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Computer modelling and artificial intelligence with big data for better diagnostics and therapy of cardiovascular disease

Abstract: In silico clinical trials are the future of medicine and virtual testing and simulation are the future of medical engineering. The use of a computational platform can reduce costs and time required for developing new models of medical devices and drugs. The computational platform in different projects, such as SILICOFCM, was developed using state-of-the-art finite element modelling for macro simulation of fluid-structure interaction with micro modelling at the molecular level for drug interaction with the cardiac cells. SILICOFCM platform is used for risk prediction and optimal drug therapy of familial cardiomyopathy in a specific patient.
STRATIFYHF project is to develop and clinically validate a truly innovative AI-based Decision Support System for predicting the risk of heart failure, facilitating its early diagnosis and progression prediction that will radically change how heart failure is managed in both primary and secondary care. This rapid expansion in computer modelling, image modalities and data collection, leads to a generation of so-called “Big Data” which are time-consuming to be analyzed by medical experts.
In order to obtain 3D image reconstruction, the U-net architecture was used to determine geometric parameters for the left ventricle which were extracted from the echocardiographic apical and M-mode views. A micro-mechanics cellular model which includes three kinetic processes of sarcomeric proteins interactions was developed. It allows simulation of the drugs which are divided into three major groups defined by the principal action of each drug.
The presented results were obtained with the parametric model of the left ventricle, where pressure-volume (PV) diagrams depend on the change of Ca2+. It directly affects the ejection fraction. The presented approach with the variation of the left ventricle (LV) geometry and simulations which include the influence of different parameters on the PV diagrams are directly interlinked with drug effects on the heart function. It includes different drugs such as Entresto and Digoxin that directly affect the cardiac PV diagrams and ejection fraction.
Computational platforms such as the SILICOFCM and STRATIFYHF platforms are novel tools for risk prediction of cardiac disease in a specific patient that will certainly open a new avenue for in silico clinical trials in the future.

Keywords: heart modelling, fluid-structure interaction, machine learning, big data, drug modelling

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1. Introduction

Cellular and molecular biology have a very strong influence on our understanding of the structure and function of the heart at the microscopic level. At the macroscopic level, the heart functions as a pump that continuously pumps blood throughout the human body. It is necessary to apply an interdisciplinary approach in order to understand the integrated function of the heart, which includes electricity, physical chemistry, solid mechanics, and fluid dynamics (multiphysics simulation). To better understand different events that occur during a cardiac cycle, both microscopic and macroscopic mechanisms should be taken into account in the development of an integrated model.

Familial cardiomyopathies (FCM) are most commonly diagnosed, or progress of the disease is monitored through in vivo imaging, with either echocardiography or, increasingly, cardiac magnetic resonance imaging (MRI). The treatment of symptoms of FCM by established therapies could only in part improve the outcome, but novel therapies need to be developed to more fundamentally affect the disease process and time course.

It is very important to use a detailed, complex, and anatomically accurate model of the whole heart electrical activity which requires extensive computation times, dedicated software, and even the use of supercomputers (Gibbons et al., 2006, Pullan et al., 2005). We have recently developed a methodology for a real 3D heart model by using the linear elastic and orthotropic material model based on Holzapfel experiments. Using this methodology, we can accurately predict the transport of electrical signals and displacement field within heart tissue (Kojic et al., 2019). Muscles in the body except the heart muscle are activated by electrical signals, transmitted from the nervous system to muscle cells, affecting the change of the cell membranes potentials. Additionally, calcium current and concentration inside muscle cells are the main cause of generating active stress within muscle fibers. Clinical validation in humans is very limited since simultaneous whole heart electrical distribution recordings are inaccessible for both practical and ethical reasons (Trudel et al., 2004). The rapid development of information technologies, simulation software packages and medical devices in recent years provides the opportunity for collecting a large amount of clinical information. Creating comprehensive and detailed computational tools has become essential to process specific information from the abundance of available data. From the point of view of physicians, it becomes of paramount importance to distinct "normal" phenotypes from the appearance of the phenotype in a specific patient in order to estimate disease progression, therapeutic responses and future risks. Recently developed computational models have significantly improved integrative understanding of the heart muscle behaviour in HCM and DCM cardiomyopathies. The development of novel integrative modelling approaches could be an effective tool in distinguishing the type and severity of symptoms in, for example, multi-genic disorder patients, and assess the degree to which normal physical activity is impaired.

Some of the main problems in developing fast and accurate algorithms for automatic LV segmentation in apical images are the presence of speckle, low signal to noise ratio, weak echoes etc., which commonly occur in ultrasound images. Additional-

ly, there is no simple connection between the pixel intensity values in images and physical characteristics of the tissue of interest, which makes thresholding algorithms impossible to use in segmentation in ultrasound images (Moradi et al., 2019). As a result, many authors tried to address the problem of segmentation using different approaches, including active shape, active contours, appearance methods, as well as machine learning-based methods (Noble & Boukerroui, 2006). Their main focus is the endocardial border detection on one echocardiography image frame. The literature shows that the level-set approaches are not that sensitive to initial conditions, but instead their main limitations are the imaging conditions. In contrast, deformable templates are robust to imaging conditions, however they are very sensitive to the initialization conditions (Bosch et al., 2002).

