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v.0.5	Detailed information on User Requirements	01/10/2018
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Disclaimer

Executive summary

This document corresponds to D1.1 – "Requirements Analysis", the first deliverable of WP1 – "Requirements & Conceptual Architecture". The deliverable is the outcome of Task 1.1 – "State-of-the-Art and Requirements Analysis". This document presents the result of the stakeholders' requirements collection and analysis process that started on M1 and ended on M6 of the SILICOFCM project. A user-centred approach was followed during which the technical partners closely collaborated with the clinical and research experts of the SILICOFCM Consortium.

This document is closely related to:

- Task 1.2 – "SILICOFCM Specification" and
- Task 1.3 – "SILICOFCM Reference Architecture".

We have analysed the state-of-the-art technologies and current trends in FCM monitoring. The objective of this task was to collect the user requirements, both functional and non-functional. Also, we have included a range of user specified scenarios as an additional process for eliciting user requirements. The rational for this is the fact that Scenarios have proven useful for eliciting, validating, and documenting requirements. Scenario-based approaches help to bridge the gap between the user/stakeholder view and the functional view of the future system so that the future system will meet the requirements of its users.

This document is structured as follows:

Section 1 – Introduction: presents the overview of the SILICOFCM concept, the purpose and the scope of this deliverable, project's target audience as well as description of methodology and actions implemented within Task 1.1 in order to be in compliance and address all the related Description of Action.

Section 2 – State-of-The-Art in FCM monitoring presents the state-of-the-art in the FCM monitoring, focusing on current trends and best clinical practice in FCM monitoring.

Section 3 – State-of-The-Art technologies presents the state-of-the-art technologies that are essential part of the SILICOFCM platform such as: i) Cardiac Magnetic Resonance Imaging methods and imaging analysis ii) description of SILICOFCM Tools (MUSICO Tool, ALYA Solver Tool, PAK Solver Tool, Bioinformatics Tool, Data Analytics Tool, Multiple Criteria Decision Making Tool, Virtual Population Tool), as well as the similar commercial *in silico* Cloud platforms.

Section 4 – The Requirements Capturing Process presents the process used to obtain user requirements: i) requirements types and definition process, ii) characteristics of a good requirements statement and iii) good practices in requirements definition.

Section 5 – User and regulatory requirement analysis presents the main users of the SILICOFCM platform (support users and end-users), the user requirements analysis that was performed based on created Questionnaires (for i) Clinicians, ii) Bioengineers and Researchers and iii) Pharmaceutical companies) and the analysis of the available similar systems. User Requirements Analysis is presented under four topics (General User Requirements, Data Governance Requirements, SILICOFCM Tools Usage Requirements, Visual Analytics and User Interfaces) which are also included within Use Cases and Usage Scenarios. The Section 5 is also related to the analysis of regulation processes, recommendations of regulatory bodies and their feedback on SILICOFCM project as part of *in silico* clinical trials.

Section 6 – Deviation from the work plan presents the deviations from the work plan.

Section 7 – Conclusions presents the conclusions of this document.

Section 8 – References presents the list of references used during the writing of this deliverable.

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List of Abbreviations

Abbreviation	Explanation
ADC	Apparent Diffusion Coefficient
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
AST	ALYA Solver Tool
BAM	Binary Alignment Map
BT	Bioinformatics Tool
CNV	Copy Number Variant
CMRI	Cardiac Magnetic Resonance Imaging
CPU	Central Processing Unit
CWL	Common Workflow Language
DAT	Data Analytics Tool
DCM	Dilated cardiomyopathy
DGR	Data Governance Requirements
DSI	Diffusion Spectrum Imaging
DSS	Decision Support Systems
DTI	Diffusion Tensor Imaging
DW	Diffusion Weighted
ECG	Electrocardiography
EMA	European Medicine Agency
EP	Electrophysiology
IST	In Silico Trials
ISCT	In Silico Clinical Trials
ITF	Innovation Task Force
FASTQ	List of reads generated with quality scores for each read
FCM	Familial Cardiomyopathy
FDA	Food and Drug Administration
FE	Finite Element
FEA	Finite Element Analysis
GDD	Global Drug Development
GDPR	General Data Protection Regulation

GPU	Graphic Processing Units
GUR	General User Requirements
HCM	Hypertrophic Cardiomyopathy
HPC	High Performance Computing
KPI	Key Performance Indicators
KPP	Key Performance Parameters
LGE	Late Gadolinium Enhancement
LV	Left Ventricular
MCDM	Multiple Criteria Decision Making Tool
ML	Machine Learning
MOE	Measures of Effectiveness
MOP	Measures of Performance
MUSICO	Muscle Simulation Code
M&S	Modelling and Simulation
MSWP	Modelling and Simulation Working Party
MT	MUSICO Tool
N/A	Not applicable
NIBR	Novartis Institutes for BioMedical Research
NGS	Next Generation Sequencing
PST	PAK Solver Tool
R&D	Research and Development
RCM	Restrictive Cardiomyopathy
SAWP	Scientific Advice Working Party
SNR	Signal to Noise Ratio
STSRI	Structure Tensor Synchrotron Radiation Imaging
STUR	SILICOFCM Tools Usage Requirements
TPLC	Total Product LifeCycle
uBAM	Binary file with unaligned / unmapped read
UC	Use Cases
US	Usage Scenario
UI	User Interface
UN	User's Need
ULM	Unified Modelling Language
URA	User Requirements Analysis
VCF	Variant Calling Format
VPT	Virtual Population Tool
2D	Two dimensional
3D	Three dimensional

1. Introduction

1.1 SILICOFCM Concept

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

SILICOFCM is a multi-modular, innovative in silico clinical trials solution for the design and functional optimization of whole heart performance and monitoring effectiveness of pharmacological treatment, with aim to reduce the animal studies and the human clinical trials. The SILICOFCM platform is based on the integrated multidisciplinary and multiscale methods for analysis of patient-specific data and development of patient-specific models for monitoring and assessment of patient condition from current through the progression of disease.

When a new patient comes to the hospital the patient will be subjected to genetic testing by using Next Generating Sequencing (NGS) technology. Based on the NGS assay, the set of variants present in the genes of interest in the sequenced sample will be determined and annotated with information regarding functional impact prediction. Genetic data, extracted by the use of various bioinformatics tools, together with the patient's personal medical record and imaging data will be given as inputs to SILICOFCM for computer aided detection of risk stratification. Based on available data, the SILICOFCM system will classify patient as low or high risk regarding to FCM. Based on medical expert decision, patients classified as high risk will be subjected to further analyses of disease progression and outcome prediction such as: (1) SILICOFCM data mining-based modelling of cardiomyopathy and (2) SILICOFCM 3D imaging-based modelling of cardiomyopathy. The SILICOFCM concept and flowchart are given in Figure 1.

