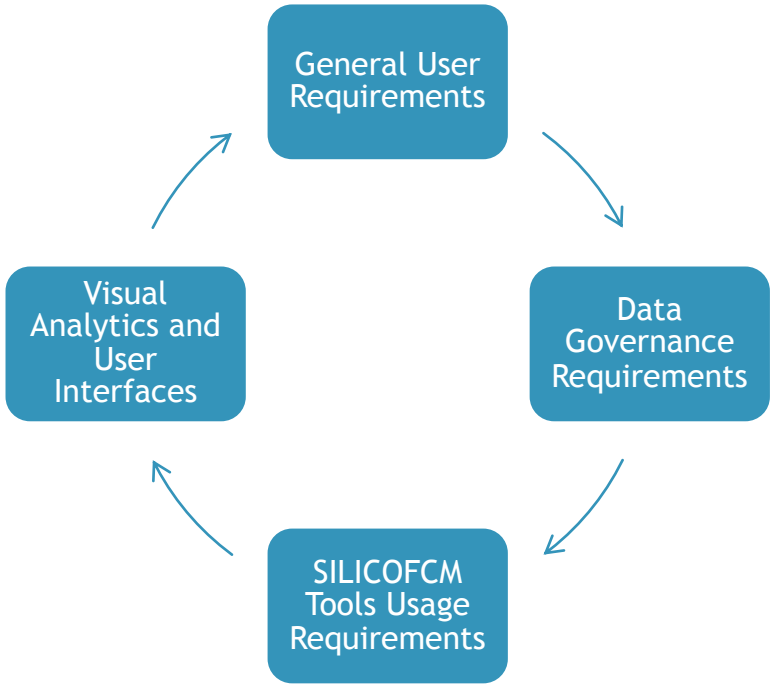
WP1 Requirements & Conceptual Architecture

Leader BIORIC

M1-M6

Main objective

- To collect and analyse the state-of-the-art technologies, user requirements and hardware requirements for innovative SILICOFCM Reference Architecture



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WP2 Protein and cell data, Imaging processing

Leader UNIKENT

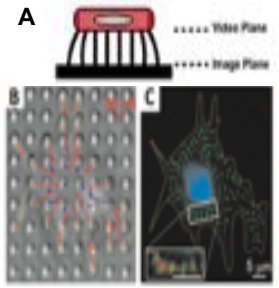
M1-M26

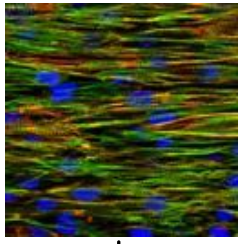
Main objective

- To provide protein and cell data as well basic physiological experiments for heart disease
- To acquire medical images

3D engineered **Tissue-level mechanics** heart tissue (EHT)

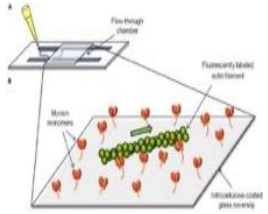
Cell Contraction/Relaxation (micropost arrays)



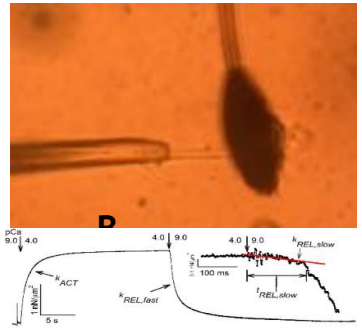


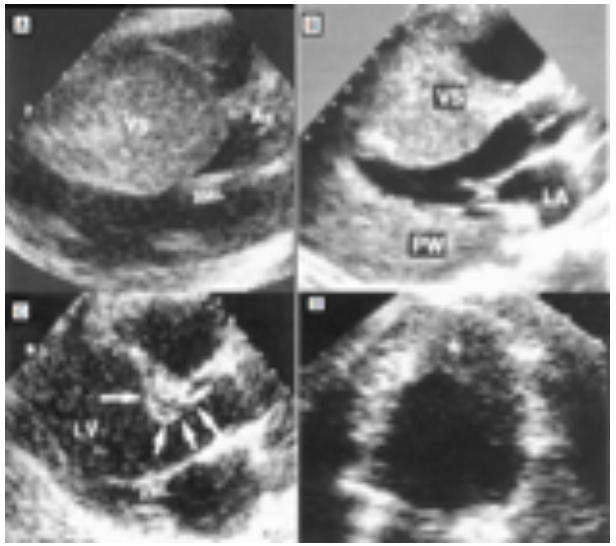
Cell contractility/Ca^{2+} transients

Actin-Myosin mechanics and energetics (in vitro motility/micro-needle assay)



Isolated Myofibrils contraction/relaxation kinetics





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WP3 Clinical retrospective and prospective studies

Leader UNEW

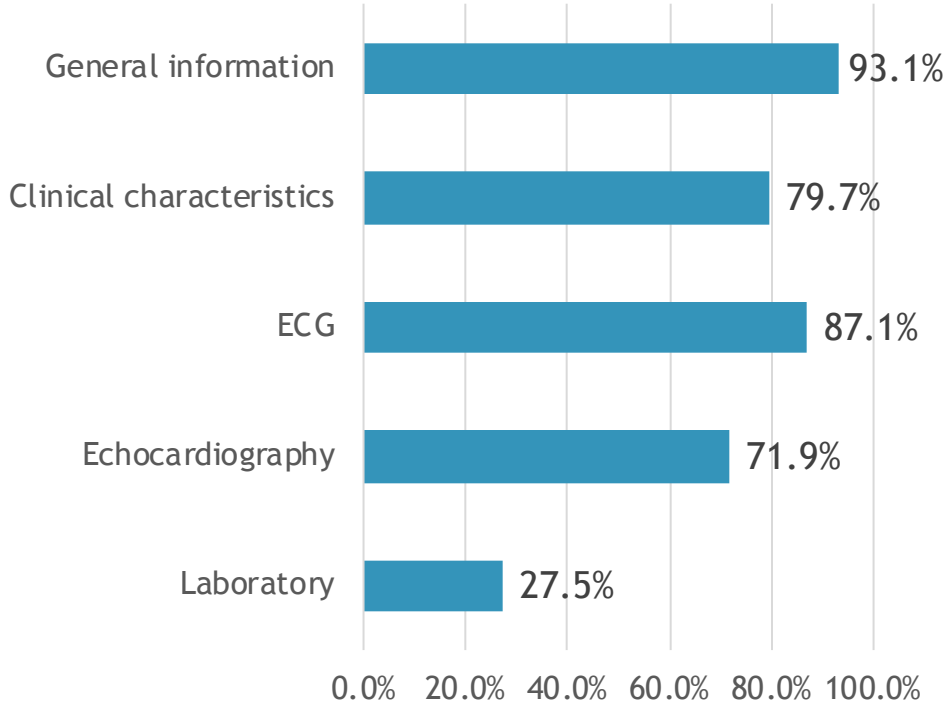
M1-M42

Main objective

- **To create the clinical data** for fitting and validation of the mechanical models (WP5), training and testing of the risk stratification tool (Task 4.4) and the data mining model for prediction of cardiomyopathy outcome (WP7)

Data completeness

- ICVDV 90.3%
- UNIFI 94.4%
- UNEW 78.7%
- UHREG 67.9%



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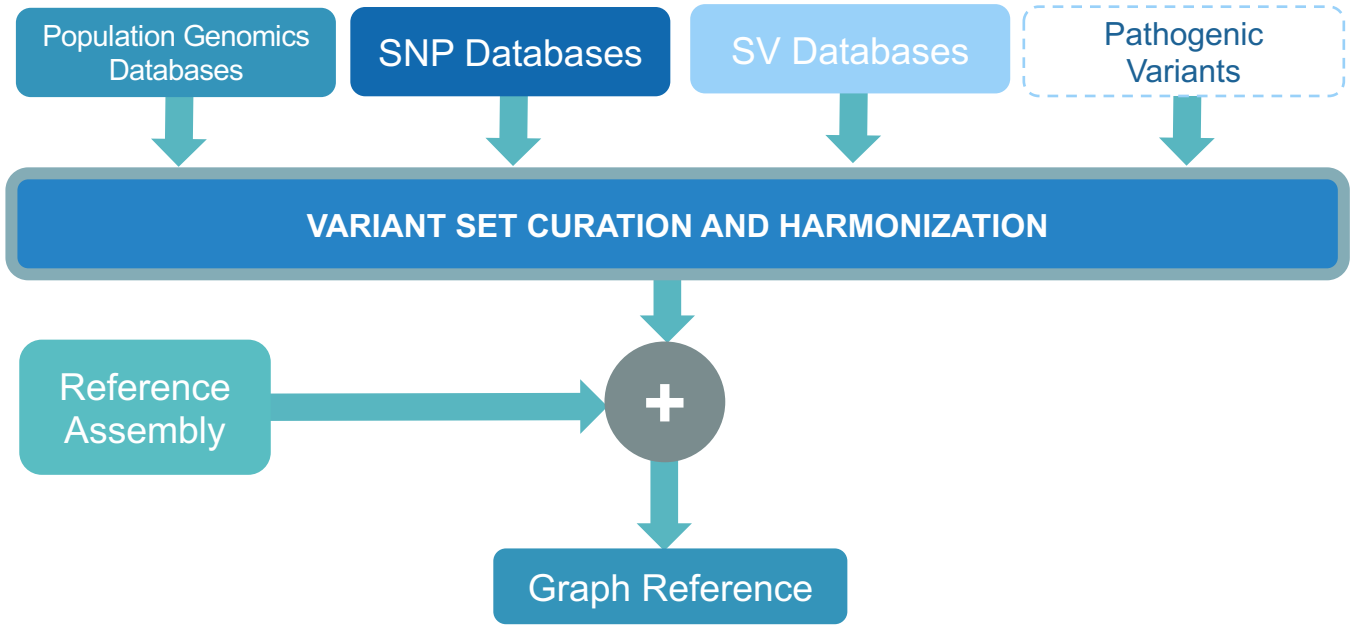
WP4 Bioinformatics and risk stratification

Leader SBG

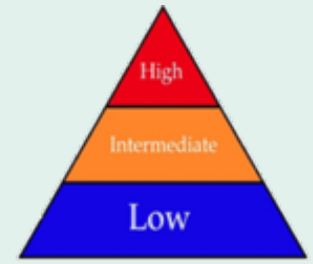
M1-M24

Main objective

- To put in place the genomic component in the SILICOFCM platform and integrate it with the SILICOFCM sub-components
- To develop the cardiomyopathy risk stratification system



Learning performance evaluated with cross-validation ROC analysis approach and other performance measures



risk stratification outcomes for unseen/new patients

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SILICOFCM

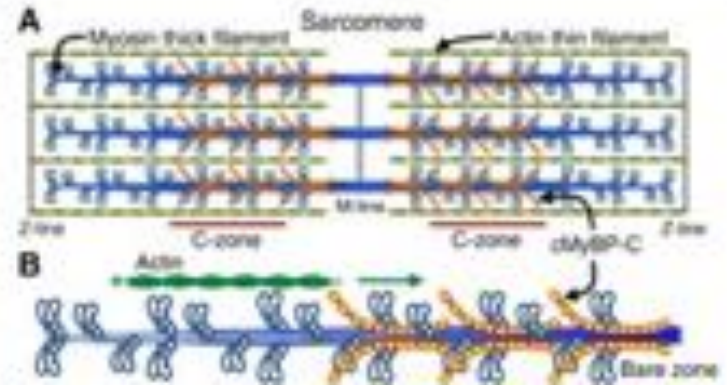
WP5 Integration of Modelling and Simulation Platform