As a result, Big Data technologies contain new frameworks for processing medical data playing an important role in data management, organizing, and analysis through the use of machine learning and deep learning approaches (Kouanou et al., 2018). It also enables fast data access via the NoSQL database (Kouanou et al., 2018). In the area of medical image analysis, due to significant improvement in image collecting equipment, the data is relatively huge (going to Big Data), which makes image analysis challenging (Razzak, Naz & Zaib, 2018). It is said that due to digitalization of medical repositories in hospitals, as well as the use of medical images, digital medical archives size is growing at exponential rate (Ashraf et al., 2020). According to the McKinsey Global Institute, if US healthcare uses Big Data creatively and efficiently, the sector could generate more than $300 billion in value per year. Two-thirds of the value would be realized through lowering US healthcare spending (Belle et al., 2015). This fast expansion in medical imagery and modalities necessitates considerable and time-consuming efforts by medical experts, who are subjective, prone to human error, and there are also interpersonal differences. Using machine learning techniques to automate the diagnosis process is an alternative response to aforementioned challenges; however, typical machine learning methods are unable to cope with complex problems (Razzak, Naz & Zaib, 2018). The successful combination of high-speed computers with machine learning promises the ability to cope with large amounts of medical image data for accurate and fast diagnosis (Razzak, Naz & Zaib, 2018). In recent years, machine learning (ML) and artificial intelligence (AI) have advanced quickly, finding their role in medical image processing, computer-aided diagnosis, image fusion, registration, image segmentation, as well as image-guided treatment. ML techniques extract information (called features) from images and effectively perform decision making (Razzak, Naz & Zaib, 2018).

The main focus of the SILICOFCM project (www.silicofcm.eu) has been on multiscale modelling of familial cardiomyopathy, taking into consideration a comprehensive list of patient-specific features such as genetic, biological, pharmacologic, clinical, imaging and cellular aspects. The main result of the project is the in silico clinical platform with biomechanics of the heart as its main part. The platform is developed using state-of-the-art finite element modelling for macro simulation of fluid-structure interaction with micro modelling at the molecular level for drug interaction with

the cardiac cells. The platform can be used for risk prediction and optimal drug therapy of familial cardiomyopathy in a specific patient. The overarching aim of STRATIFYHF project is to develop and clinically validate a truly innovative AI-based Decision Support System (DSS) for predicting risk of heart failure (HF), facilitating its early diagnosis and progression prediction that will radically change how HF is managed in both primary and secondary care. The DSS integrates patient-centred data obtained using existing and novel technologies, a digital patient library and AI-based algorithms and computational modelling.

2. Method

2.1 Image reconstruction from echocardiography

The proposed methodology for echocardiography image reconstruction is divided into two sections: the first section includes the methods used to analyze apical view, while the second one includes the methods used to analyze M-mode view. A detailed description is provided in Fig. 1. DICOM image format is used as the input to the system. The end user (expert) selects which view is best represented by the image and feeds it to the algorithm.

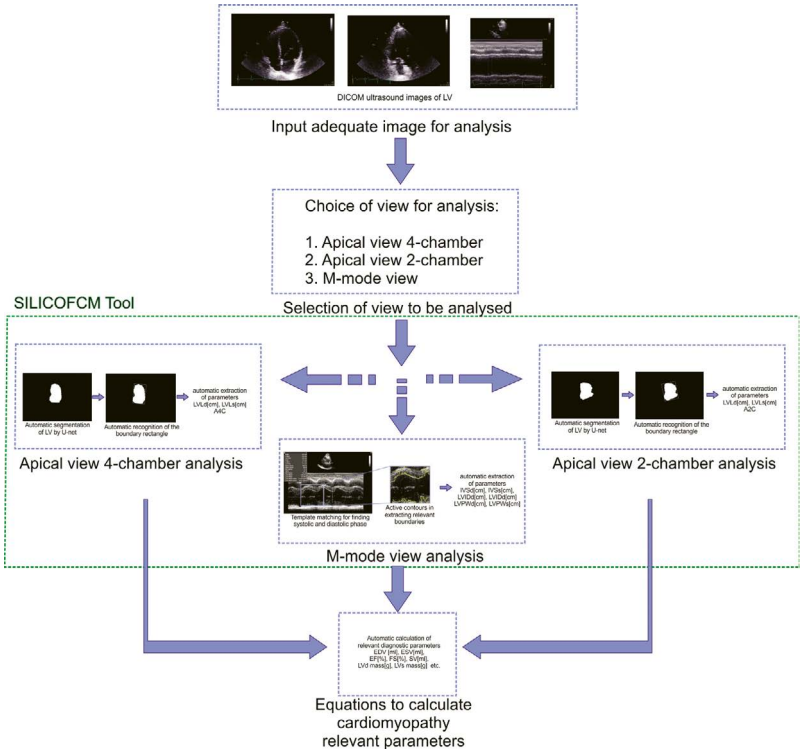

Fig. 1 Description of the proposed methodology for the automatic heart ultrasound segmentation and geometric parameter extraction.