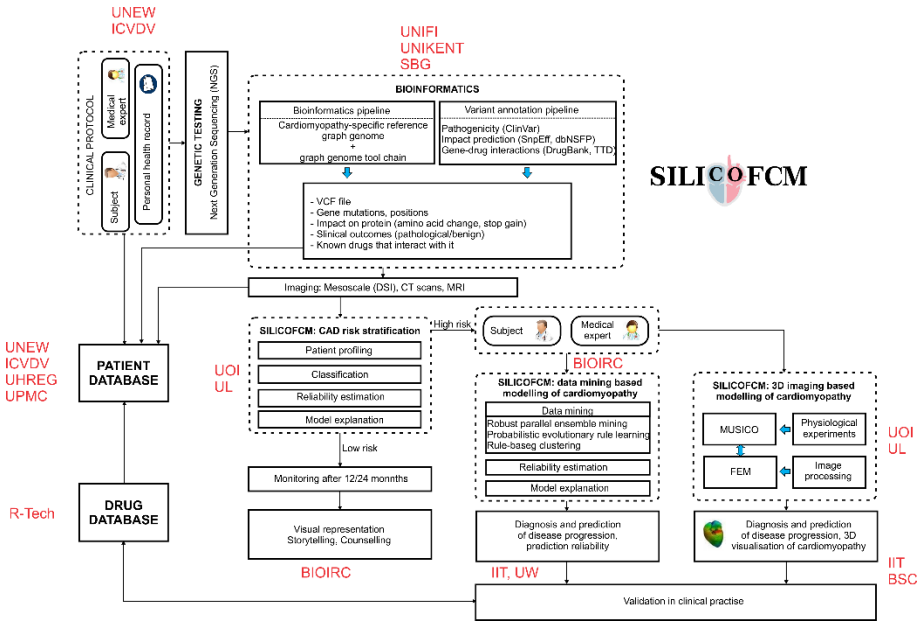


Figure 1. The SILICOFCM concept and flowchart.

SILICOFCM aims to become a respectable *in silico* solution with potential to develop into a computational cloud platform in all areas and levels of health care by combining the data from multiple data sets collected at multiple scales with sophisticated and continuously developing computational models and, therefore, following the information flow across all length scales from a gene mutation to organ dysfunction.

1.2 Purpose and scope of the deliverable

This document presents overview of current trends and state-of-the art technologies in the area of FCM, as well as the FCM monitoring. Collecting and analysing the general and user requirements, the functional and non-functional specifications, the outcome of Task 1.1 helps to design architecture and integration plan of the SILICOFCM platform, which will be part of Task 1.2 and Task 1.3. User requirements collected in terms of functionalities, ease of use and interfaces, are translated into functional specifications and subsequently formulate the architecture of SILICOFCM platform.

1.3 Target Audience

This SILICOFCM project document intended to support the collaboration of all partners, Cardiologists, Bioinformatics experts, Bioengineers, Modelling experts, Software engineers, Data mining/analysis experts, in order to compile the system and user requirements, which are needed to define the functional specifications and design the conceptual architecture and guide the integration of the SILICOFCM platform.

1.4 Relation with the SILICOFCM DoA

The following table presents the DoA description of Task 1.1 and how this deliverable addresses the description of the Task.

DoA Task Description	Addressed by D1.1
This task will undertake the technological state-of-the-art review, comparative analysis and evaluation of best practices and techniques, and the identification, analysis and homogenization of the FCM monitoring. This task aims at the developing an innovative approach and computational platform for specific patient *in silico* trial. Some critical technological domains that this task is going to investigate are CMR methods, biomechanical finite element simulation, management of collected data, big data management, parallel computing, optimisation, data mining etc. Current state of-the-art technologies are going to be investigated, analysed and evaluated, so as to proceed with the definition of the SILICOFCM Reference Architecture (Task 1.3).	Analysis of the state of-the-art technologies related to SILICOFCM approach has been performed in detail (Section 3). The current trends in FCM are analysed (Section 2), as well as the technologies that SILICOFCM platform relies on. Also, three Questionnaires are created in order to collect users' needs (Section 5.3). The regulations which follow the approval process of in silico trials have been also analysed (Sections 5.7-5.8). The definition and analysis of the users (Section 5.1), the SILICOFCM tools, their dependencies and communications, as well as the functional and non-functional user requirements (Section 5.5), use cases and usage scenarios (Section 5.6), will enable creation of the SILICOFCM Reference Architecture - an effective Cloud-based system for a new drug development and

	optimized clinical therapy of patients with Familial cardiomyopathies.

2. Current trends in FCM monitoring

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 (CMRI). There are four major classifications of cardiomyopathy: hypertrophic (HCM), dilated (DCM), restrictive (RCM), and arrhythmogenic right ventricular (ARVC) [1]. The treatment of symptoms of FCM by established therapies could only in part improve the outcome, but novel therapies need to be developed to affect the disease process and time course more fundamentally.

Genetic cardiomyopathies are more commonly diagnosed, largely because surveillance for and awareness of the condition has improved. Large number of single genes have been identified as linked to familial cardiomyopathies, and the majority of these elicit disease as dominant mutations. Most of the genetic mutations affect myosin, titin or regulatory proteins that modulate cardiac contractile function. The majority of these mutations also induce the structural changes associated with disease classification, impaired systolic or diastolic performance, endomyocardial fibrosis, or progressive fibro-fatty replacement of right ventricular myocardium associated with ventricular arrhythmias (ARVC).

Currently, there are no interventions available that specifically treat or prevent cardiomyopathies resulting from mutations in sarcomere proteins. Current standard of care is designed to manage progression of heart failure, thus novel therapies are needed to affect the disease process and time course more fundamentally. There is a need for novel therapies and approaches which may prevent, delay, or even reverse FCM that involves genetic defects, altered sarcomere function, perturbed intracellular ion homeostasis, and impaired myocardial energetics.

2.1 Best clinical practice in FCM monitoring

After two decades of clinical and basic science research, the relation between sarcomere mutations and clinical outcome in patients with hypertrophic cardiomyopathy (HCM) has proved unreliable, attributable largely to genetic and phenotypic heterogeneity thus disputing the notion that specific single mutations can determine prognosis [2]. Therefore, despite much optimism and (perhaps unrealistic) expectations for a molecular paradigm to predict outcome and direct management of hypertrophic cardiomyopathy, this aspiration has been largely unrealised [3]. However, possible exceptions are emerging, including preliminary data suggesting that double, triple, or compound sarcomere mutations (evident in 5% of patients with hypertrophic cardiomyopathy) could be associated with greater disease severity, including sudden death without conventional risk factors [4].

Currently, the most compelling reason for genetic testing in clinical practice is to identify family members of patients with hypertrophic cardiomyopathy who do not have left-ventricular hyper-trophy but may be at potential risk of developing disease. If a pathogenic mutation is identified in a relative expressing the phenotype, the genetic status of other family members can be resolved definitively, thereby eliminating anxiety associated with potential diagnosis and removing the need for future screening with cardio-vascular testing [5].

Genetic testing can also clarify diagnosis in patients with metabolic storage disorders for whom clinical presentation and pattern of left-ventricular hyper-trophy is similar to hypertrophic cardiomyopathy but with different pathophysiology, natural history, and management [6].