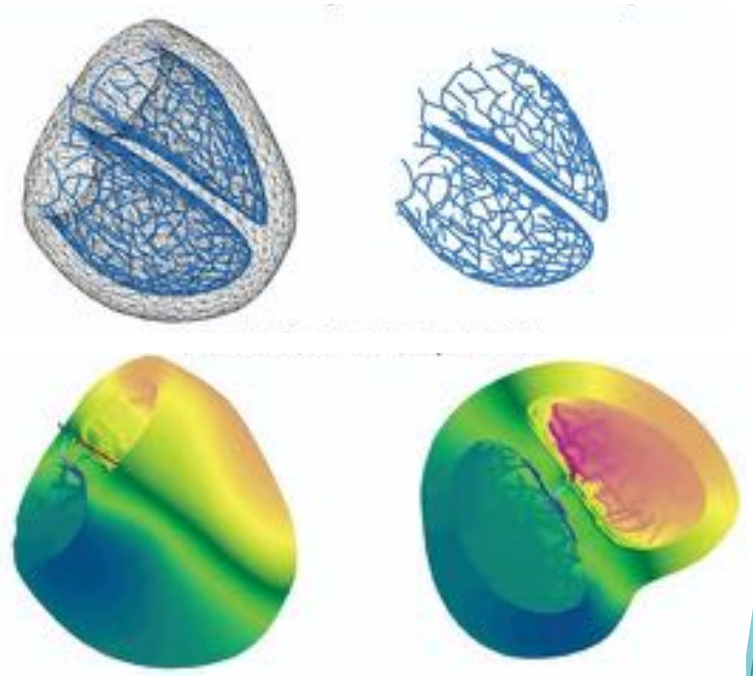
Leader IIT

M4-M28

Main objective

- To link the data from molecular interactions to the whole organ function by coupling Bioinformatics tool, MUSICO and FE solvers (ALYA and PAK)





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SILICOFCM

WP6 Virtual patients models repository

Leader UL

M10-M28

Main objective

- To develop virtual FCM patients models repository and perform pattern identification from heterogeneous data by using data mining algorithms

SILICOFCM virtual population model - DRAFT

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SILICOFCM

WP7

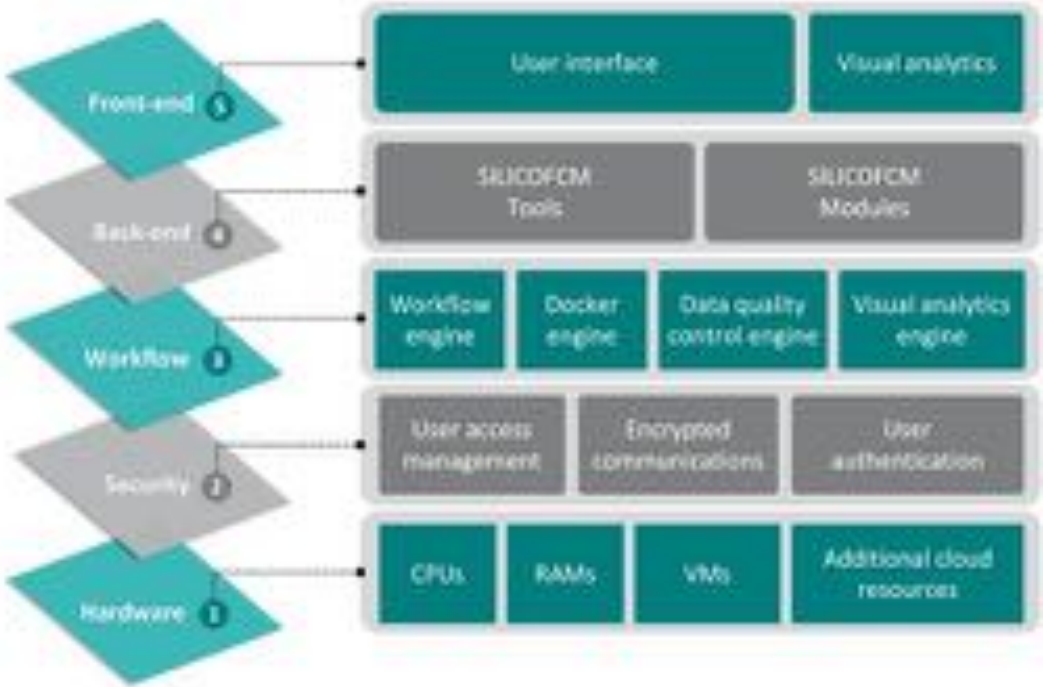
Building *in Silico* Cloud Platform, Integration, Testing and Refinement

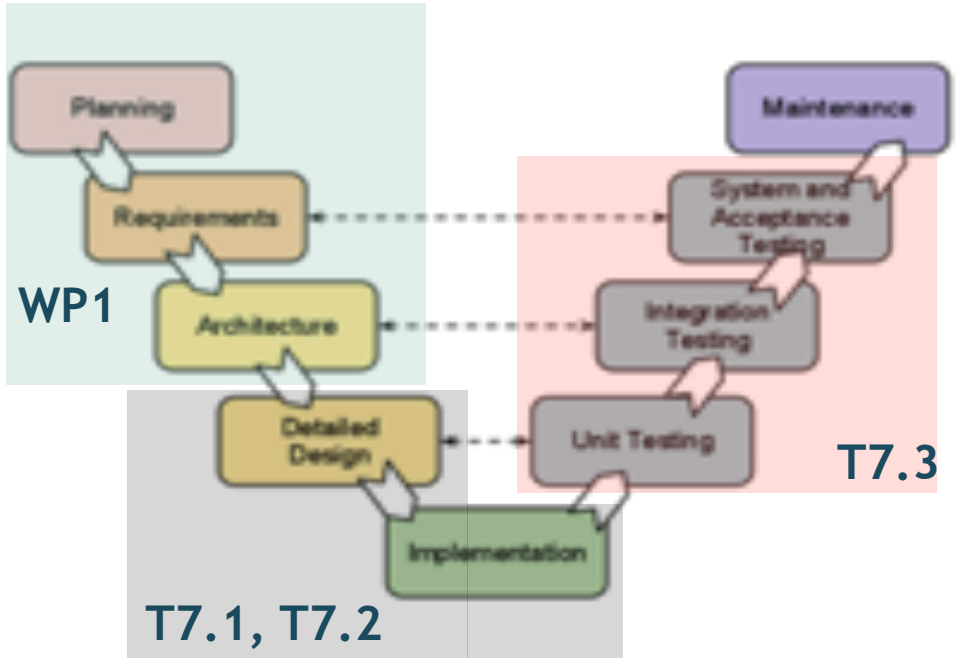
Leader UOI

M12-M32

Main objective

- To integrate the SILICOFCM subsystems into the platform guaranteeing a smooth, secure, and standard integration





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SILICOFCM

WP8 Report to FDA or EMA

M24-M42

Leader R-Tech

Main objective

- To perform regulatory approval processes of the project results towards EMA or FDA

Task 8.1 Development workflow assistant for EMA/FDA approval — Leader BioIRC, M24-M36

Task 8.2 Set up R&D computation pipelines for drug testing — Leader IIT, M24-M36

Task 8.3 Interface drug database — Leader UOI, M24-M40

Task 8.4 Development report tool — Leader R-Tech, M24-M42

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

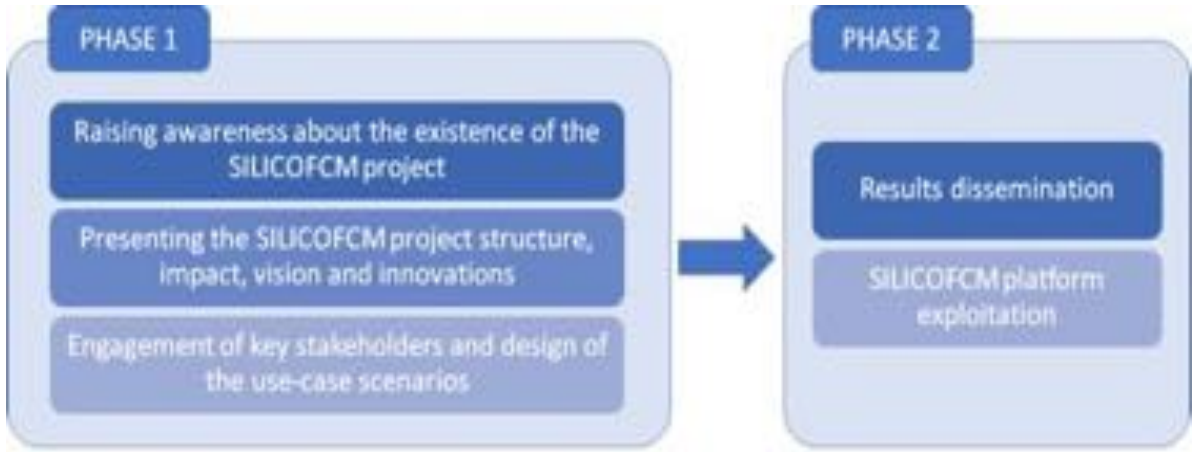
WP9 Exploitation and Dissemination

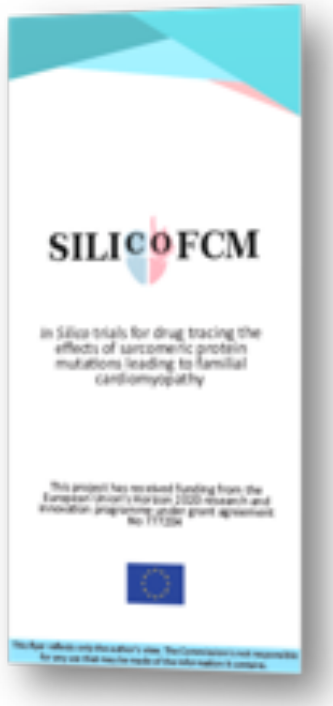
Leader BioIRC

M1-M42

Main objective

- To promote the widespread utilisation and exploitation of the project results





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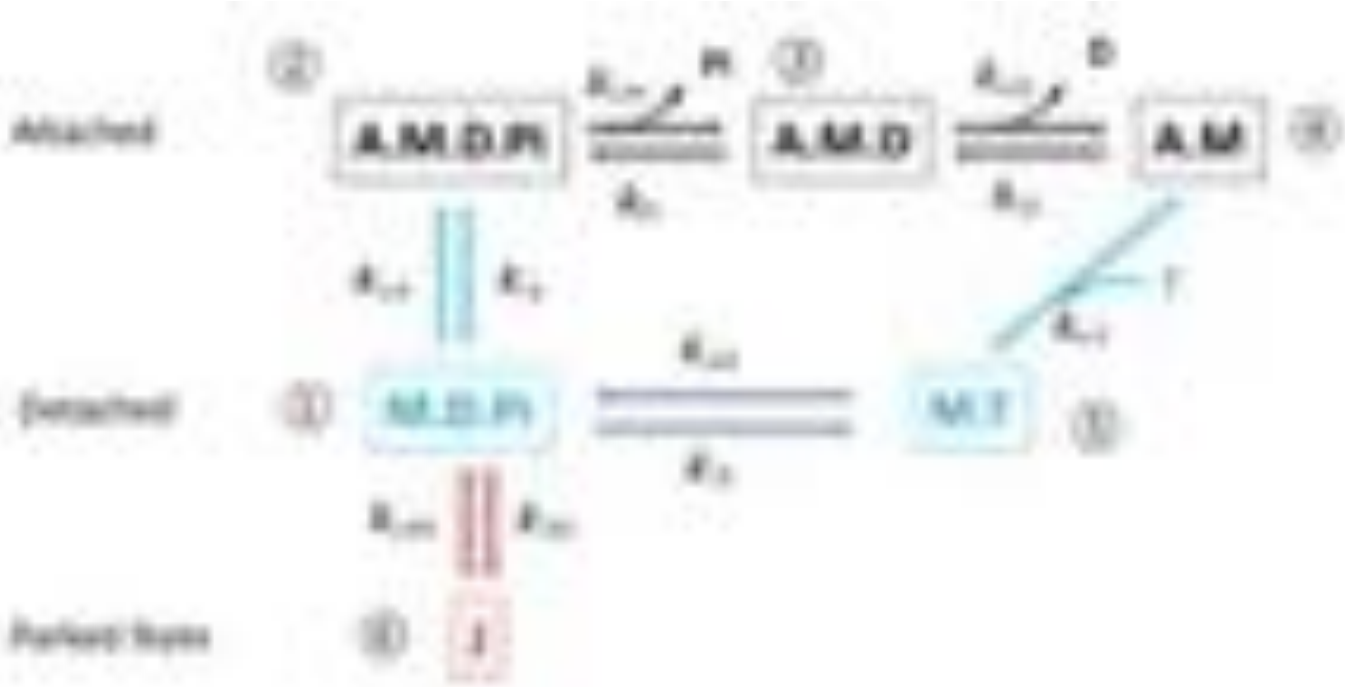
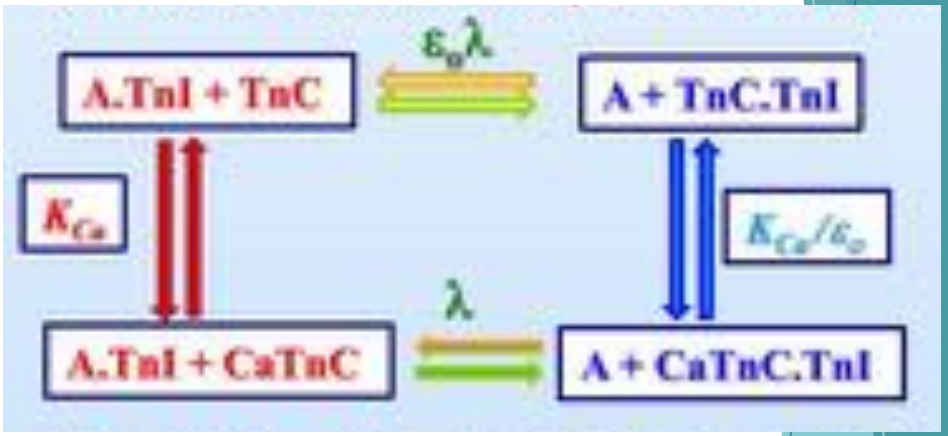
SILICOFCM