Three alternatives are provided by the SILICOFCM tool: 4-chamber, 2-chamber, or M-mode. This tool will further analyze the images depending on the view mode:

1. **Apical 4-chamber view analysis** includes segmentation of the LV using the U-net previously trained and calculating the bordering rectangle as shown in Fig. 1 (left side), based on which parameters LVLd [cm] and LVLs [cm] A4C will be calculated. The user should define if the view represents the systolic or diastolic phase.
2. **Apical 2-chamber view analysis** includes segmentation of the LV using the U-net previously trained and calculating the bordering rectangle as shown in Fig. 1 (right side), based on which parameters LVLd [cm] and LVLs [cm] A2C will be calculated. The user should define if the view represents the systolic or diastolic phase.
3. **M-mode view analysis** includes bordering of the characteristic areas of the LV – septum in diastole, diameter in diastole, LV wall in diastole, septum in systole, diameter in systole and LV wall in systole (Fig. 1 - middle). Based on these areas, parameters IVSd [cm], IVSs [cm], LVIDd [cm], LVIDs [cm], LVPWd [cm], LVPWs [cm] will be calculated. The user should define that the view is M-mode.

If the user has all three views in systolic and diastolic phase available (which should be the case when imaging the patient), then all relevant parameters are calculated from these three views and automatic calculation of relevant cardiomyopathy diagnostic parameters can be further performed (i.e. – EF [%], ES [%], SV [ml], LVd mass [g], LVs mass [g], etc.).

2.2 Big Data Technologies for Medical Image Processing

Parallel computing is detected as critical infrastructure for managing Big Data. It can perform analysis on a cluster of devices or supercomputers at the same time. Big Data technology with Artificial Intelligence (AI) and massively parallel computing can be used for a revolutionary way of prediction and personalized medicine (Dilsizian & Siegel, 2014). Novel parallel computing models, such as Google's MapReduce (Dean & Ghemawat, MapReduce: simplified data processing on large clusters, 2008), have been proposed in recent years for a new large data infrastructure. Apache has launched Hadoop (White, 2015), an open-source MapReduce software for distributed data management. Concurrent data access to clustered servers is supported via the Hadoop Distributed File System (HDFS). Hadoop-based services may also be thought of as cloud computing platforms, allowing for centralized data storage as well as remote access through the Internet. As such, cloud computing is a revolutionary concept for distributing customizable computational resources across a network (Armbrust, Fox & Griffith, 2010), and it may function as an infrastructure, platform, and/or software to provide an integrated solution. Furthermore, cloud computing may increase system speed, agility, and flexibility by eliminating the need to maintain hardware or software capacity and necessitating less resources

for system maintenance, such as installation, setup, and testing. Cloud technologies are at the heart of many emerging Big Data applications (Luo, Wu, Gopukumar, & Zhao, 2016). Additionally, Hadoop and Spark frameworks have been identified as optimal and efficient architecture for biomedical image analysis (Kouanou et al., 2018).

In addition, High Performance Computing (HPC) uses parallel processing and advanced programs, or software packages speed up massive calculations. In that sense, Finite Element Method (FEM), which represents a continuum method for very powerful scientific computation analysis, strongly relies on advanced computer technology and HPC. Traditional database and software techniques cannot be used for these large-scale computations (Demchenko, Grosso, De Laat, & Membrey, 2013). High Performance Computing (HPC) can be used in medicine contained in Big Data (Lavignon et al., 2013). Massive multiscale computation with multiscale material models, or finite element computation with adaptive mesh refinement can be run only on supercomputers with Big Data on parallel disk systems (Parashar, 2014). A detailed, complex, and anatomically accurate model of the whole heart electrical activity which requires extensive computation times, and the use of supercomputers are already established in the literature (Gibbons Kroeker, Adeeb, Tyberg, & Shrive, 2006; Kojic et al., 2019). The authors of

