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

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

SILICOFCM Concept

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

3D IMAGE SEGMENTATION tool

USER 2: Pharmaceutical company

USER 3: Researcher

Virtual experiments database

BIOINFORMATICS tool

Virtual population database

DATA ANALYTICS tool

RISK STRATIFICATION

Finite element solver (ALYA, PAK)

Drug efficacy

Cardiomyopathy disease progression

USER 1: Medical doctor

Experiments

MUSICO tool

Virtual population database

Patient data (genetic, biological, pharmacologic, clinical, imaging and patient specific cellular aspects)
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Scenario 2

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

3D IMAGE SEGMENTATION tool

Virtual population database

BIOINFORMATICS tool

Data analytics tool

Drug efficacy

Finite element solver (ALYA, PAK)

Virtual experiments database

Experiments

User 2: Pharmaceutical company

Drug efficacy

Cardiomyopathy disease progression

MUSICO tool

Experiments

Scenario 2

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Scenario 3

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

3D IMAGE SEGMENTATION tool

Virtual population database

Virtual experiments database

USER 3: Researcher

MUSICO tool

BIOINFORMATICS tool

DATA ANALYTICS tool

RISK STRATIFICATION

Finite element solver (ALYA, PAK)

Drug efficacy

Cardiomyopathy disease progression

Experimental database

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**SILICOFCM Impact**

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

**SILICOFCM**
WPs Interaction
Main objective

To collect and analyse the state-of-the-art technologies, user requirements and hardware requirements for innovative SILICOFCM Reference Architecture.
WP2 Protein and cell data, Imaging processing

Leader UNIKENT

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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Clinical retrospective and prospective studies

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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**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
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)
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
Main objective

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

Main objective

- To promote the widespread utilisation and exploitation of the project results
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Penetration of Fast (α) and Slow (β) Myosin Isoforms

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

Effect on Hill Coefficient and Calcium Sensitivity

<table>
<thead>
<tr>
<th>Isoform Mixture</th>
<th>Hill Coeff</th>
<th>pC₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% α 0% β</td>
<td>2.302</td>
<td>5.890</td>
</tr>
<tr>
<td>90% α 10% β</td>
<td>2.342</td>
<td>5.899</td>
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<tr>
<td>50% α 50% β</td>
<td>2.531</td>
<td>5.933</td>
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<tr>
<td>10% α 90% β</td>
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<td>5.966</td>
</tr>
<tr>
<td>0% α 100% β</td>
<td>2.889</td>
<td>5.973</td>
</tr>
</tbody>
</table>
Fit to Kreutziger Experiments - Rat Trabeculae 100% Mutants

Kreutziger - Predicted Penetrance (Rat Trabeculae)
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
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

c) Detailed model of left and right ventricular with Purkinje fibers
Fluid-solid interaction-PAK
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.
The Heart Physiology as an Electro-Mechanic System

**Electrophysiology**

- Ion channels
- Whole cell
- Myocardium
- Ventricles
- Electrocardiogram

**Biomechanics**

- Sarcomere
- 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:

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

ALE + Immersed Boundaries
Navier -Stokes for Incompressible Flow

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Fully Coupled Electro-Mechanics-Fluid simulation

Number of elements: 4M total
240 cores, 12 hrs, 400 ms
Boundary Conditions and Physiological motion
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High Resolution MRI of Male and Female Human Hearts

Segmentation and Surface representation
Endocardial structures included are ≥ 1 mm² cross-section

Biventricular Detailed Octree Volumetric Meshes

MAXIMUM ELEMENT SIDE LENGTH: 0.4 mm

Male Heart
Female Heart

Human Biventricular Geometry Reconstruction

Human Biventricular Geometry Reconstruction

Segmentation and Surface representation
Endocardial structures included are ≥ 1 mm² cross-section

Biventricular Detailed Octree Volumetric Meshes

MAXIMUM ELEMENT SIDE LENGTH: 0.4 mm

n° elements: 86,318,429
Volume: 394.2 cm³
n° points: 14,994,563

n° elements: 65,501,799
Volume: 299.2 cm³
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

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

Male Phenotype

Voltage (mV)
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15/6/2018 Kragujevac, Kick-off meeting
Impact of endocardial structures on electro-mechanics
Human Ventricular Wedge Preparation
Human Cardiac Wedge Preparation

Number of elements: 13,807,755
Nodal points: 2,480,801
48 cores, 2 hrs
260 ms
ELECTROPHYSIOLOGY SUBJECT-SPECIFIC SIMULATIONS

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