MUSICO: Six State Crossbridge Model & Calcium Kinetics with TnC



Cardiac Muscle



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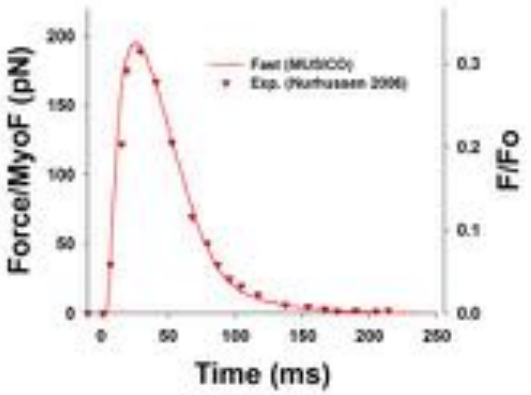
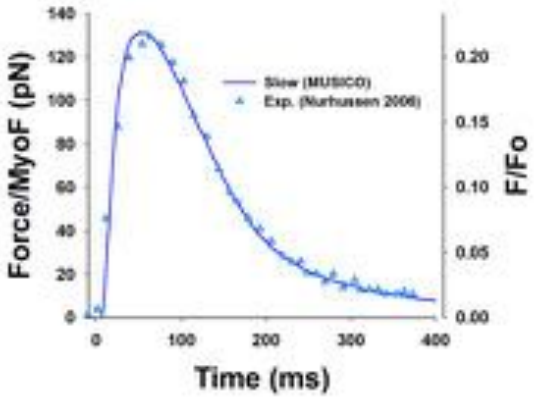
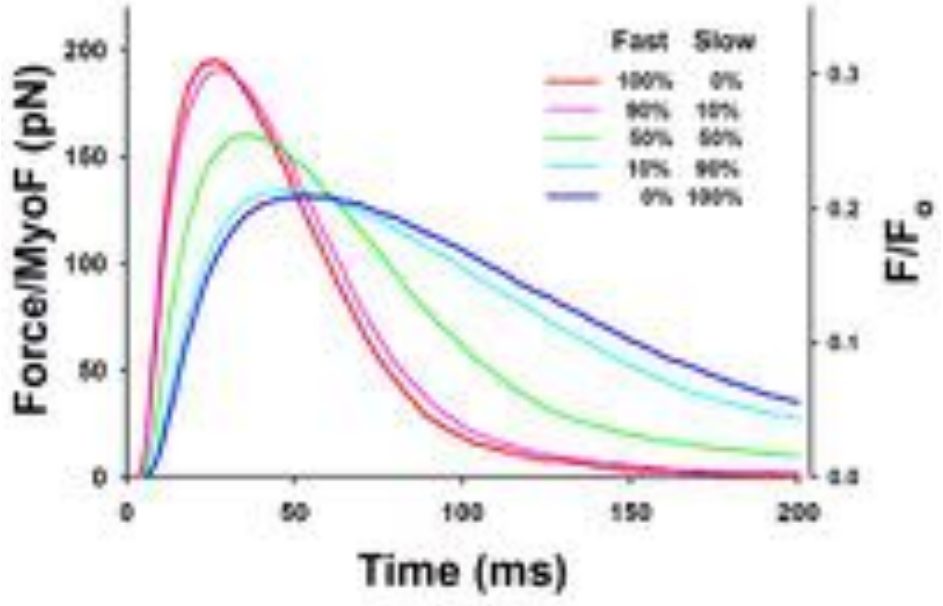
Penetrance of Fast (α) and Slow (β) Myosin Isoforms

Fast Twitch Contraction



Slow Twitch Contraction





- The calcium transient:
- Peak of 1.6 μM at 6 ms
- Decays to low calcium concentrations at about 35 ms.

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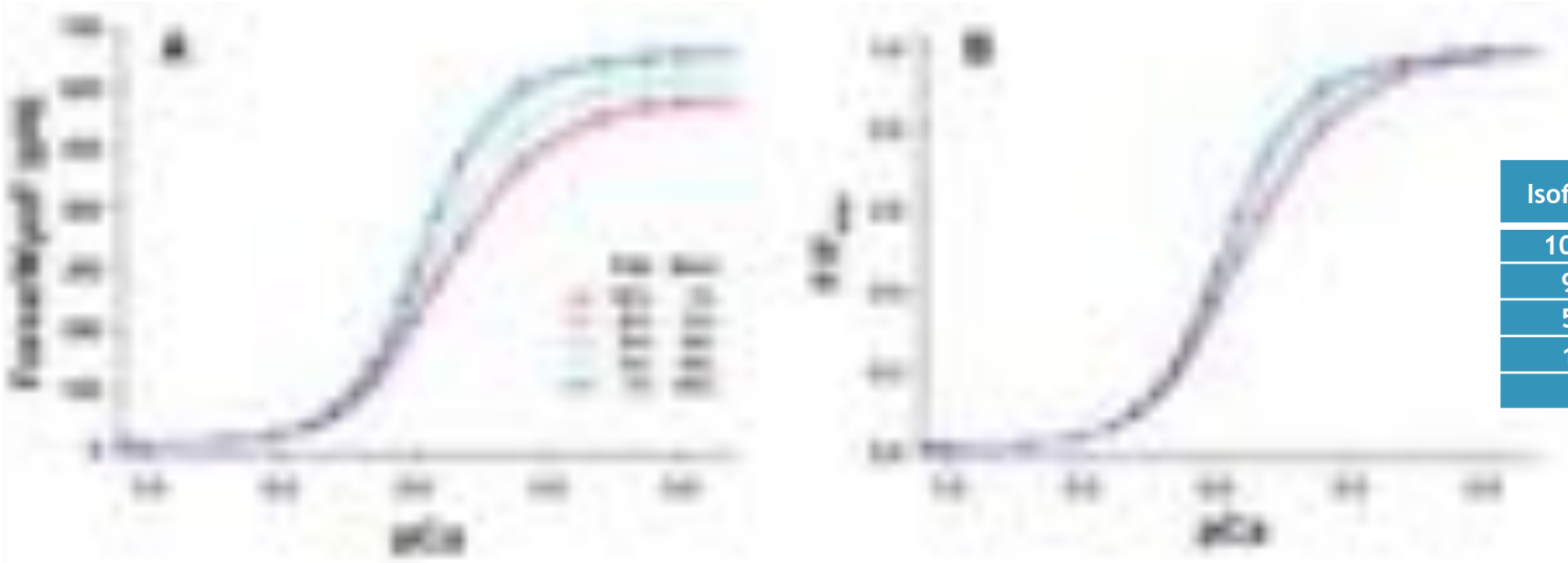
Myosin Isoform Penetrance

Effect on Hill Coefficient and Calcium Sensitivity



Isoform Mixture	Hill Coeff	pCa_{50}
100% α 0% β	2.302	5.890
90% α 10% β	2.342	5.899
50% α 50% β	2.531	5.933
10% α 90% β	2.807	5.966
0% α 100% β	2.889	5.973

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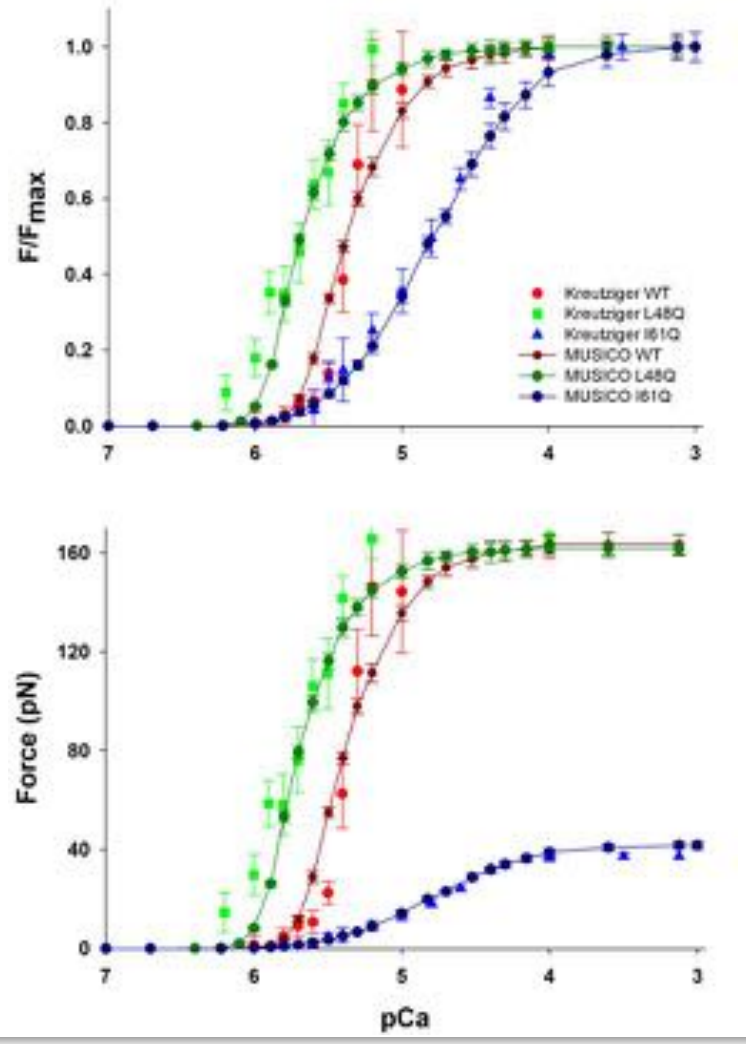
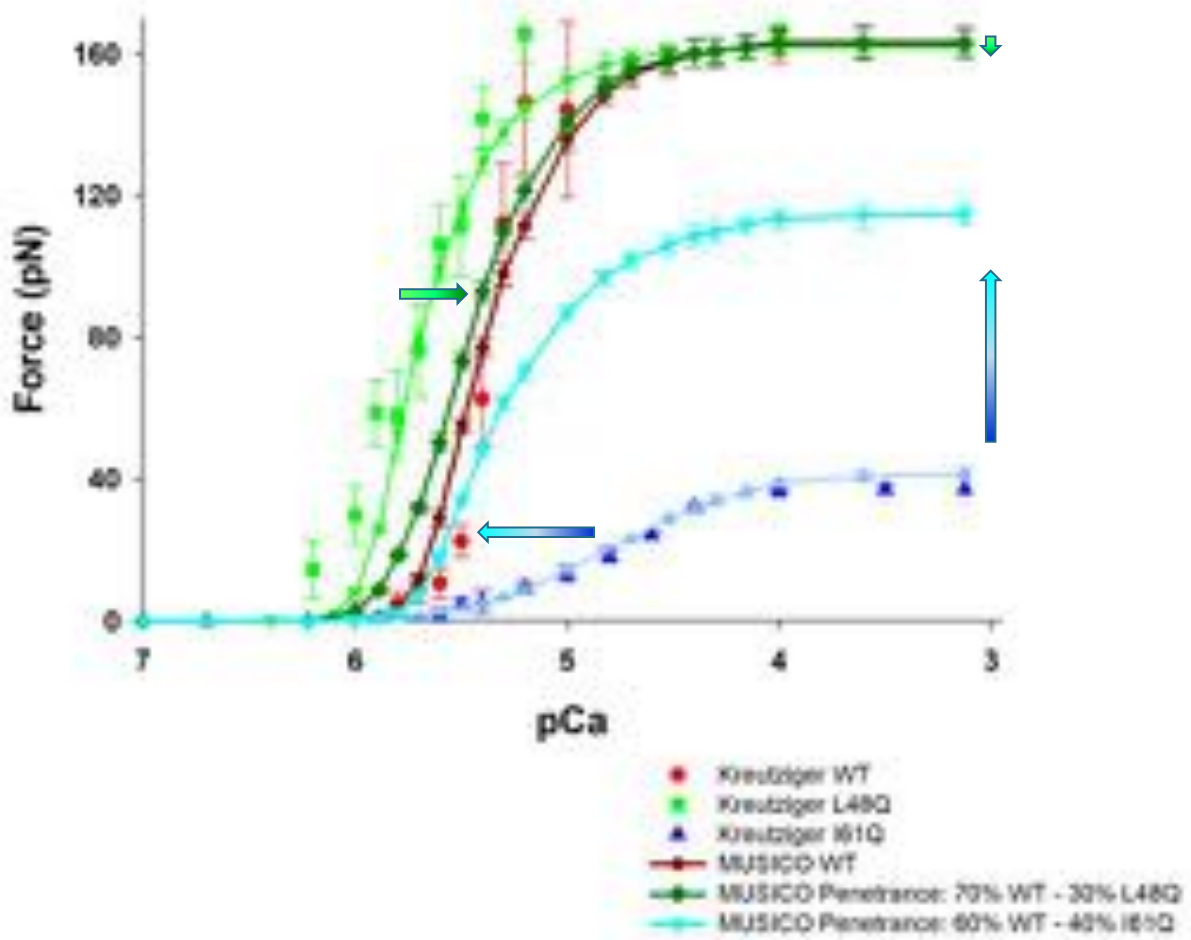
cTnC Penetrance