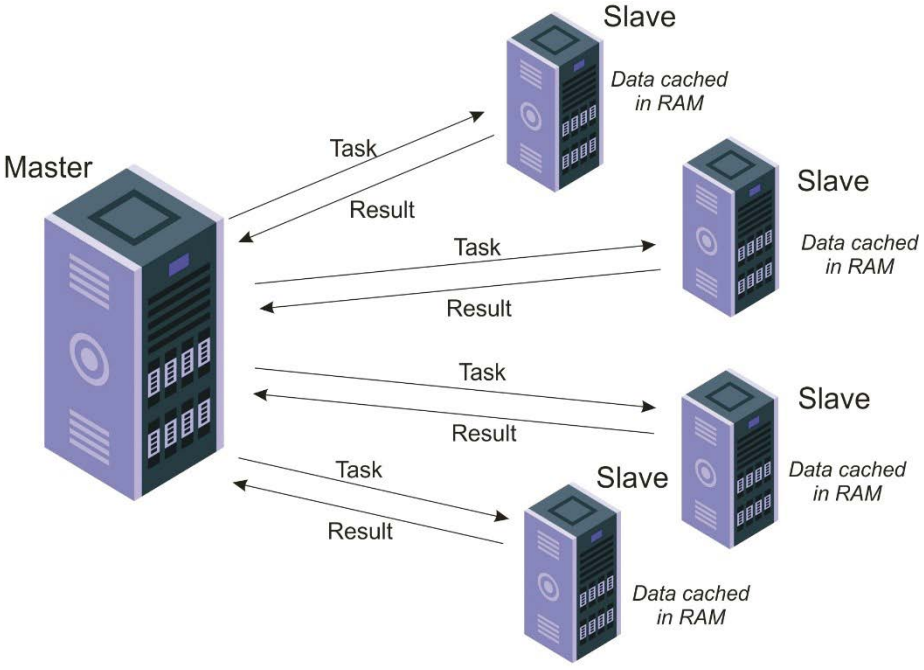

Fig. 2. Job execution using Spark technologies – one master cluster and four slaves

this paper have recently developed a methodology for a real 3D heart model, by using the linear elastic and orthotropic material model based on Holzapfel experiments. Using this methodology, the transport of electrical signals and displacement field within heart tissue can be accurately predicted (Filipovic et al., 2022). Clinical validation in humans is very limited since simultaneous whole heart electrical distribution recordings are inaccessible for both practical and ethical reasons (Filipovic et al., 2022).

On the other hand, Apache Spark is a distributed computing platform that has become one of the most powerful frameworks in the Big Data situation. Spark provides a consistent and comprehensive framework for managing the needs for Big Data processing using a range of datasets (graph data, image/video data, text data, and so on) from various sources (batch, real-time streaming) (Tchito Tchapga et al., 2021). According to its designers, the Spark framework was intended to address the shortcomings of the Hadoop framework. In some cases, the Spark framework has shown to be quicker than Hadoop (more than 100 times in memory). Performance can be quicker than other Big Data technologies with advantages such as in-memory data storage and near real-time processing (Tchito Tchapga et al., 2021). The Spark framework can prepare data for iteration, query it frequently, and load it into memory. The main program (driver) in the Spark framework supervises many slaves (workers) and collects their results, whilst slaves' nodes read data partitions (blocks) from a distributed file system, run various computations, and write the results to disk (Fig. 2). This means that the master controls and assigns jobs to slaves.

Spark, like Hadoop, is built on parallel processing MapReduce, which seeks to process data in a simple and transparent manner across a cluster of computers. Spark enables SQL queries, streaming data, machine learning, and graph processing data in addition to Map and Reduce operations (Kouanou, et al., 2018). In Spark, program can occasionally run the algorithm on several clusters at the same time. Although the number of slaves can be increased due to dataset size, the increase in the number of slaves results in an increase in processing time.

2.3 Cellular model (Mijailovich-Prodanovic MP surrogate and drug model)

The finite element (FE) solvers require calculation of active tension and variable muscle stiffness in each element integration point over all finite elements. Moreover, a relatively fine FE mesh and, therefore, a large number of finite elements are required to precisely calculate the change of heart geometry during a heartbeat. On the other hand, calculation of instantaneous active tension and muscle stiffness by, for example, sliding filament cross-bridge models, requires a solution of partial differential equations (PDE) or Monte Carlo approaches (Mijailovich et al., 2019). Furthermore, coupling of FE solvers to simulate muscle function at the organ level (Mijailovich et al., 2021) with even simpler models, involving the solution of PDEs by the method of characteristics, requires extremely large computational memory and a prolonged time for the execution of simulations even if the simulations are limited to coarse FE meshes.

Parameters for the MP surrogate model were obtained through an automated process of parameter fitting based on a genetic algorithm. The goal was to minimize the root mean square error (RMSE) for obtaining the muscle prediction that would be the closest fit to the one provided by MUSICO Fiber (Mijailovich et al., 2021).

Since the relaxation period is generally harder to fit, RMSE was weighted, giving the fitness of the second part of force development a greater impact on the resulting error.