Suspicion of hypertrophic cardiomyopathy usually follows the onset of symptoms or a cardiac event but can also arise from recognition of a heart murmur or abnormal 12-lead electrocardiogram (ECG) during routine or preparticipation sports examinations, or in pedigree studies [7]. Clinical diagnosis is confirmed conventionally by imaging the hypertrophic cardiomyopathy phenotype with two-dimensional (2D) echocardiography, cardiovascular magnetic resonance imaging, or both [8]. Imaging findings show an absolute increase in left-ventricular wall thickness which can also be associated with mild right-ventricular hyper-trophy [8]. Other common findings, such as mitral valve systolic anterior motion or hyperdynamic left ventricle, are not obligatory for a diagnosis of hypertrophic cardio myopathy [8].

Integration of commercial genetic testing into cardiovascular clinical practice has facilitated recognition of a subset of family members who have sarcomeric mutations but who do not have left-ventricular hyper trophy (although ECGs are abnormal in 50%). These gene-positive phenotype-negative individuals expand the clinical spectrum of hypertrophic cardiomyopathy and show that any left-ventricular wall thickness can be consistent with this inherited cardiac disease [9]. Nevertheless, non-hypertrophied left-ventricular myocardium in such patients may show a variety of abnormalities – i.e. myocardial fibrosis by contrast-enhanced magnetic resonance imaging, collagen biomarkers, mitral leaflet and chordae elongation, subclinical diastolic dysfunction, blood-filled myocardial crypts, and ECG abnormalities [8].

At present, we do not know whether gene-positive phenotype-negative individuals are at risk of sudden death or disease progression (although two such adults with cardiac arrest have been reported), or even what proportion of such individuals will eventually develop left-ventricular hyper-trophy.[9] Currently, decisions about disqualification from competitive sports participation or prophylactic implantable defibrillators are usually resolved on a case-by-case basis, although competitive sports are permitted by a US consensus panel [9]. This emerging subset of patients' needs much longer follow-up before consistent management guidelines can be formulated.

2.2 The requirements for FCM monitoring at SILICOFCM clinics

Monitoring of HCM is necessary for the prevention of sudden cardiac deaths and management of disease. According to European Clinical Guidelines, patients with HCM require lifelong follow-up to detect changes in symptoms, risk of adverse events, left ventricular outflow tract obstruction, left ventricular function and cardiac rhythm [8]. There are very few longitudinal data on the rates of change in symptoms or cardiac function, but cross-sectional studies show that the prevalence of left ventricular systolic dysfunction and atrial arrhythmia increases with advancing age [11].

The frequency of monitoring is determined by the severity of disease, age and symptoms. A clinical examination, including 12-lead ECG and transthoracic echocardiography, should be performed every 1–2 years, or sooner should patients complain of new heart failure symptoms. [8]. Ambulatory electrocardiography is recommended every year (or every 6 months in the presence of left atrial dilation ≥45 mm) to detect asymptomatic atrial and ventricular arrhythmia, and is indicated whenever patients experience syncope or palpitations [8].

Cardiopulmonary exercise testing can provide objective evidence for worsening disease but need only be performed every 2–3 years unless there is a change in symptoms. There are few data on changes in myocardial fibrosis on cardiac magnetic resonance imaging during follow-up but, when available, cardiac magnetic resonance imaging evaluation may be considered every five years or every 2–3 years in patients with progressive disease [12].

A complete assessment, including ECG, echocardiography and ambulatory ECG monitoring should be performed within 1–3 months and at 6–12 months following invasive septal reduction therapies [8].

It should be noted that the management of collected data is explained in detail within the D10.6 “Data Management Plan v2”.

2.2.1 The requirements for collecting data available in SILICOFCM clinical centres

At the SILICOFCM clinics, patients with HCM will be monitored according to the guidelines detailed above. Those patients with no genetic testing performed earlier will be subject to genetic testing using new generation sequencing to identify any potential sarcomere mutations. In order to ensure best prognosis and outcomes, patients with HCM will have regular monitoring and follow-up assessments every 6 to 12 months including, physical examination, ECG, echocardiography and functional capacity. Advanced methods and technologies will be included such as advanced cardiac magnetic resonance imaging with tissue tagging and spectroscopy, and non-invasive cardiac stress testing. Novel technologies and home-based monitoring using wearable device should also be explored and used by HCM patients and their clinical care teams.

3. State-of-The-Art technologies

3.1 Cardiac Magnetic Resonance Imaging (CMRI) methods and imaging analysis

Cardiac Magnetic Resonance Imaging (CMRI) is the most accurate technique for assessing cardiac mass, volumes and function, hyper-trophy distribution, apical aneurysm, intracavitary gradient, tissue function, oedema, and offers the unique ability to assess regional myocardial fibrosis by late gadolinium enhancement (LGE). It offers insight into four hallmark features of HCM that are potential causal contributors of disease progression:

1. abnormal microcirculation,
2. diffuse fibrosis,
3. myoarchitectural disarray and
4. altered cardiac energetics.

Most recently, CMR methods have been extended on experimental methods for assessment of myofibre orientation/disarray by diffusion tensor imaging (DTI) and diffusion spectrum imaging (DSI) MRI.

The essential information necessary for finite element analysis is the orientation of fibres due to two reasons:

1. the direction of active forces is aligned with the direction of fibres and
2. the electricity travels much faster along muscular fibres than across.

Thus, a correct anatomical description of the arrangement of muscle fibres is probably the most important element in obtaining a realistic model of the heart (Figure 2).

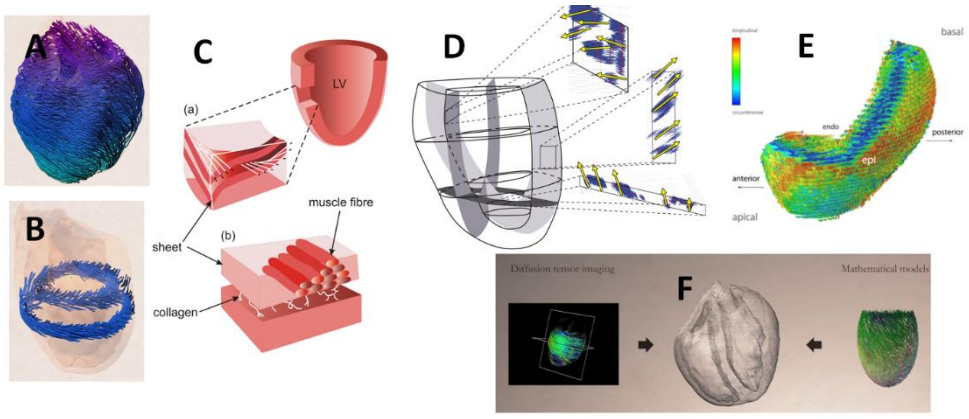


Figure 2. Determining fibre orientation across the ventricle walls.