Fit to Kreutziger Experiments - Rat Trabeculae 100% Mutants



Kreutziger - Predicted Penetrance (Rat Trabeculae)



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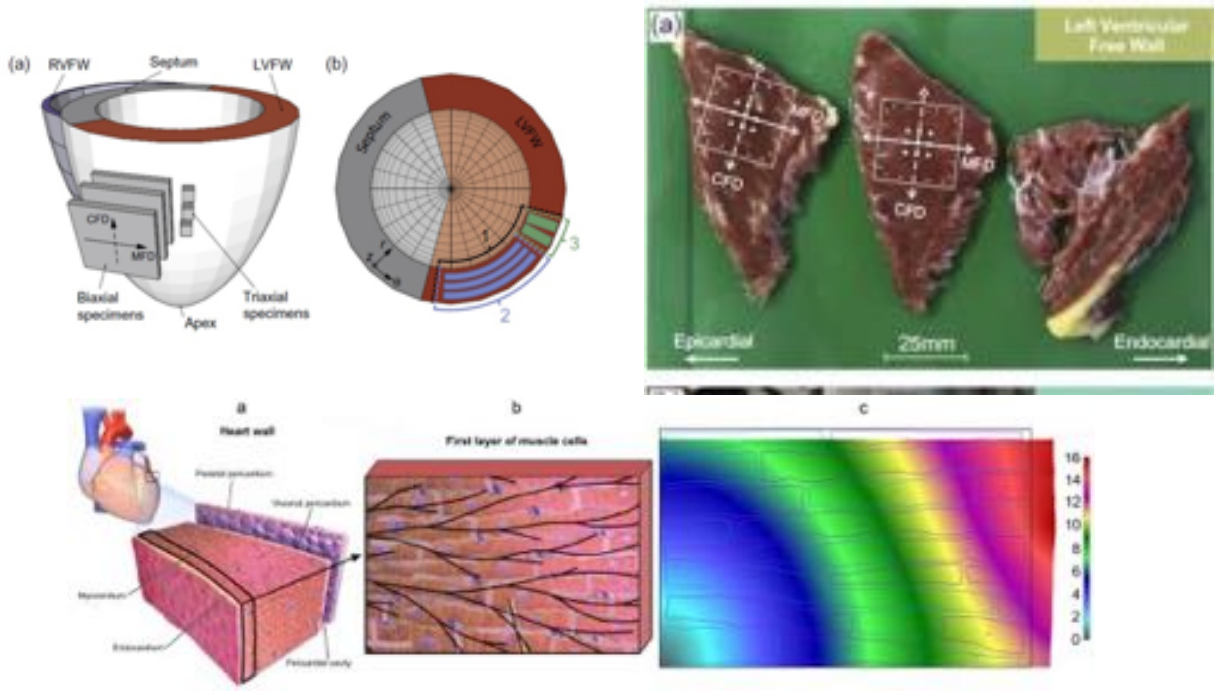
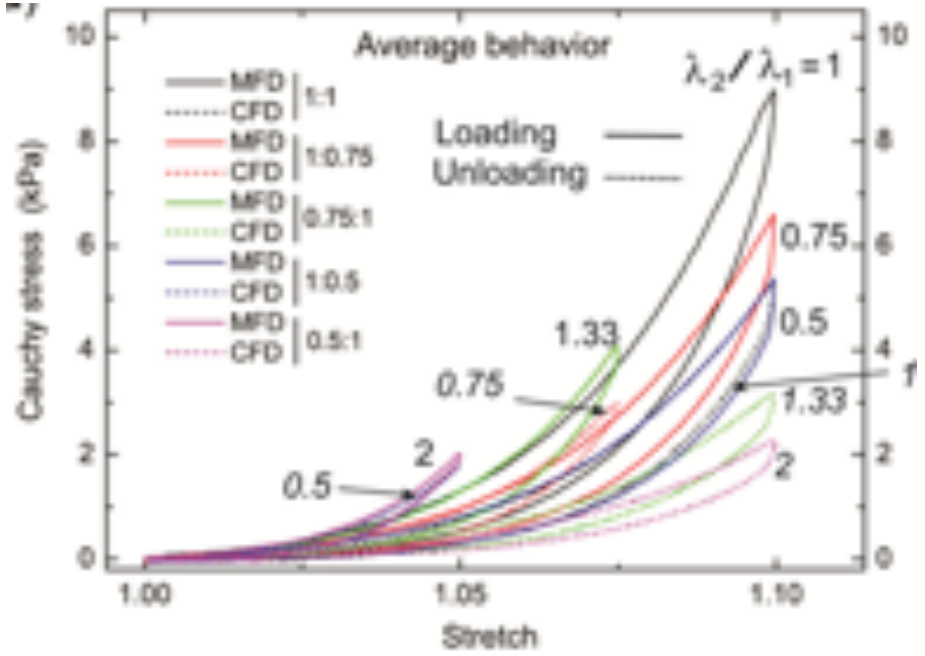
Upgrade FE biomechanical simulation
PAK Solver

- Implementation and testing of Heart mechanical model, according to (Holzapfel et al 2015):



Field of displacements in heart tissue due to uniaxial straining



Experimental curves with hysteresis for biaxial loading of myocardium tissue

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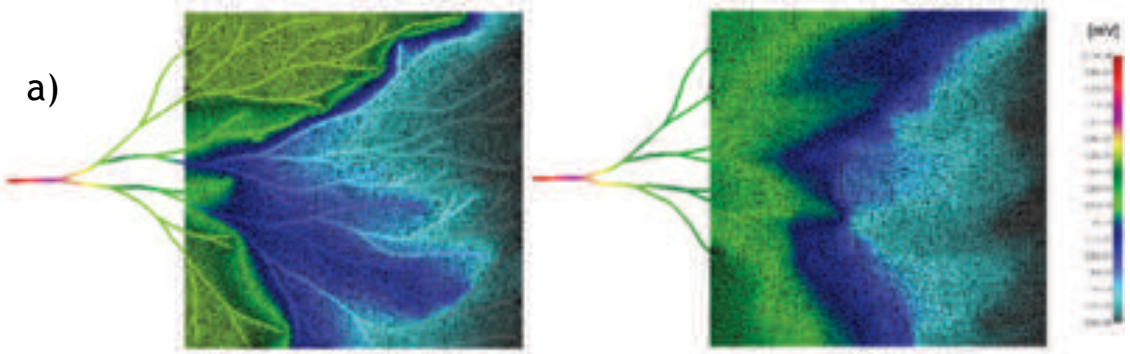
Upgrade FE biomechanical simulation
PAK Solver

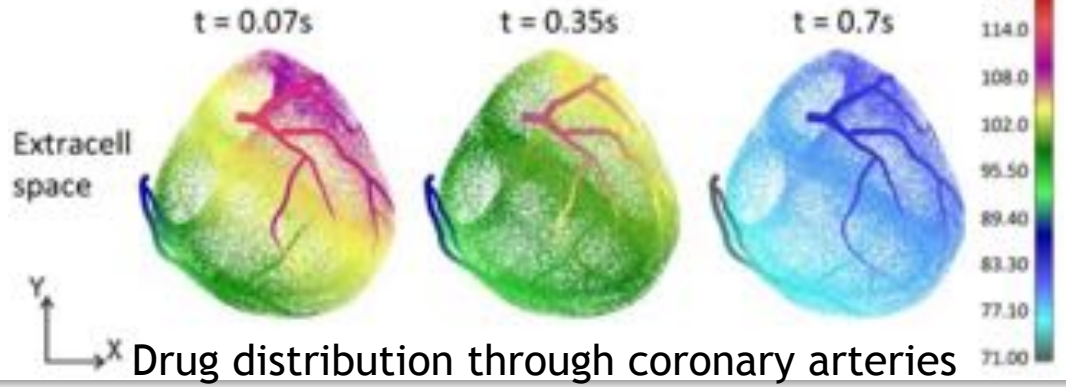
- Application of CSFEM to real heart model (coupled electrophysiology and mechanics)

a)



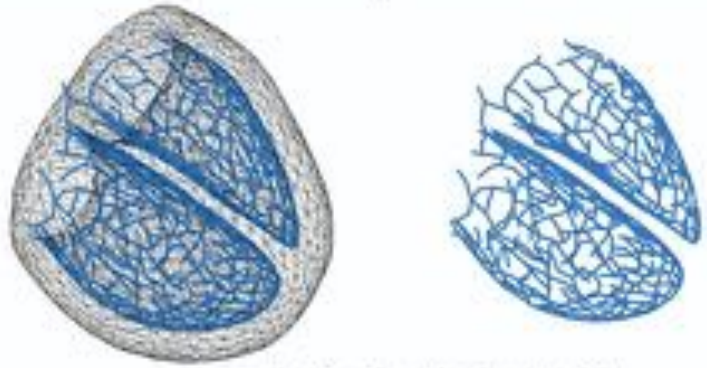
Potential distribution through Purkinje fibers

b)