2.4 Drug testing workflow

The drug actions are different for treating a variety of symptoms associated with cardiomyopathies. In particular, drugs simulated using MUSICO (Mijailovich et al., 2021) are divided into three major groups or pathways defined by the principal action of each drug, such as the effect on modulating calcium transients or changing kinetics of contractile proteins. Each group consists of two subgroups based on a type of cardiomyopathy:

I Modulation of [Ca2+] transients

HCM – Disopyramide, which lowers peak and baseline levels of [Ca^{2+}] transient during twitch contractions,

DCM – Digoxin, which increases peak of [Ca^{2+}] transient during twitch contractions, but does not change time to peak and relaxation time,

The workflow for testing these types of drugs is shown in Fig. 3. The experimental observations in action potentials and changes in ionic currents are simulated using O'Hara-Rudy electro-physiological model that produces intracellular calcium transients as an input for MUSICO and MP surrogate models.

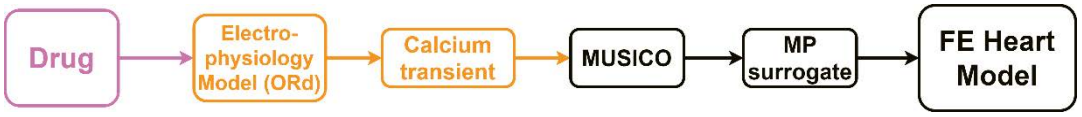

Fig. 3 Pathway 1: Drug action via modulation of calcium transients through changes in ionic currents or membrane properties.

II Changes in kinetic parameters

HCM – Mavacamten, which is associated with the regulation of kinetics rates of transition between disordered myosin detached states and ordered SRX state,
DCM – dATP, which modulates cross-bridge cycle rates,

The workflow for testing these types of drugs is shown in Fig. 4. The experimental observations in the experiments in vitro that quantify the effect of specific drug (dose) are used for the estimation of parameters for MUSICO and MP surrogate models.

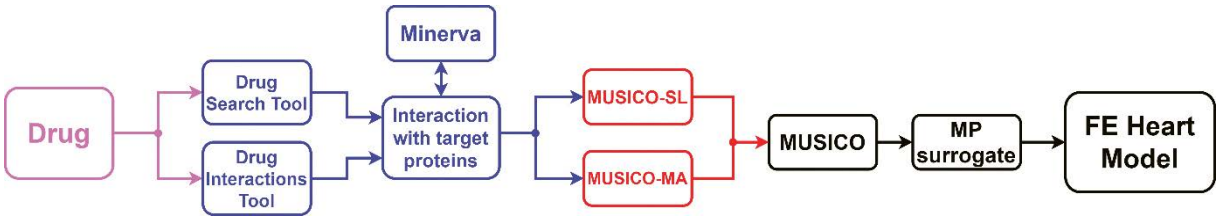

Fig. 4 Pathway 2: Drug action through changes in kinetics of contractile proteins.

Since drugs in groups I and II directly affect MUSICO and MP surrogate parameters, we were able to predict with our tools the outcome on force generation in sarcomeres during twitch contractions.

III Changes in macroscopic parameters

HCM – Entresto®, which acts on remodelling of heart ventricle walls and modulates the elasticity of blood vessels, typically reducing resistance to blood flow and improving cardiac output in HCM. The workflow for testing these types of drugs is shown in Fig. 5. The experimental observations in many clinical trials are used as an input for FE models yielding the precise model of Entresto® action.

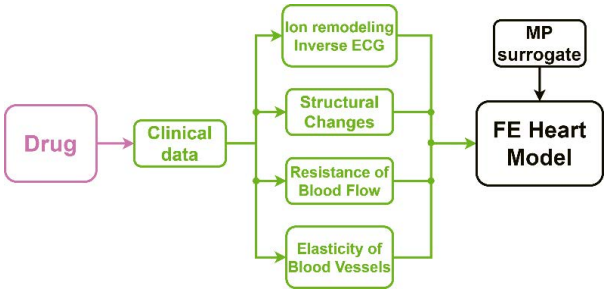

Fig. 5 Pathway 3: Drug action through macroscopic structural and boundary condition changes.

3. Results

The simulations using virtual loading predict left ventricular pressure and volume changes between healthy and HCM and DCM hearts. The predicted traces of the pressures and volumes during heartbeats can be plotted as left ventricular Pressure-Volume loops (Fig. 6). These simulations were obtained using the MP model parameters and experimental calcium transients, with modified lower basal calcium levels and by changing a "force-scaling" mechanical

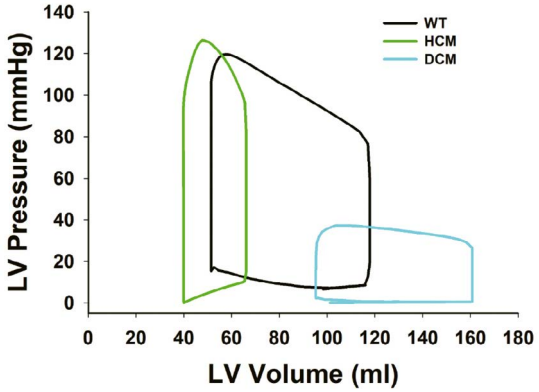

Fig. 6 Left ventricular (LV) Pressure-Volume (P-V) loops during two consecutive heart beats for normal heart (WT, black line), hypertrophic (HCM, green line) and dilated cardiomyopathy (DCM, blue line) obtained with FE coupled with MP surrogate micro model.

parameter, *eta*, in MP model in order to increase twitch peak tensions to observed level.