Note: (A) Reconstructed fibres from DTI imaging of the heart; (B) at each cross section the fibres create sheets that change orientation across the thickness of the wall; (C) illustration of the distribution of angles across left ventricle wall (a) and the muscle fibres form layers 3-4 cells thick (b). The layers are interconnected by collagen; (D) newly developed method to obtain direction of fibres at any position in arbitrary cross-section (yellow arrows). These directions are directly implemented in finite elements integration points along with other active and passive material characteristics; (E) reconstructed directions of muscle fibres across and along ventricle wall; (F) The reconstructed DTI images in concert with fine finite element mesh realistically represent the geometry of fibrous and layered structure of ventricle walls.

Cardiac fibres are spatially organized to enable coordination to allow the contraction of heart cavities in a coordinated, stable and efficient way. Today we can achieve much better description of the fibres using a technique called diffusion tensor imaging, using magnetic resonance map of diffusion along biological fibres.

Diffusion Tensor Imaging (DTI) is an MRI-based neuroimaging technique, was originally created to estimate the location, orientation, and anisotropy of the brain's white matter tracts [13]. If we apply diffusion gradients in at least 6 non-collinear directions, it is possible to calculate, for each pixel, a diffusion tensor that describes this diffusion anisotropy. The fibre's direction is indicated by the tensor's main eigenvector. This vector can be color-coded, yielding a cartography of the tracts' position, direction (red for right-left, blue for foot-head, green for anterior-posterior), and anisotropy (as indicated by the tract's brightness) (Figure 3) [13].

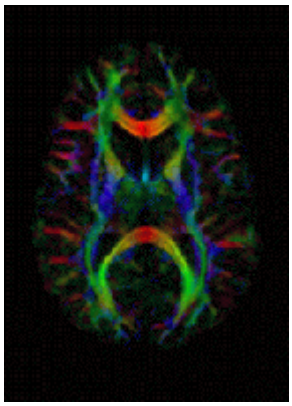


Figure 3. Diffusion Tensor Imaging colormap [13].

The diffusion of water molecules inside organic tissues is often anisotropic [14]. Namely, if there are aligned structures in the tissue, the apparent diffusion coefficient (ADC) of water may vary depending on the orientation along which the diffusion-weighted (DW) measurements are taken. Diffusion weighting by a pair of strong gradient pulses introduces a number of imaging parameters unique to diffusion imaging. This includes the magnitude (b-value) and orientations as well as the number of the least DW images (so-called b=0 images). The majority of DTI studies nowadays use b-values in the range of 700–1000 s/mm^2, leading to 30–50% signal reduction assuming the mean diffusivity of normal white matter is around 0.8 to 1.0 x 10^{-3} mm^2/s. The determination of the optimum b-value [15] is complicated by the involvement of many factors [16], including: SNR (the higher the SNR, the more accurately signal attenuation can be measured with higher b-values), echo time (the smaller the b-value, the shorter the achievable echo time), and other factors that are more difficult to assess such as eddy current and motion artifacts (in general, smaller b-values produce less artifacts) [17].

Although originally created for imaging of the brain, it is noticed that diffusion tensor imaging could be used in imaging of the heart in the form of the diffusion Tensor Magnetic Resonance [18]. Diffusion MRI in the heart, however, has proven technically challenging because of the intrinsic non-rigid deformation during the cardiac cycle, displacement of the myocardium due to respiratory motion, signal inhomogeneity within the thorax, and short transverse relaxation times [19]. Recently developed accelerated diffusion-weighted MR acquisition sequences combined with advanced post-processing techniques have improved the accuracy and efficiency of diffusion MRI in the myocardium. In the review by MacGowan et al., they describe the solutions and approaches that have been developed to enable diffusion MRI of the heart in vivo, including a dual-gated stimulated echo approach, a velocity- (M1) or an acceleration- (M2) compensated pulsed gradient spin echo approach, and the use of principal component analysis filtering [18].

Nielles-Vallespin et al. [20] have now used this technique to produce data further elucidating how the layers of the left ventricular (LV) behave during contraction. The human data, though novel, are relatively limited. For instance, a significant proportion of the dilated cardiomyopathy patients have LV ejection fractions ≥50%, meaning a mild phenotype. It would be very interesting to have a more comprehensive range of ejection fractions to see whether there is a threshold effect, whereby below a certain level of ejection fraction (or even better, fibre shortening) the sheetlet reorientation is severely limited. It would also be interesting to know, in the setting of hypertrophic cardiomyopathy, whether a patient's genotype predicts sheetlet behaviour. However, the significance of the study and the technique is that it will help us answer important and interesting questions about mechanisms of LV dysfunction. One of the consequences of the spiral orientation of the fibres is that the obliquely oriented epicardial fibres cause torsion of the LV during systole. During diastole, the recoil of this torsion occurs very rapidly, largely during isovolumic relaxation, and is thought to help in early diastolic filling of the LV [21]. Over the last decade, developments in diffusion tensor MRI (DTI) have permitted the noninvasive measurement of the self-diffusion of water through tissue. The diffusion of water molecules, driven by their thermal energy, is restricted by the tissue microstructure. In fibrous tissue, water diffuses preferentially in the fibre direction.

Basser et al. [22] showed that a symmetric tensor representing the mean path of water diffusion may be computed from multiple images obtained with different gradient weightings. By comparing the principle eigenvector of the DT at each image voxel with the fibre orientation measured histologically, one can see that the principle direction of water diffusion in cardiac tissue is parallel to the fibre long axis [23]. More recently, it was also suggested that the secondary and tertiary eigenvectors of the DT correlate with the laminar structure of the ventricles [24, 25] with the tertiary eigenvector defining the surface normal to the laminar sheets. However, evidence suggests that in the myocardium, the secondary and tertiary eigenvalues are similar in magnitude. Pierpaoli et al. [26] showed that under those conditions and in the presence of noise, the rotationally invariant diffusion indices that describe anisotropic diffusion and require sorting of eigenvalues based on their magnitude are statistically biased. For example, the ratio between the largest and smallest eigenvalues is particularly susceptible to sorting error. Furthermore, once the eigenvalues are sorted, the assumptions of random sampling are violated and therefore standard statistical tests are no longer valid [13]. This "sorting bias" (i.e., incorrect classification of secondary vs. tertiary eigenvalues) also introduces a bias in the mean and variance of the sample eigenvectors (principle directions), and degrades the characterization of tissue anisotropy [27]. The complexity of the cardiac architecture combined with errors in classifying the secondary and tertiary eigenvalues and eigenvectors presents a significant challenge to investigators who seek to measure laminar structure using DTI. One novel research by Helm et. al. [28] developed a novel hypothesis-testing method and used to show that distinct populations of secondary and tertiary eigenvalues may be distinguished at reasonable confidence levels ($P \leq 0.01$) within the canine ventricle. Fibre inclination and sheet angles are reported as a function of transmural depth through the anterior, lateral, and posterior left ventricle (LV) free wall. Within anisotropic regions, two consistent and dominant orientations were identified, supporting published results from histological studies and providing strong evidence that the tertiary eigenvector of the diffusion tensor (DT) defines the sheet normal.