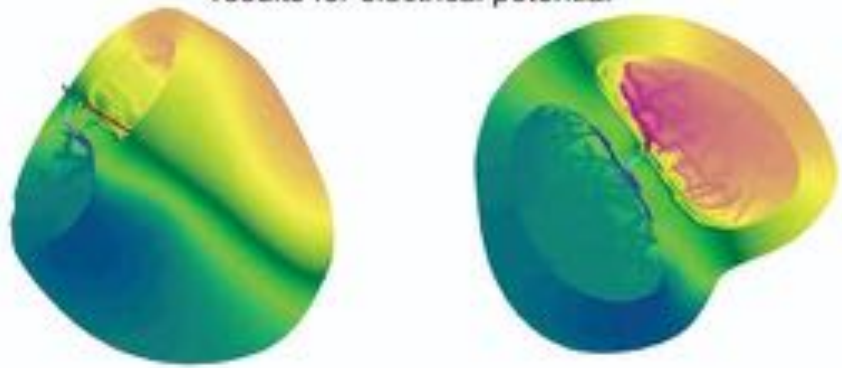


Drug distribution through coronary arteries

detailed model of left and right ventricular with Purkinje fibers



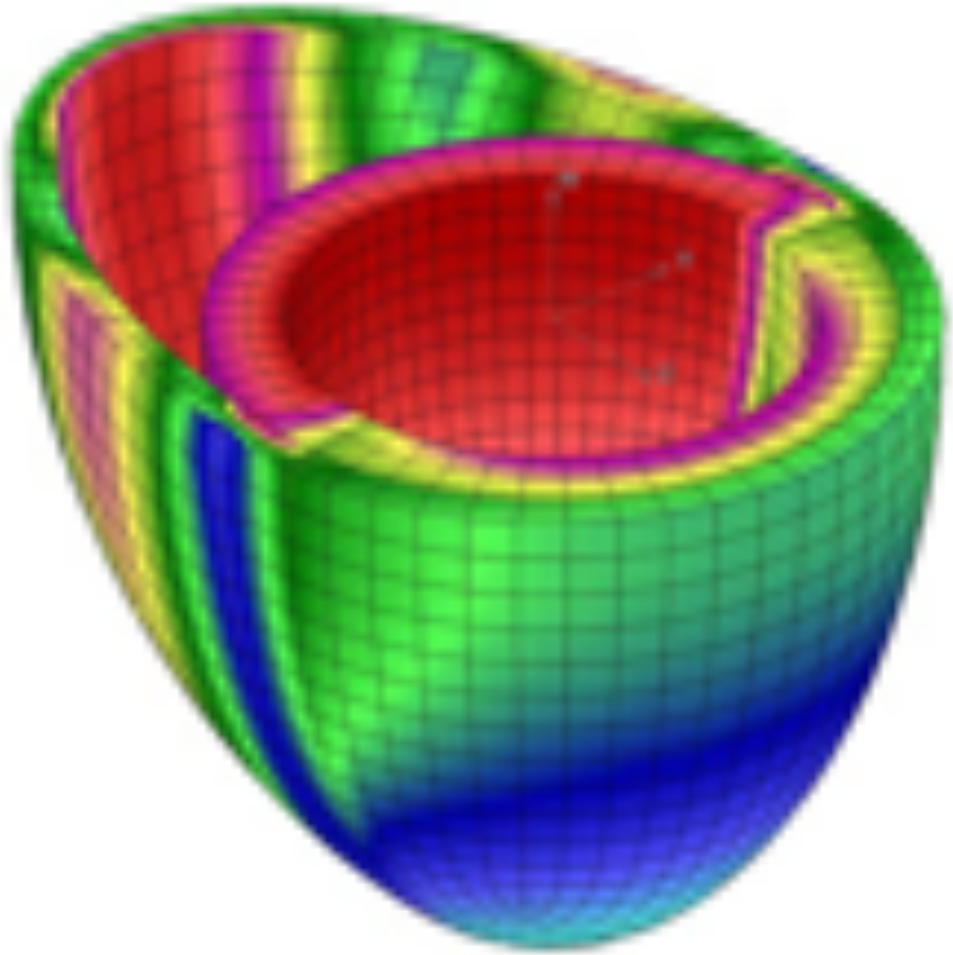
c) results for electrical potential



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

SILICOFCM

Fluid-solid interaction-PAK



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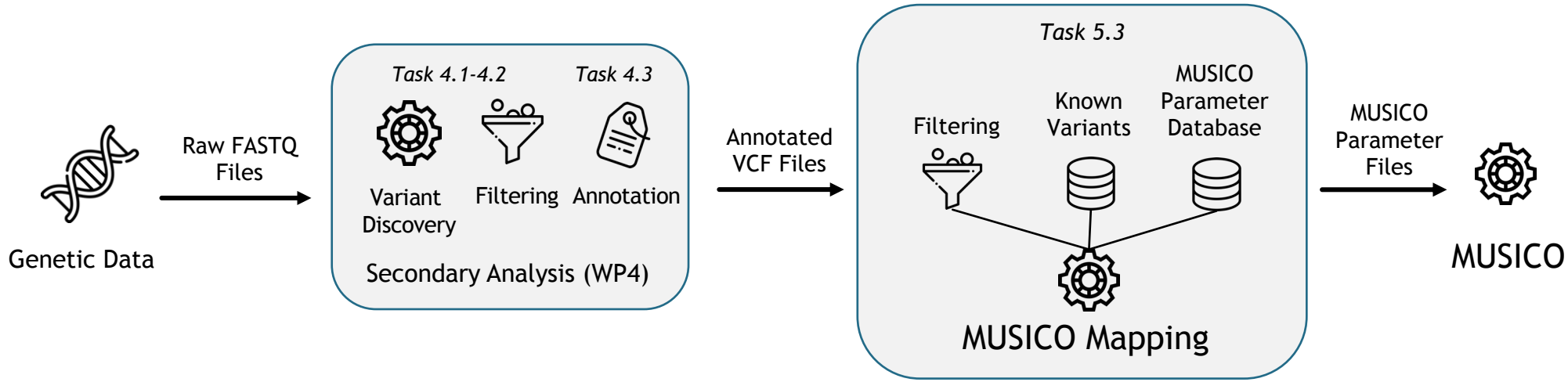
Linking bioinformatics and MUSICO

- The identified variants as part of Task 4.2 will be annotated with the annotation pipeline developed as part of Task 4.3.
- The annotated variants will be then filtered once more to reduce the variant call sets to variants of interest to MUSICO platform.
- The filtered mutations of interest then will be converted to a set of physiological parameters which will be the input for the MUSICO Platform.
- The associated tools were prepared during first 12 months, and corresponding databases will be populated and tested with known variants and experimentally determined associated parameters in the upcoming 6 months.



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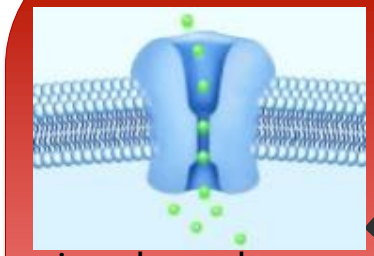
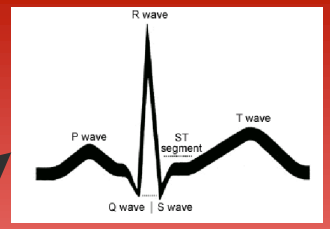
The Heart Physiology as an Electro-Mechanic System

Electrophysiology

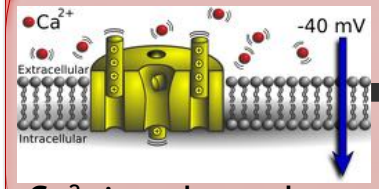


ion channels



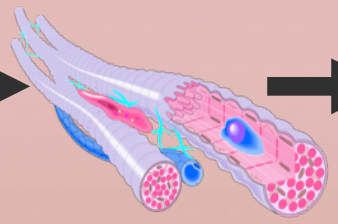
ventricles

electrocardiogram

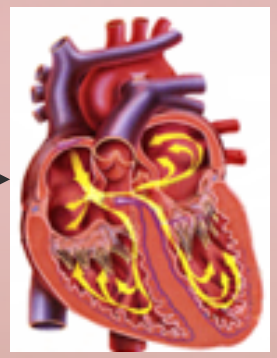


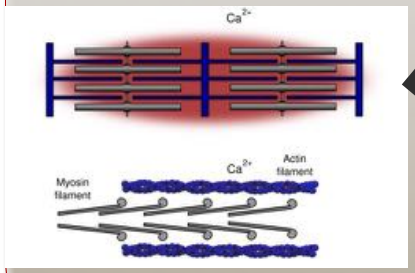
Ca^{2+} ion channels

whole cell



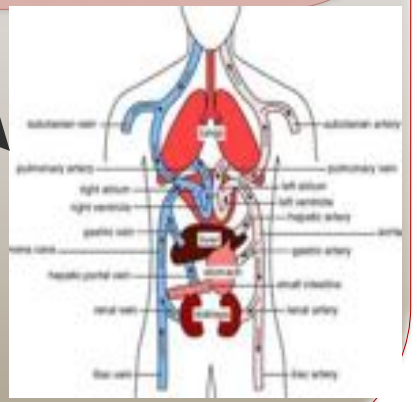
myocardium





sarcomere

Biomechanics



circulation

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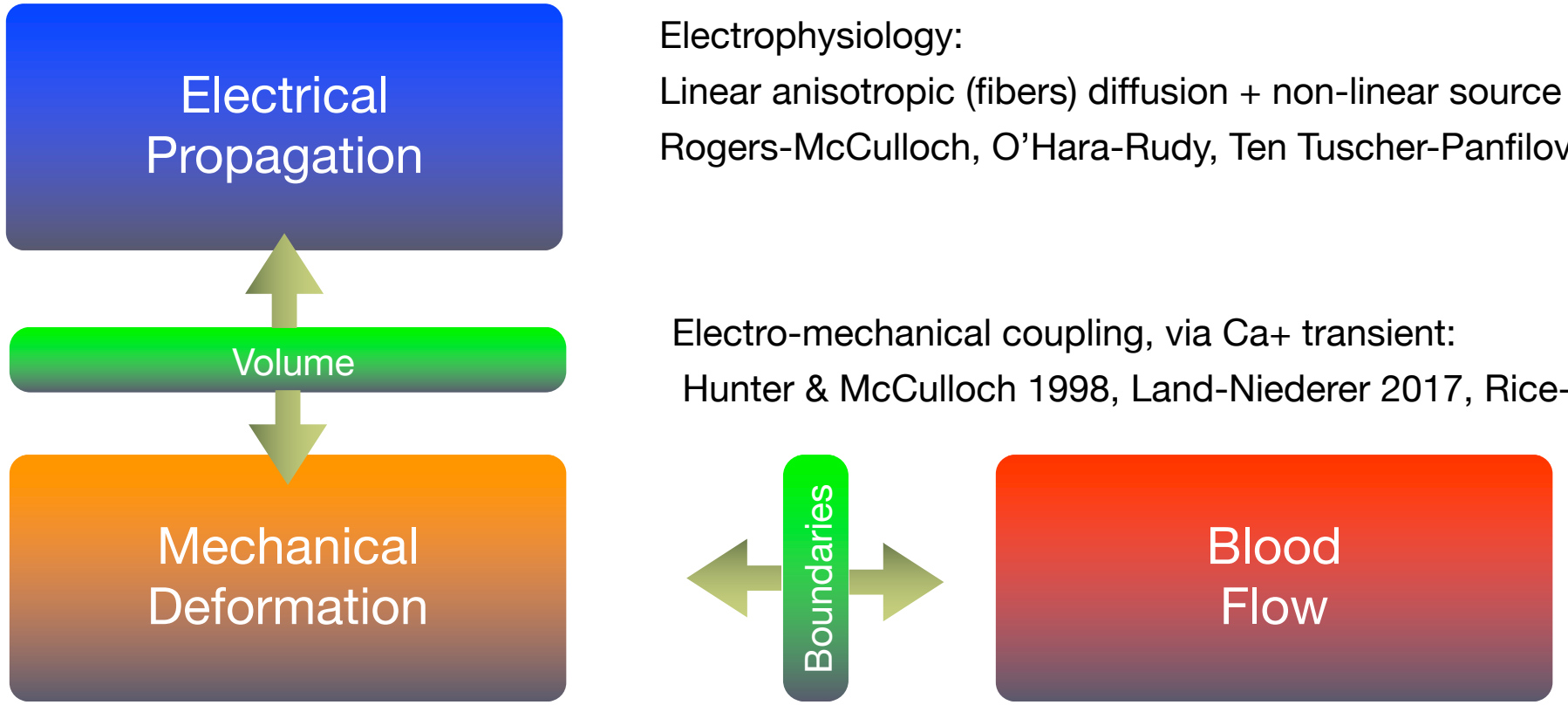
Fluid-Electro-Mechanic Cardiac Model - The Heart as a Multi-Physics Coupled System



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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SILICOFCM