3.1 Entresto drug influence

ENTRESTO® (Sacubitril/valsartan) has been shown to be superior to enalapril in reducing the risks of death and hospitalization for heart failure (HF). There are also publications which evaluate the effects of sacubitril/valsartan on clinical, biochemical, and echocardiographic parameters in patients with heart failure and reduced ejection fraction (HFrEF).

3.2 Numerical results from the SILICOFCM platform for patients before and after Entresto treatment

Here, we tried to mimic patient cases before and after Entresto drug treatment. Before Entresto treatment PV diagram, pressure diastolic distribution and pressure systolic distribution are presented in Fig. 7. It represents a typical hypertrophic cardiomyopathy patient with decreased ejection fraction and higher systolic pressure (Fig. 7 left, pressure volume diagram).

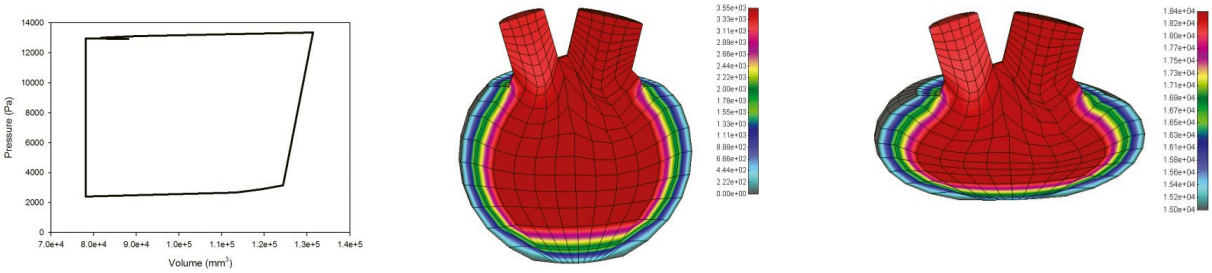

Fig. 7 PV diagram, pressure diastolic distribution, pressure systolic distribution for the case before Entresto treatment.

After Entresto treatment (Fig. 8), we can observe a lower systolic pressure as well as an increasing difference between the end of diastolic and the end of systolic volume. It directly leads to the increase in the ejection fraction. The pressure-volume diagram, velocity distribution in the diastolic and systolic phase for the case after Entresto treatment is presented in Fig. 8.

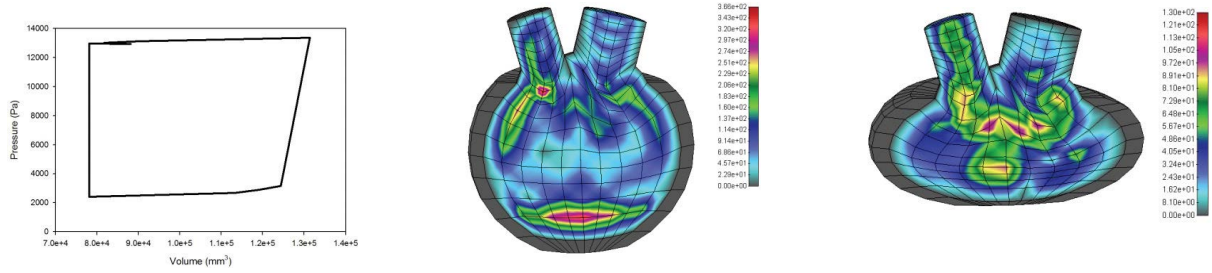

Fig. 8 PV diagram, velocity distribution in the diastolic phase, velocity distribution in the systolic phase for the case after Entresto treatment.

3.3 Realistic geometry of the heart model with left chamber and atrium parts

Using experimental data and DICOM files provided from specific patient, we have reconstructed a realistic heart model as STL format with left atrium (Fig. 9a, marked blue) and chamber part (Fig. 9a, noted yellow) with the accompanying mitral valve cross-section between (Fig. 9a, marked green), and also aortic part (Fig. 9a, marked orange) of the model with aortic cross-section included in fluid part of the model, which is surrounded by solid wall (Fig. 9a, wireframe). Finite element model consists of 1.5M hexahedral 3D elements, divided by 1M nodes. Model geometry is generated using STL files. Solid nodes are constrained around inlet/outlet cross-sections (Fig. 9a; red and magenta rings), and in the zone close to the mitral valve cross-section. Other solid nodes are free. In the Fig. 9c, two cross- section regions are marked to define prescribed inlet and outlet zones. Inside the fluid domain, mitral valve cross-section is presented (part of the model between ventricle and atrium; Fig. 9c, red line). Fiber direction in the solid domain of the realistic heart model is shown in Fig. 9b, and section C on the same Fig. shows distribution of the velocity field in the realistic heart model, at 0.1s. It can be seen that velocity values are the highest at inlet and outlet boundary cross-sections (red and green lines, Fig. 9c), which is logical due to prescribed inlet function and prescribed values at that cross-section at the beginning of simulation. Regarding the material models used, we have selected Holzapfel material model for obtaining passive stresses in the heart wall, and for muscle activation Hunter material model for active stresses is used.