Teh et al. [29] examine DTI because it is affected by many factors, therefore robust validation is critical. They say that it is sensitive to a wide range of physical and biological processes, and validation is vital to improving our understanding of DTI, and its acceptance in clinical practice. They performed the first validation of DTI across the whole intact heart, and without additional preparation following DTI. Structure tensor synchrotron radiation imaging (STSRI) affirmed the correspondence of v1, DT with the dominant cardiomyocyte long-axis in the whole heart, and suggests that v2, DT and v3,

DT generally correspond to the sheetlet and sheetlet-normal orientations, corroborating histological findings and independently informing the interpretation of cardiac DTI. STSRI opens up exciting possibilities in 3D quantification of cell morphology in large fields-of-view without distortion, augmentation of structure-based electro-mechanical modelling, validation of in vivo contrast-enhanced imaging measurements of extracellular volume, and validation of advanced diffusion MRI methods for assessing biophysical parameters such as cell size, shape and dispersion. The next step would be to use STSRI to improve characterization of abnormal myocardium, and to validate DTI measurements in cardiac disease such as myocardial infarction and hyper-trophy.

As far as modelling of fibres in heart is considered, Wong et al. [30] generated fibre orientation maps in human heart models using Poisson interpolation. The creation of fibre orientation maps for computational analyses remains one of the most challenging problems in cardiac electrophysiology and cardiac mechanics. They show that Poisson interpolation generates smoothly varying vector fields that satisfy a set of user-defined constraints in arbitrary domains. Specifically, they enforce the Poisson interpolation in the weak sense using a standard linear finite element algorithm for scalar-valued second-order boundary value problems and introduce the feature to be interpolated as a global unknown. User defined constraints are then simply enforced in the strong sense as Dirichlet boundary conditions. They demonstrate that the proposed concept is capable of generating smoothly varying fibre orientations, quickly, efficiently. Pravdin et al. [31] introduce a theoretical rule-based model for anatomy and fibre orientation of the LV of the heart and to compare it with experimental data. They suggest explicit analytical formulae that allow to obtain the left ventricle form and its fibre direction field. The ventricle band concept of cardiac architecture given by Torrent-Guasp is chosen as the model postulate. Perez et al. [32] analyse sixty representative 3D cardiac computational models developed and published during the last fifty years, describing their information sources, features, development methods and online availability. This paper also reviews the necessary components to build a 3D computational model of the heart aimed at biophysical simulation, paying especial attention to cardiac electrophysiology, and the existing approaches to incorporate those components. They assess the challenges associated to the different steps of the building process, from the processing of raw clinical or biological data to the final application, including image segmentation, inclusion of substructures and meshing among others.

All this shows that despite many difficulties, the field of cardiac diffusion imaging is slowly but steadily making progress. In vivo and ex vivo diffusion imaging of the heart has shown that the technique has great potential to better understand cardiac function, characterize cardiac pathology, and understand myofiber remodelling in response to injury or disease [33].

In our cardiac simulator, we use DTI, which will allow us to validate the theory with experiments at organ level. In Figure 2 we showed the methodology how we can extract the direction of fibres from fibre tracks. We will use DTI to resolve 3D tissue microstructure in intact heart (Figure 4). To achieve this, we adapted MRI *in vivo* imaging technique developed by Sosnovik et al [34]. The patients will be imaged on a 3-T clinical system (e.g. Achieva, Phillips, Best, Netherlands) with a maximum gradient strength of 80 mT/m per axis. A motion-compensated 2D diffusion-encoded, single shot, spin echo echoplanar imaging sequence will be used. Data acquisition was ECG triggered and performed in midsystole during free breathing with the use of a respiratory gating navigator.

Analysis of the human DTI data sets will be performed with software developed at MGH and used in our IIT lab daily. The diffusion-weighted images will be spatially registered, and the dyadic diffusion tensor will be calculated in each voxel.

Images processed using DTI are input for FE solvers (PAK and ALYA).

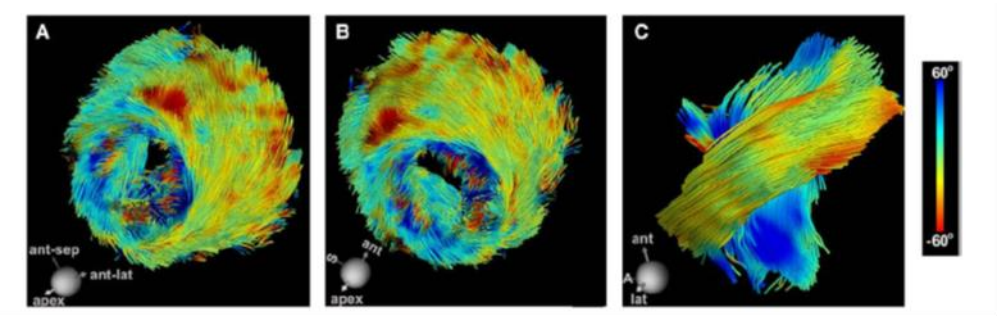


Figure 4. *In vivo* diffusion tensor magnetic resonance imaging tractography of the left ventricle in a normal human volunteer.

It should be noted on the previous figure that the tracts are color-coded by helix angle. Positions A and B depict: Coherent tracts with the correct orientation can be resolved in all regions of the myocardium. (Dispersion of helix angle over the papillary muscles and trabeculations of the left ventricle is a normal finding.) Position C depicts: Magnified view of fibres crossing a region of interest in the midlateral wall of the left ventricle. The characteristic crossing pattern of myofibres in the subendocardium and subepicardium can be clearly seen. A indicates apex; ant, anterior; lat, lateral; S, septum; and sep, septal.

3.2 MUSICO Tool (MT) description

The computational platform MUSICO (MUscle SImulation COde) has been developed with the aim to simulate a wide variety of experimental muscle behaviour and it is based on modelling realistic sarcomeric systems. MUSICO module is an essential part of the SILICOFCM platform with a role to make a connection between genetic data obtained from gene analysis and their consequences on heart behaviour (muscle fibres or modulated heart function) that is simulated using finite element solvers (ALYA or PAK).

The platform offers a modular program structure that allows extension and replacement of any part of sarcomeric system (calcium activation, cross-bridge cycle, sarcomere geometry, etc.). The current version of the MUSICO involves a number of sarcomere geometry models including the three-dimensional spatial models of multi-sarcomere geometry [35]. Furthermore, multiple actomyosin cycle models and calcium regulatory models are also incorporated. Nonlinear mechanical behaviour of extensible filaments and cross-bridges is addressed using iterative finite element scheme. MUSICO input parameters for the particular genetic variant are read from the predefined lookup table that maps genetic variants to the related MUSICO parameters. These parameters will be obtained by fitting MUSICO results with a number of experiments performed on modulated tissues.

The MUSICO can be used in two ways:

1. as an independent tool for analysing impact of genetic variants or drugs;
2. as the input (results form MUSICO) into modules for simulations of heart behaviour.

In the first scenario, user can obtain knowledge about muscle fibre behaviour and muscle proteins functions based on the impact of genetic variants or drugs. In the second scenario, the MUSICO is used to calculate material properties in each integration (Gaussian) point of each finite element (FE) in the muscle geometry mesh. With obtained material properties, the macro scale FE model with be used for numerical simulations (i.e. using PAK or ALYA).