Fully Coupled Electro-Mechanic-Fluid simulation

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

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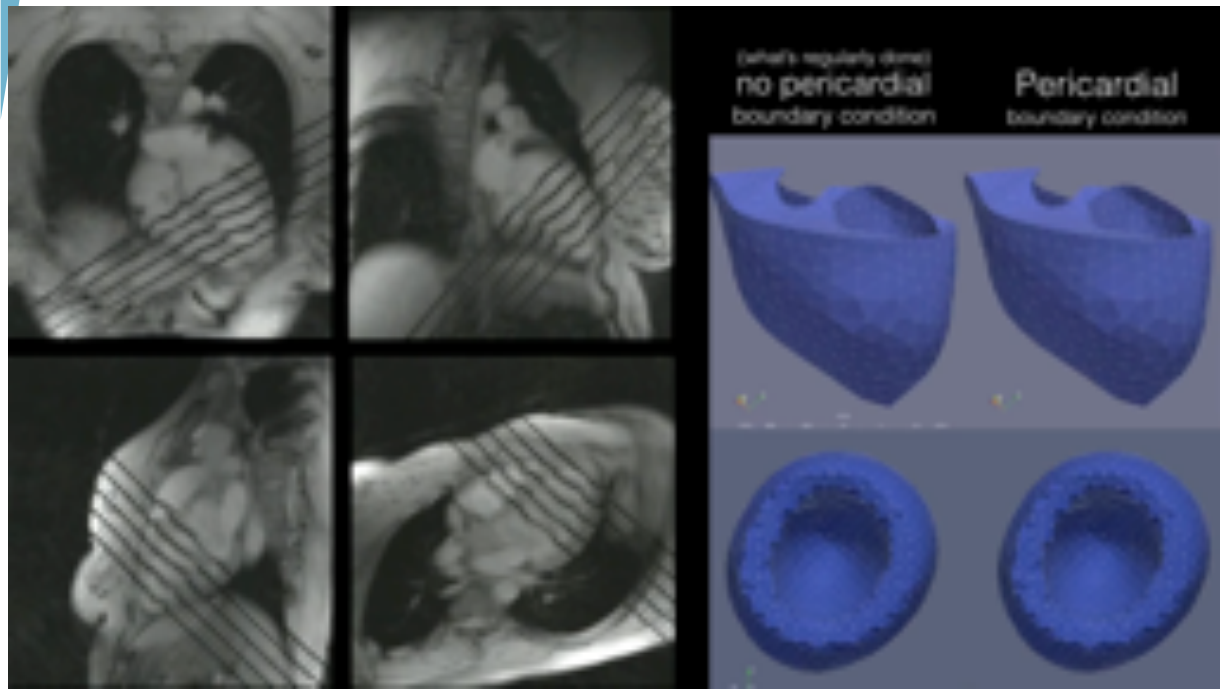
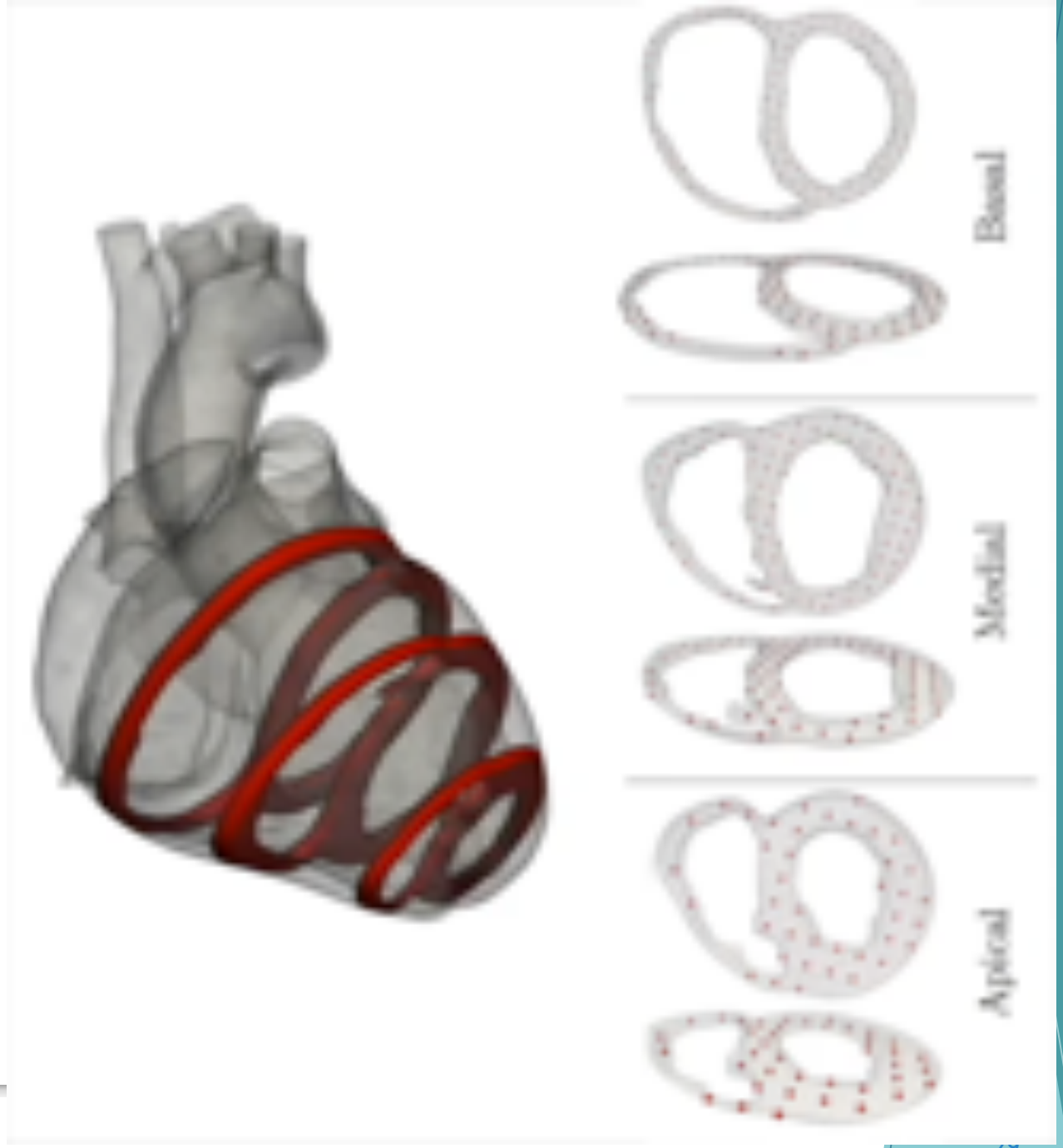
SILICOFCM

Boundary Conditions and Physiological motion





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SILICOFCM

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

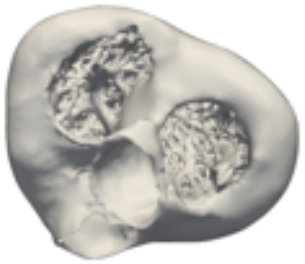
Endocardial structures included are ≥ 1 mm² cross-section

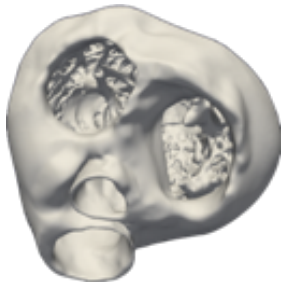
AUTODESK MESHMIXER

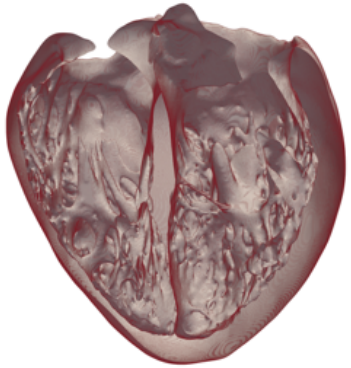
Fiji Is Just ImageJ

Seg3D

ReMESH

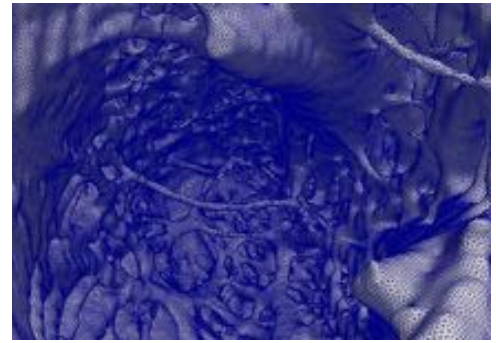




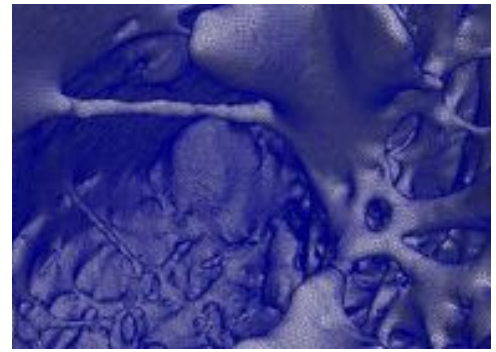


Biventricular Detailed Octree Volumetric Meshes

MAXIMUM ELEMENT SIDE LENGTH: 0.4 mm



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

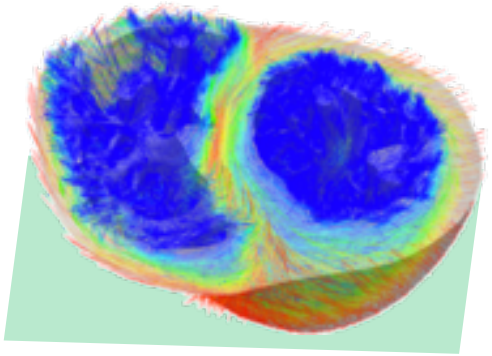


n° elements: 65.501.799
Volume: 299.2 cm^3
n° points: 11.416.445

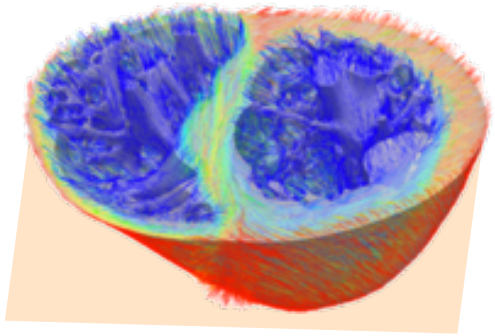
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

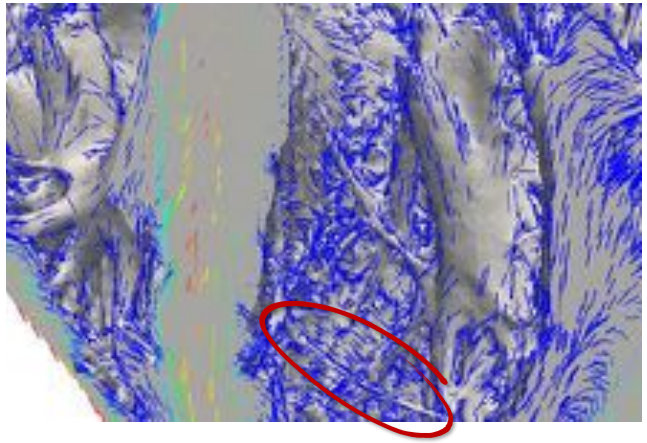
Fiber orientations

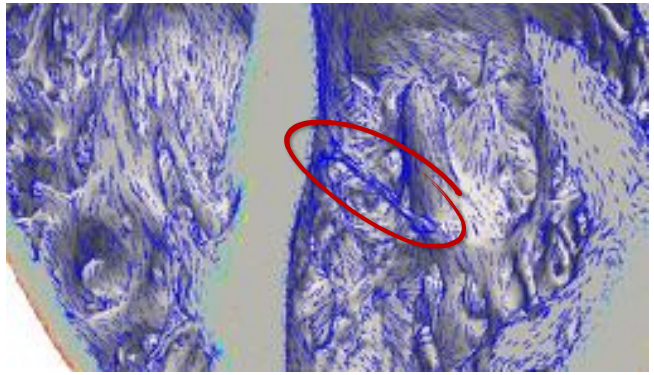
- *Male Heart*



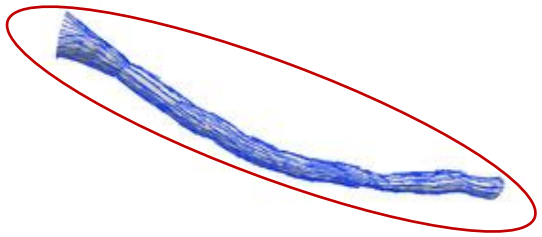
- *Female Heart*

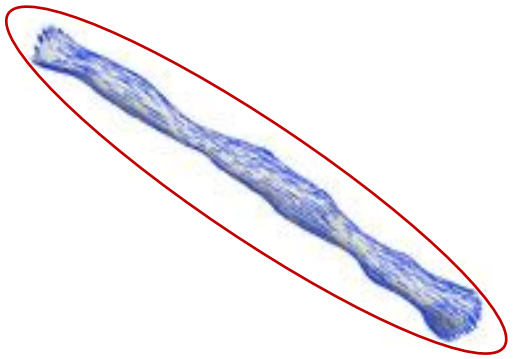






False Tendons





A Rule-Based Method to Model Myocardial Fiber Orientation for Simulating Ventricular Outflow Tract Arrhythmias. Doste et al. FIMH 2017