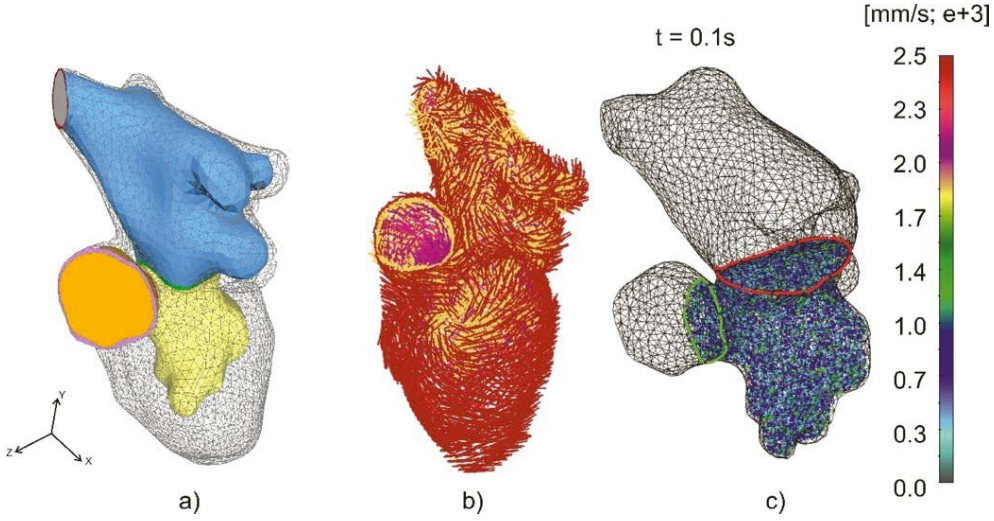

Fig. 9. a) Realistic heart FE model with representative cross-sections and fluid parts; b) Direction of fibres in solid part of realistic model; c) Fluid velocity field at 0.1s (mitral and aortic cross-section noted)

The prescribed inlet velocity function profile is shown in Fig. 10a, and aortic valve cross-section, while outlet velocity function profile is shown in Fig. 10b. Activation of the muscle is achieved using calcium function, displayed in Fig. 10c.

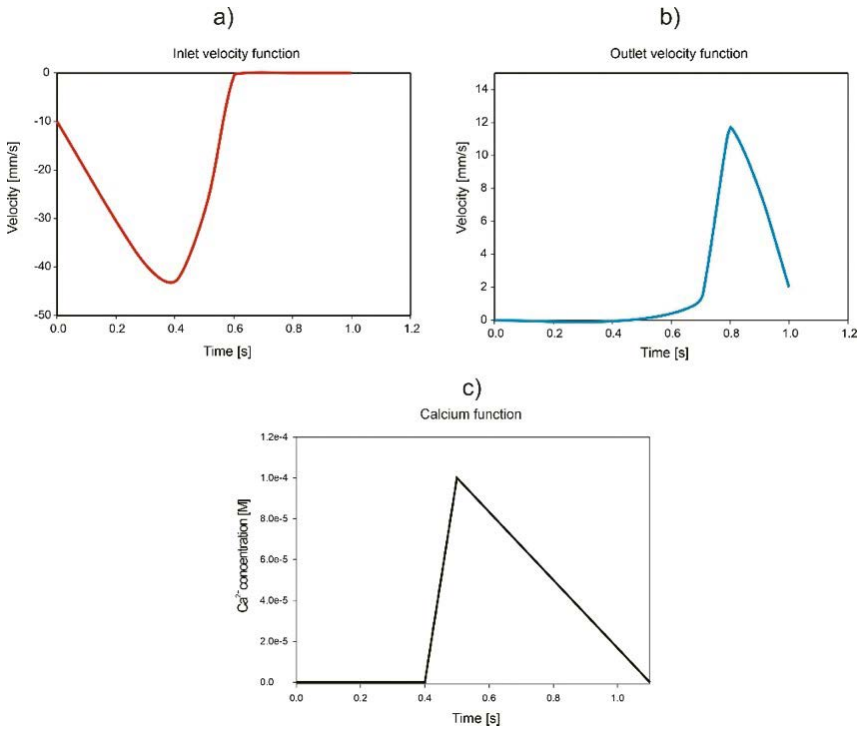

Fig. 10. a) Inlet function of velocity, at mitral valve cross-section; b) outlet velocity function – at aortic valve cross-section; c) Calcium concentration function used for activation of the muscle

Field of displacements in solid wall of realistic model of heart, during four different time steps of one cardiac cycle, is given in Fig. 11. At first step (0.1s), just the passive part of the material model has an impact on solid wall structure and until 0.4s of simulation model volume is increasing until the mitral cross-section is opened and fluid flows into the left chamber part. When the mitral valve is closed and injection of fluid is finished, fluid starts to eject from the chamber through the aortic cross-section, calcium function inside Hunter material model starts to act (0.5s), causing the start of the muscle contraction until the 0.9s of simulation after which model slowly returns to its undeformed state.