Since the MUSICO calculations are time consuming, MUSICO will be used to calibrate mass-action models, which are more suitable for application in FE simulations, in order to ensure that obtained results are well fitted for complex simulations. Moreover, in order to speed-up simulations, the platform is provided with parallelized computational algorithm.

3.3 Biomechanical Finite Element Programs

This section provides information regarding the Finite Element solvers that will be used during SILICOFCM project. This includes Alya RED (developed by BSC) and PAK (developed by BioIRC).

3.3.1 ALYA Solver Tool (AST) description

Alya Red is a cardiac computational modelling tool specifically designed to run efficiently in supercomputers. It is based on Alya [36], a parallel simulation code for multiphysics and multiscale problems, which can deal with all the complexity of biological systems simulations. The final goal is to simulate the pumping action of the heart: the model includes the electrical propagation, the mechanical contraction and relaxation and the blood flow in the heart cavities and main vessels [37].

Alya is specially well-suited for the parallel solution of coupled multiphysics problems. Parallelization can be:

- External
- Internal
- Hybrid - Both parallelization strategies are used at the same time. This is very well suited for clusters of multicore CPUs.

It is one of the two Finite Element Solvers that will be used during this project.

During this project Alya RED FE solver will be coupled with previously mentioned MUSICO platform or its adequate surrogate models (mass action or data-driven models). The result of the coupling will be simulation of the heart model (from sarcomere to the whole heart) in order to understand familial cardiomyopathies and sarcomeric protein mutations that lead to it.

In order to perform simulations using ALYA RED FE solver, next data are needed:

Imaging Data:

Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) images for the reconstruction of cardiac anatomies (biventricular or only left ventricle) for the initial, preliminary pipeline testcase.

Diffusion tensor MRI from data acquired from patients (otherwise, rule-based mathematical fibre orientations or high-resolution imaging on ex-vivo hearts can be morphed and employed).

Functional data: like ejection fraction, tagged MRI for model parameterization and validation.

Other clinical data: Systolic and diastolic pressure

Data Processing:

Image Segmentation: Automatic threshold-based segmentation on premise, plus manual refinement by experts is required. The segmented data can then be used to create a surface mesh.

The surface mesh can then be employed for the creation of a volumetric mesh. The volumetric mesh can be done with open source meshers (like Quartet, Tetgen) or the in-house mesher developed at BSC (Iris). Generally, ALYA uses tetrahedral element meshes.

For mechanics simulations it is important to setup the boundary conditions via labelling of surfaces, and regions. Labelling can be performed manually on the volumetric mesh. Eventually, a registration algorithm between meshes can be implemented to pass the labels required as boundary conditions. The main boundary conditions that have to be defined include: Pericardium, endocardium and basal region. Fibre orientation has to be defined at each node of the volumetric mesh.

The electrophysiology and mechanics mesh can have two different resolutions. Electrophysiology meshes requires regular tetrahedral elements of a maximum side length of 400 microns. The mechanics mesh has bigger element sizes. Creation of the mechanics mesh is sufficient. ALYA can subdivide that mesh and create a mesh to solve the electrophysiology problems

3.3.2 PAK Solver Tool (PST) description

PAK is high performance finite element analysis (FEA) software for solving complex coupled multi-physics / multi-scale problems. PAK is consisted of following modules:

- Program for linear and geometrically and materially nonlinear structural analysis;
- Program for linear and nonlinear drug transport using diffusion;
- Program for laminar flow of incompressible fluid and heat/diffusion transfer;
- Program for coupled solid fluid transport;
- Program for coupled ionic and electric transport;
- Program for coupled mechanical deformations and ionic transport.

Regarding SILICO FCM project, PAK is able to solve the following:

- Multiscale modelling of drug transport using smeared model, with different compartments: blood vessels, extracellular space, cell interior including organelles; ionic transport;
- Multiscale modelling heart electrophysiology;
- Modelling blood flow within the heart interior, large vessels, capillaries and tissue;
- Modelling mechanical deformations of heart;
- Modelling coupled wall deformation and blood flow within the heart.

Together with PAK, external interface software for pre- and post-processing of results called CAD (developed in BioIRC) is available for generation of model and visualization of results.

Workflow

1. **Input (Type of input files)**
   - Input from clinicians (heart geometries of segmented DICOM images provided by clinicians)
   - Input from experimental studies (characteristics of drug transport, ionic transport and electric field: corresponding transport coefficients, continuum compartments and biological membranes)

2. **Module execution (Actions)**

- Pre-processing: Reconstructed (segmented) from DICOM files – on premise. Result: STL files with 3D mesh of heart model as input for simulations that follow.
- Pre-processing: Generation of input file for PAK using indoor CAD pre/post processing interface software.
- Action1: Drug transport simulation.
- Action2: Electric field simulation coupled with ionic transport.
- Action3: Simulation of mechanics coupled with electric field and drug transport (communication with MUSICO, and including Hill's or Hunter's muscle model).

3. Simulation solution

- drug concentration in heart model
- concentration of ions in heart model
- field of electric potentials of ions in heart model
- results of mechanical deformations

Output files: UNV (for CAD) and Paraview compatible output files (CSV, RAW, VTK) with following results:

Electrical field, action potential for different group of cells, including Purkinje network, concentrations of drug and other molecules (as calcium) relevant for heart function within different cell groups, displacement and velocity fields, stress field, and other quantities important for the project goals.

4. Results and post-processing

- Post processing action: Visualization of results (ionic concentrations, electric field, deformations, etc) in Paraview and CAD (indoor pre and post processing using interface software) and analysis of results from researchers and clinicians.

During this project PAK FE solver will be coupled with previously mentioned MUSICO platform or its adequate surrogate models (mass action or data-driven models). The goal of this coupling is the same as with Alya RED FE solver, to simulate the heart model (from sarcomere to the whole model) in order to understand familial cardiomyopathies and sarcomeric protein mutations that lead to it.

3.4 Bioinformatics Programs

The development of next generation sequencing (NGS) technologies is a major breakthrough that is revolutionizing studies of the genetic basis of human disease. NGS enables large tracts of genomic DNA to be sequenced in parallel, and thus the human genome can be sequenced more quickly, more accurately and more cost-effectively than previously possible. NGS is revitalizing the genetics of DCM and will dramatically increase the yield of mutation identification in families. A number of NGS options and platforms are currently available. Whole-genome sequencing of genes and intergenic regions provides comprehensive coverage but generates enormous amounts of data that need to be stored and analysed. An alternative strategy that is gaining widespread popularity is exome sequencing that focusses on the 1% of the human genome that is protein-coding. Since the vast majority of disease-causing variants identified to date have been located in protein-coding sequences [38] and the majority of rare coding sequence variants are predicted to have deleterious functional effects [39], exome sequencing is a powerful tool for mutation discovery [40].