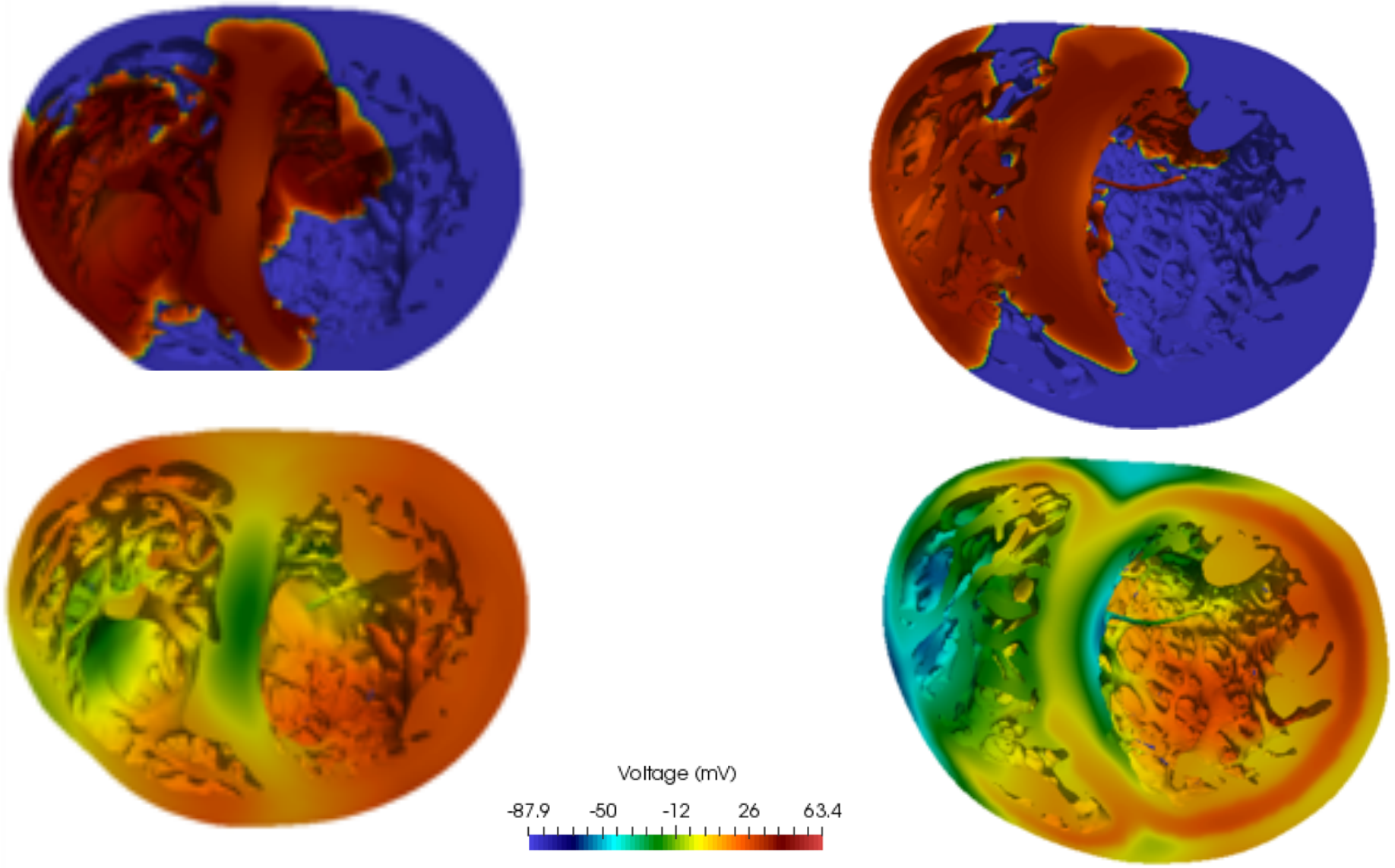
Universitat Pompeu Fabra Barcelona

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

SILICOFCM

Female Phenotype

Male Phenotype



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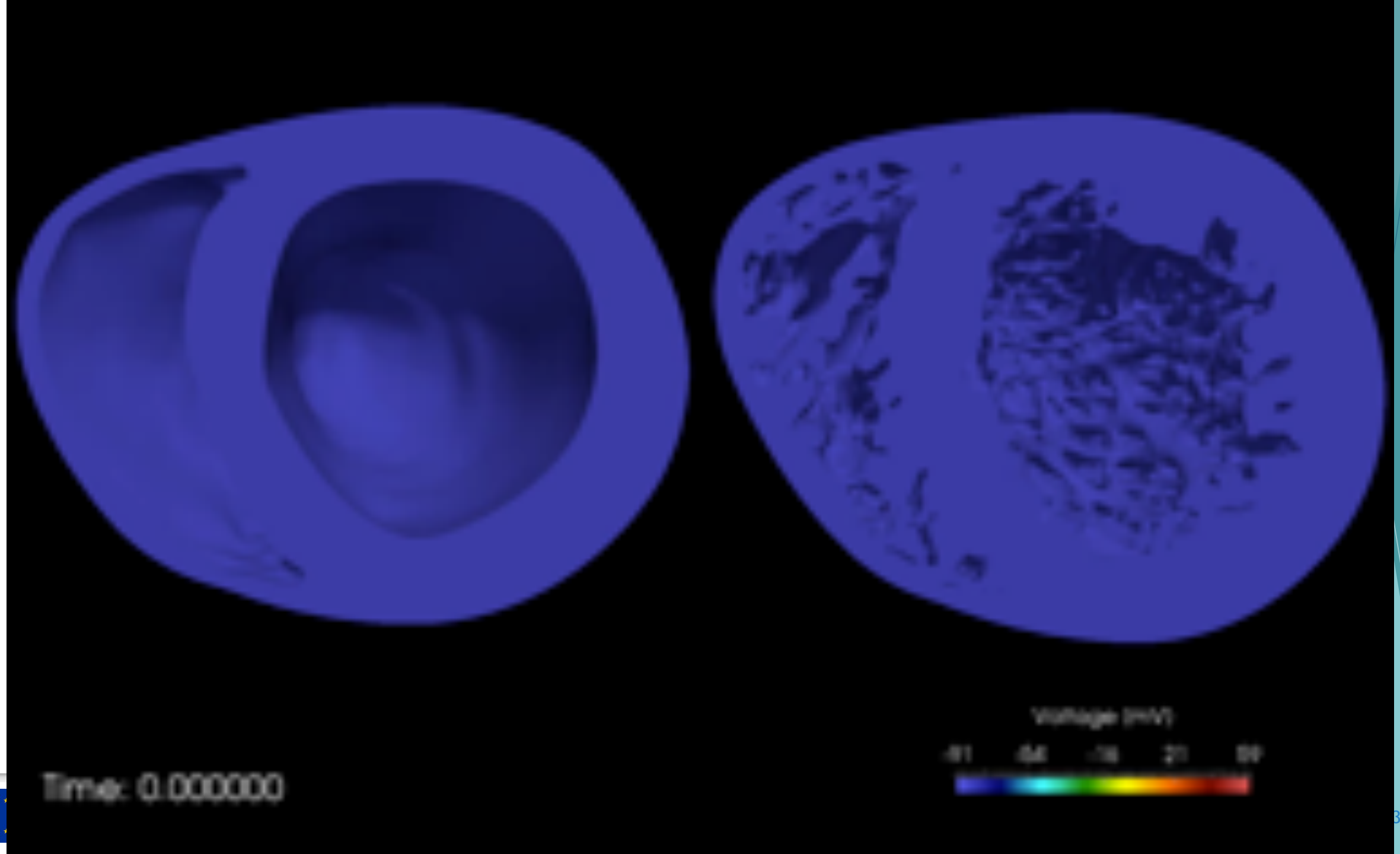
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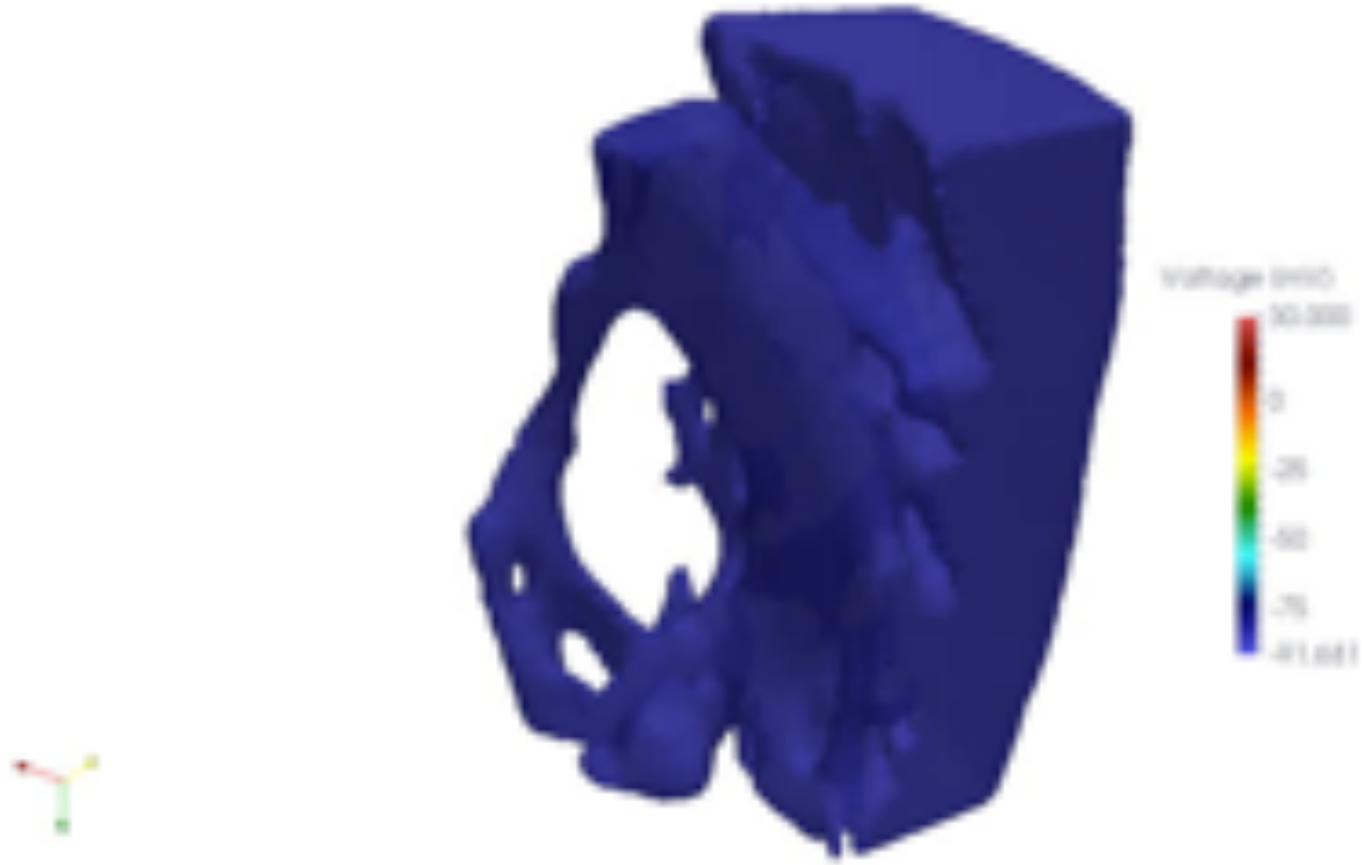
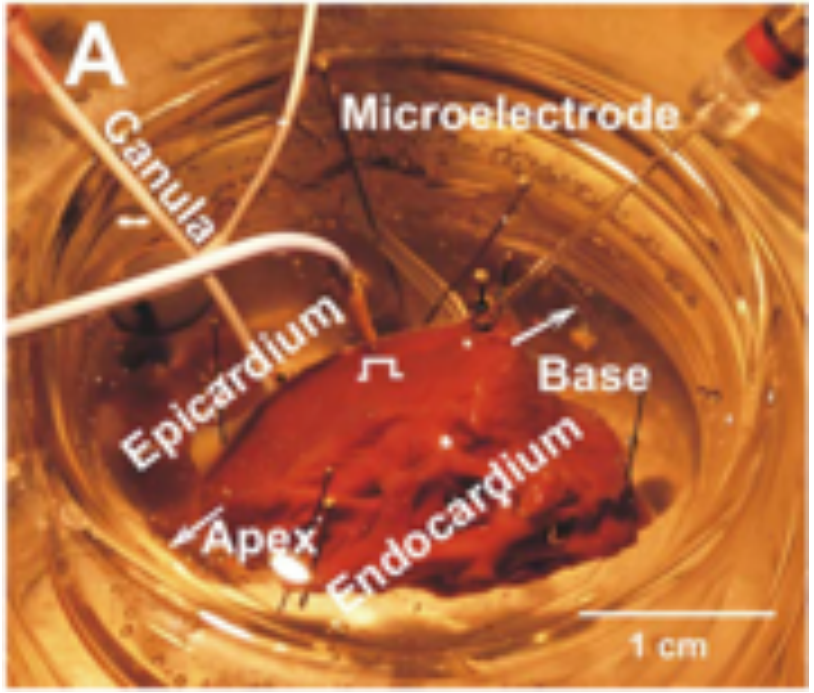
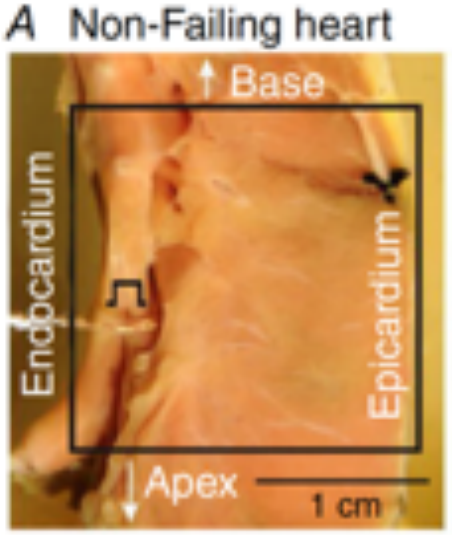
Impact of endocardial structures on electro-mechanics