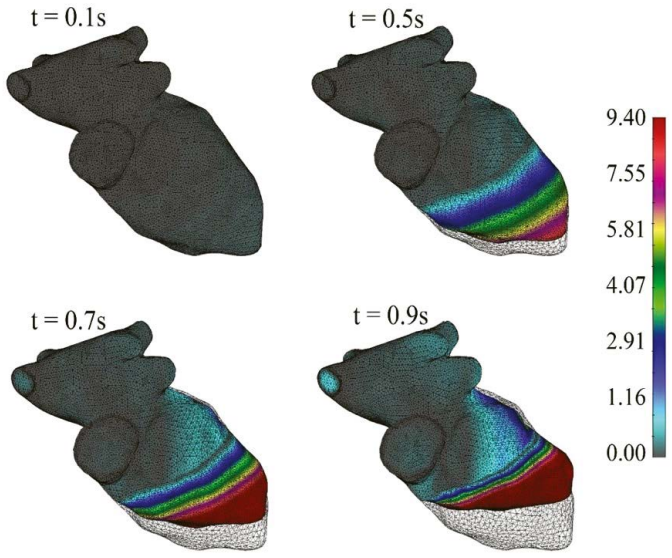

Fig. 11. Field of displacements in the solid wall of the realistic heart model; four different time periods. Undeformed configuration noted as black mesh

The large-scale model of the total heart with deformation simulation and mesh generated with 3M finite elements has been given in the Fig. 12. All of these models represent integration of Big Data technology, HPC and FEM computing. A very specific hardware and software technology has been used to support this integration. Some of the examples are EU projects SILICOFCM for in silico clinical trials.

Fig. 12. Large scale model of total heart. a) Displacement simulation b) Mesh generated with 3M finite elements

4. Discussion and Conclusions

The main result of the SILICOFCM project is a multi-modular, innovative in silico clinical trials solution for the design and functional optimization of whole heart performance and monitoring the effectiveness of pharmacological treatment, with the aim of reducing animal testing and human clinical trials. The SILICOFCM platform is based on the integrated multidisciplinary and multiscale methods for the analysis of patient-specific data and development of patient-specific models for monitoring and assessing patient condition through the progression of disease. The STRATIFYHF project is to develop and clinically validate a truly innovative AI-based decision support system for predicting the risk of heart failure, facilitating its early diagnosis and progression prediction that will radically change how heart failure is managed in both primary and secondary care

Heart modelling for cardiomyopathy and electromechanical coupling of the left ventricle were analyzed in the SILICOFCM (www.silicofcm.eu) and STRATIFYHF (www.stratifyhf.eu) project. Automatic left ventricle segmentation and the geometric parameter model which was extracted from echocardiographic apical and M-mode view was done using the U-net architecture. We have developed a model which includes three kinetic processes of sarcomeric proteins interactions: (i) kinetic transition between three cross-bridge states (a detached state and attached pre- and post-power stroke states; (ii) Ca^{2+} regulation of thin-filament switches between blocked and open states (i.e. by azimuthal movement of regulatory units (RU) containing troponin-tropomyosin complexes); and (iii) process of myosin binding to actin when RUs are in an open state. The drug actions are different for treating a variety of symptoms associated with cardiomyopathies. In particular, drugs simulated with MUSICO (Mijailovich et al., 2021) are divided into three major groups defined by the principal action of each drug, such as modulating calcium transients or changing kinetics of contractile proteins.

We have presented PV diagrams related to different patient cases, pressure diastolic distribution and pressure systolic distribution before and after Entresto and Digoxin drug treatment. Different drug pathways which directly affect the functional heart working have been analyzed. These drugs have a direct influence on the cardiac PV diagrams and ejection fraction. Triangular, parabolic, steep, shifted parabolic, parabolic wider and corresponding PV diagrams for different Ca^{2+} concentration functions have been presented.

Some limitations of the study are the lack of details regarding physical and biological properties of the heart and the need for subject-specific estimation of parameters from limited, noisy data, typically obtained using non-invasive measurements. Also, limitations are large-scale finite element calculations which can take up to several hours.

Computational platforms such as SILICOFCM and STRATIFYHF are novel tools for risk prediction of familial cardiomyopathy and heart failure in a specific patient that will certainly open a new avenue for in silico clinical trials in the future.

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