3.4.1 Bioinformatics Tool (BT) description

GATK is a well-known toolbox for NGS data analysis. It is developed in the Data Sciences Platform at the Broad Institute, and it offers a wide variety of tools with a primary focus on variant discovery and genotyping. Its powerful processing engine and high-performance computing features make it capable of taking on projects of any size[1].

Depending on the application, two or three analysis phases are needed[2]:

(1) Data Pre-processing is the first phase in all cases, and involves pre-processing the raw sequence data (provided in FASTQ or uBAM format) to produce analysis-ready BAM (Binary Alignment Map) files. This involves alignment to a reference genome as well as some data cleanup operations to correct for technical biases and make the data suitable for analysis.

(2) Variant Discovery proceeds from analysis-ready BAM files and produces variant calls. This involves identifying genomic variation in one or more individuals and applying filtering methods appropriate to the experimental design. The output is typically in VCF format although some classes of variants (such as CNVs- copy number variants) are difficult to represent in VCF and may therefore be represented in other structured text-based formats.

(3) Depending on the application, additional steps such as filtering and annotation may be required to produce a callset ready for downstream genetic analysis. This typically involves using resources of known variation, truthsets and other metadata to assess and improve the accuracy of the results as well as attach additional information.

3.5 Parallel computing

There is a number of ways to employ state-of-the-art High Performance Computing (HPC) techniques in SilicoFCM platform. As exploitable instruction-level parallelism in scientific applications is limited by design and the CPU frequency cannot be increased any further due to power consumption and heat issues, exploiting **shared-memory parallelism** with multi-core CPUs becomes unavoidable. However, for the purpose of further performance improvement, parallel implementation of methods and algorithms is essential for accelerating any kind of research supported by modelling and simulation. **Distributed-memory parallel computers** are essentially a collection of serial computers (nodes) working together to solve a problem. Each node has rapid access to its own local memory and access to the memory of other nodes via high speed communication network such as Infiniband. MPI is widely adopted standard for message passing within distributed memory systems. **GPU computing** is the use of a GPU (graphics processing unit) as a co-processor to accelerate CPUs for scientific and engineering simulations. The GPU speed-ups applications running on the CPU by offloading some of the compute-intensive and time-consuming portions of the code. Hundreds of small GPU cores operate together to crunch through the data in the application. Newest GPU accelerators reach the performance of almost 13 TFLOPS. There is also a possibility to mix mentioned parallel modes (**hybrid approach**), such as MPI-GPU, MPI-Threads, etc.

A number of SILICOFCM modules already employ various HPC algorithms to reach production ready performance. The computational platform MUSICO (MT) employs thread level parallelism with a plan to be extended to the distributed memory level based on MPI during the project cycle. This extension can be performed without much effort since MUSICO itself is based on *Deal.II framework*

[1] https://software.broadinstitute.org/gatk/
[2] https://software.broadinstitute.org/gatk/best-practices/

[41], which supports MPI out of the box. Since certain use cases of MUSICO include parametric analysis (e.g. experiment fitting) of the actomyosin cycle models and calcium regulatory models, the job distribution for those use cases is trivial. Besides that, certain models such as Huxley's are made available on the GPU, reaching speedups of few dozen compared to a standard CPU run.

PAK solver tool (PST) which will be directly coupled with MUSICO (MT) also employs parallel techniques such as OpenMP in system assembly phase and PETSc (iterative solver) or MUMPS (direct solver) in the linear system solving phase. Implementing multi-scale approach with coupling finite element on the macro level with direct molecular approach based on Huxley's actomyosin cycle model on a micro level has been shown as possible by Ivanovic et al. [42]. This approach employs hybrid MPI-GPU parallelization method, but requires tremendous computing resources to reach production level readiness. In order to model the heart cycle using such approach, few hundreds of CPUs supported by few dozens of GPUs represent just a lower resource limit.

However, another contemporary approach is possible to bring such informative multi-scale models to everyday clinical practice. With the recent advances in machine learning and especially deep learning, it is possible to "imitate" dynamic behaviour of various actomyosin models using deep neural networks. This way, a user is provided with almost instant approximate solution, and if he/she wants to go further, there is always a possibility to run "real" multi-scale model which requires significantly longer computational time and much more HPC resources. Running already trained models is relatively cheap, but training these models still require strong GPU support. Fortunately, today all relevant machine learning libraries already include comprehensive (multi)GPU implementations.

Parallelization in ALYA solver is mainly done externally via MPI. A domain decomposition strategy has been implemented. It only uses parallelism at task level, which is provided by MPI. For that reason, a hybrid code is developed in order to take advantage of all the levels of parallelism that a multicore architecture offers and also to enable one MPI task accessing all the memory of a node. To exploit the thread-level parallelism of multicore architecture OpenMP has been used in the most time-consuming routines of solid [43].

3.6 Big Data mining and decision-making approach

The data collection has grown enormously and is beyond the ability of commonly used software tools to capture, manage, and process them within a desirable elapsed time. The basic challenge for the Big Data services is the exploration of large amount of data and the extraction of useful information or any novel knowledge discovery outcome [44]. Improving the efficiency of single-source knowledge discovery methods through the expansion of existing data mining methods contributes to the foundation for global knowledge discovery in multisource data mining [45].

The data mining services of the SILICOFCM platform includes machine learning algorithms, that offer a potential to identify complex genotype-phenotype relationships. Data mining techniques are expected to be of great interest in terms of their predictive ability and their usability for doctors. Based on machine learning, the SILICOFCM is able to provide cardiomyopathy prognosis that can assist cardiologists by predicting the outcome of the disease for individual patients. In order to train, test and validate data mining-based SILICOFCM Tools for cardiomyopathy prognosis the two databases, clinical and virtual database, will be used. Thus, the Data Analytics Tool, based on machine learning / data mining services, needs to be integrated within the SILICOFCM platform.

3.6.1 Data Analytics Tool (DAT) description

The Data analytics Tool, based on machine learning / data mining, provides services to end-users in terms of analysing the SILICOFCM datasets and focusing on two tasks:

1. predictive modelling and prediction evaluation for virtual patients (WP6, Tasks 6.3 and 6.4),
2. providing cardiomyopathy risk stratification of patients (WP4, Task 4.4).

The aim of *Virtual Patients Repository Modelling* is to apply algorithms for explanation of predictive models and predictions, which will help to identify disease patterns from large volumes of heterogeneous and noisy data. Visualized medical knowledge that explains interdependencies between patterns in data and disease occurrences will be provided.

The aim of *Risk Stratification of FCM patients* is to develop a cardiomyopathy risk stratification tool based on data mining algorithms which will enable identification of high-risk patients (sudden cardiac death or life threating arrhythmias). This tool will be provided and supplemented by prediction reliability estimates.

The outputs of the DAT are expected to be used by end-users (medical experts in the field of cardiomyopathy) to aid them perform risk assessment of patients, simulate outcomes of different therapies and provide explanations for the onset of cardiomyopathies or therapy outcomes.

3.6.2 Multiple Criteria Decision Making Tool (MCDM) description

Multi-Criteria Decision-Making (MCDM) is a discipline aimed at supporting decision makers who are faced with numerous and conflicting decisions. MCDM aims at deriving a quantitative and unambiguous way to come to an optimal compromise in a transparent process. MCDM tool within the SILICOFCM system will provide support in the selection of different alternatives/treatments of heart diseases, e.g. surgery, medication, therapies etc.