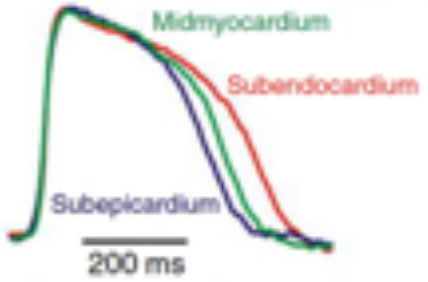


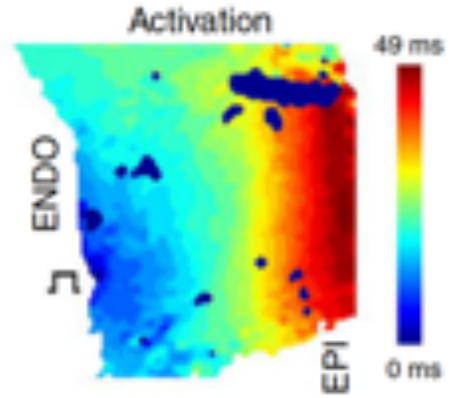
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

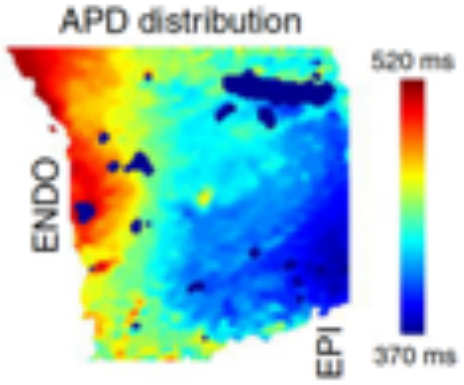
Human Ventricular Wedge Preparation







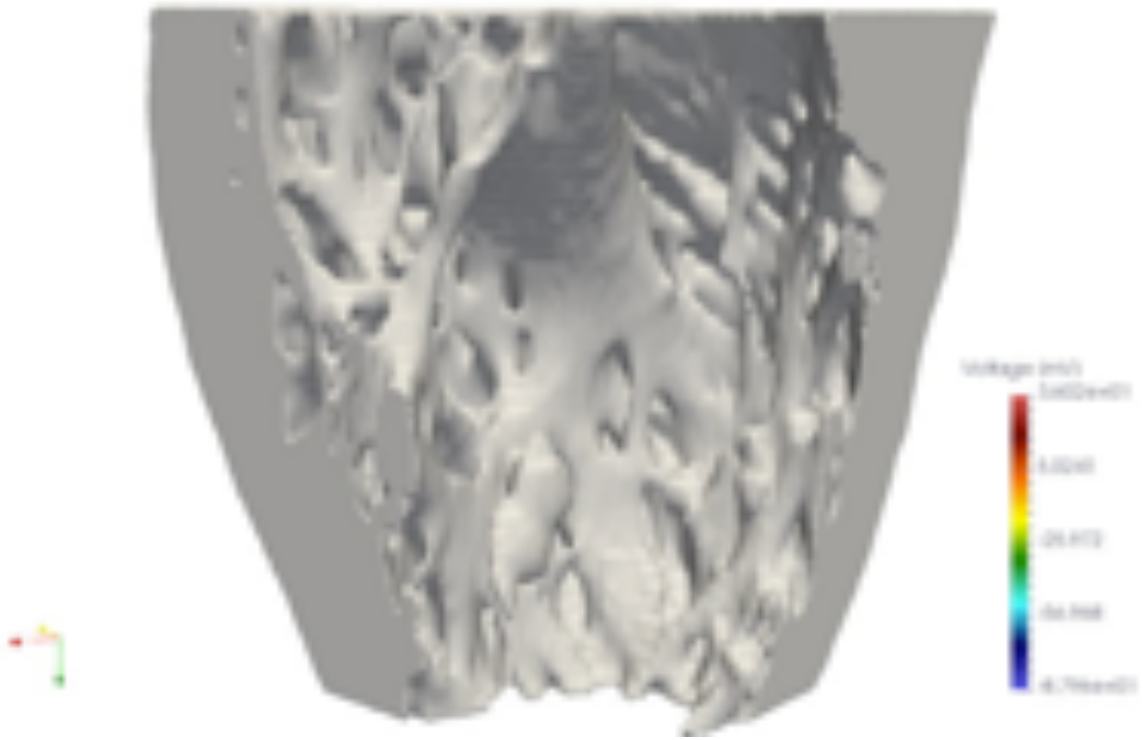




This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

SILICOFCM

Human Cardiac Wedge Preparation



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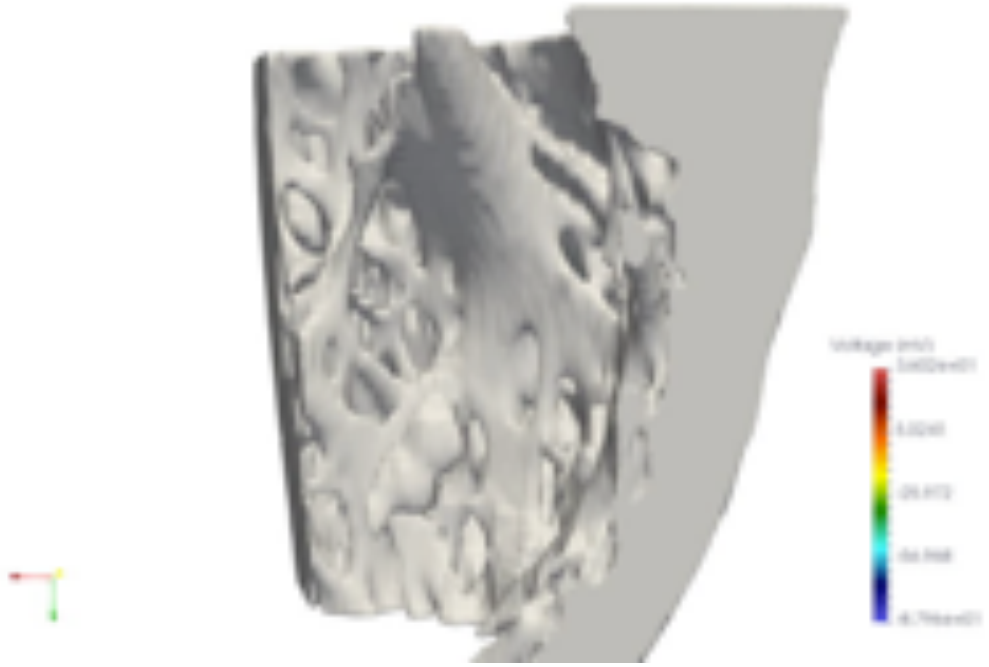
Nodal points: 2,480,801
48 cores, 2 hrs
260 ms



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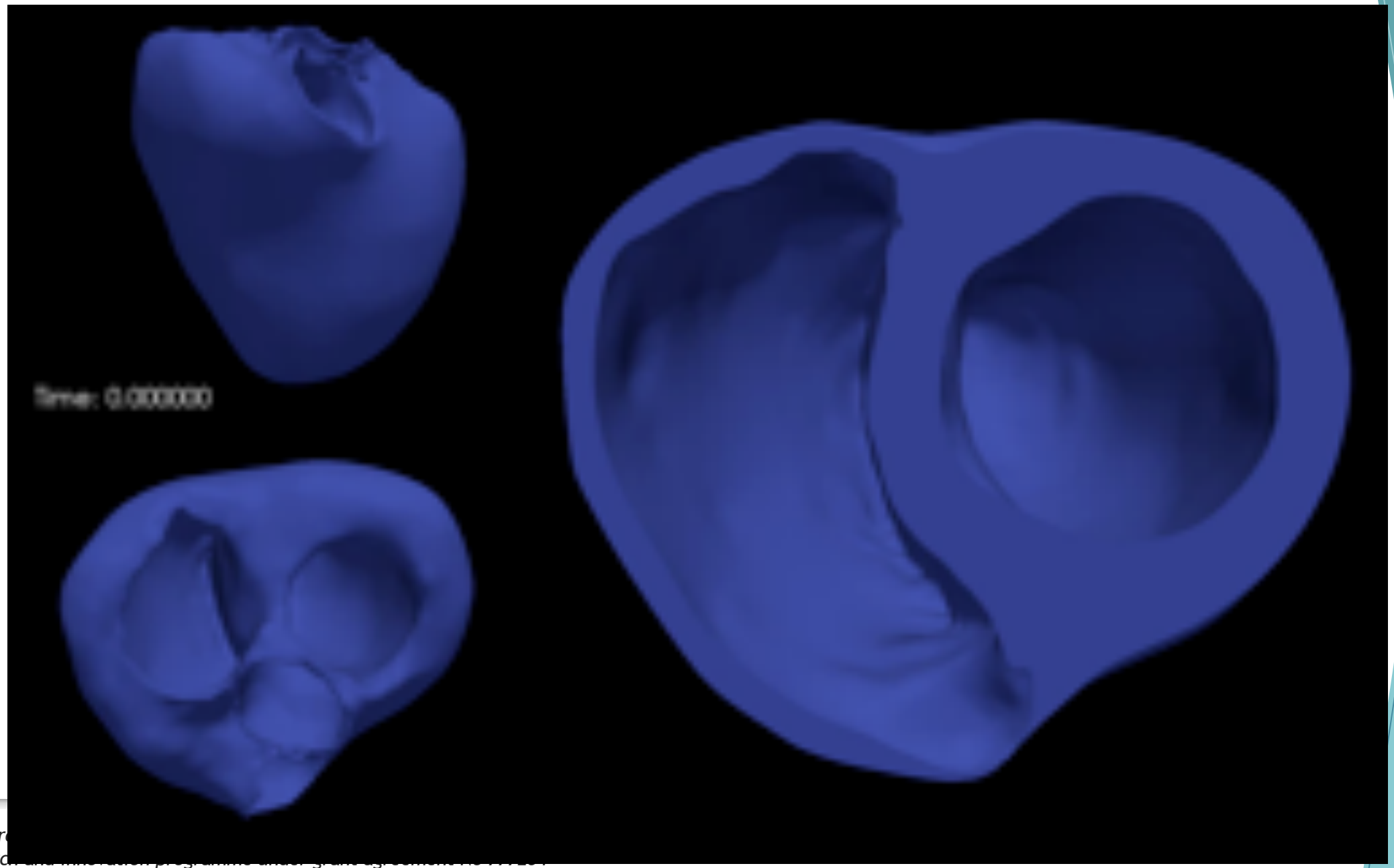
ELECTROPHYSIOLOGY SUBJECT-SPECIFIC SIMULATIONS



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research and innovation programme under grant agreement No