Background

Multiple Criteria Decision Making Tool is an important tool that enables user to choose the best alternative out of a number of available versions in the absence of the apparently dominant alternative. The MCDM methods are based on using a decision-making matrix $\mathbf{R} = \|r_{ij}\|$ with values r_{ij} of the criteria $R_1, R_2, \ldots, R_m$ describing the considered process and the vector $\mathbf{\Omega} = (\omega_j)$ of the significances (weights) of these criteria. The use of the MCDM methods is based on the integration of the criteria values r_{ij} and their weights ω_j or obtaining the standard of evaluation, which is the criterion of the method. The weights of the criteria quantitatively express their significance and influence on the evaluation result. The criterion weights can be subjective, i.e. based on the estimates assigned by the experts, and the so-called objective, i.e., those which assess the structure of the data array at the time of evaluation. The evaluation data on the criterion weights also depend on the mathematical methods used for calculations and the estimation scales. In determining the objective weights, several methods assessing various properties or characteristics of the data array's structure are usually employed. Therefore, the use of the procedures, improving the accuracy of the evaluation of the weights' values and the integration of the obtained data into a single value, is often required. A number of methods demonstrating the specific features of the data structure (a decision-making matrix) are commonly used simultaneously for determining the objective weights. Therefore, the need arises for improving the accuracy of the obtained weights, as well as the integration of the estimates assigned by the experts from various groups and the objective weights obtained by using various

methods into an overall estimate. Moreover, to achieve the most accurate evaluation of the criteria weights, the estimates of the objective and subjective weights should be combined [46].

3.7 Virtual Population Tool (VPT) description

SILICOFCM provides virtual models of different cohorts (classified patient groups which differ in physiology and heart morphology). A virtual population that reflects individual subject and population-level characteristics of a typical clinical cohort provides increased confidence that prospective simulations of response to novel therapeutics will reflect the intersubject variability seen in the clinic, and may help to identify responders and nonresponders to treatment [47].

The general flow of the generation of virtual population that match distributions of clinical cohorts or populations is [48]:

1. Implement an ordinary differential equation (ODE) model that describes the biological system of interest;
2. For each state (variable) in the model, define a lower and upper limit for assessing if a steady state solution is plausible (all states between lower and upper limits) or not;
3. For each parameter of the model also define a plausible lower and upper limit for the search algorithms;
4. Optimize, using one of four algorithms, for solutions of the model that are plausible patients (PP);
5. Collect the PPs generated by the optimization into a plausible population, terminating the search for PPs when the optimization achieves a preset number of PPs in the plausible population;
6. Perform acceptance/rejection sampling on the plausible population to select the VPs from the PPs that allow us to match the statistics of the target clinical population.

The SILICOFCM virtual patient model library enables the testing of a new drug under different boundary conditions. The Virtual Patients 3D Library contains the geometry data as well and material data and physiological parameters repository which provides the ability to end-user select and simulate heart behaviour under different boundary conditions. This library can be published and used in other simulation environments.

3.8 Similar commercial *in silico* Cloud platforms

InSilicoTrials

InSilicoTrials[3] was founded in 2016 as a spin-off of a company specialized in technological solutions for clinical trials. It provides healthcare companies and researchers with easy-to-use tools to perform computational modelling and simulation in pharmaceutical and medical devices development. Figure 5 presents the concept of this platform.

The platform offers users two computational options:

- to select the model of choice from the digital library
- to develop or to upload their own model

[3] https://insilicotrials.com

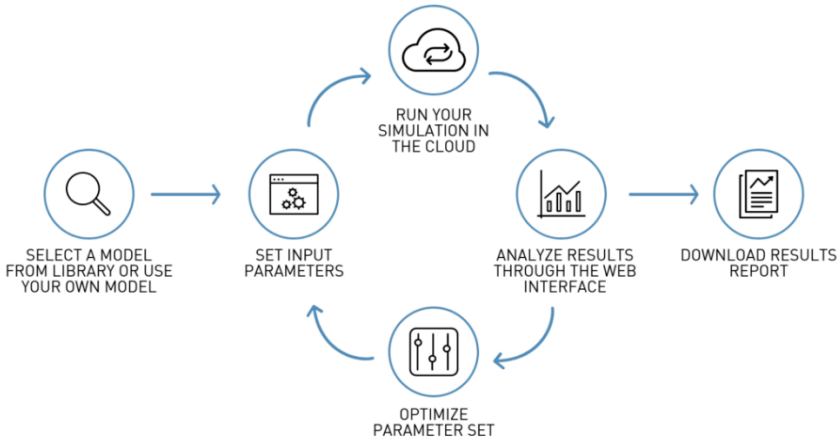


Figure 5. InSilicoTrials platform.

The platform enables users to input parameters of choice into the model. For a model from the digital library, parameters choices are guided by best practice ranges. Completion of the modelling and simulation is notified to the users via e-mail. The platform enables users to view and analyse the modelling and simulation results and to optimize modelling and simulation scenario's depending on objectives.

Insilico Biotechnology - Insilico Simulation Platform

The Insilico Simulation Platform[4] features next simulation tools:

The **Gene Perturbation Screening Tool** allows users to screen millions of combinations of up to ten different genes for perturbations. This tool not only considers the impact of gene perturbations on product formation but also its impact on cell growth and by-product formation, thus allowing goal-oriented rational strain development.

The **Tool for the Adaptation of Feed Compositions and Feed Strategies** facilitates the identification of over or underfeeding scenarios prior to the start of fermentation, thus saving valuable process development time.

The **Pathway Screening Tool** provides the possibility to simulate new or alternative pathways in a host cell in parallel. The tool considers more than 8,000 biochemical reactions contained in Insilico's reaction database. Moreover, the tool is able to integrate new reactions bearing resemblance to known reactions. Hence the effort needed to adapt a host cell to produce a new product can be predicted. Thus, the potential and risks of a new project can be assessed, and novel Intellectual Property can be created.

The **Tool for Simulation of Stratified Local and Systemic Drug Effects** allows for the calculation of bioavailability, efficacy and toxicological risk of drugs. Variations in enzyme expression patterns between different patient subpopulations can be taken into account. The prospective in vivo toxicity can be estimated on the basis of in vitro data integrated into the model.

FEops - TAVIGuide

FEops is developing future generation procedure planning technology for transcatheter structural heart therapies. Their product TAVIguide™ is a cloud based pre-operative planning service for

[4] http://www.insilico-biotechnology.com/en/technology#3

Transcatheter Aortic Valve Implantation (TAVI). TAVIguide[5] predicts the interaction between the TAVI device and the specific patient, combining routine preoperative CT imaging with advanced computer simulations.

Insilico Medicine

Insilico Medicine, Inc[6] is an artificial intelligence company. The company and its scientists are dedicated to extending human productive longevity and transforming every step of the drug discovery and drug development process through excellence in biomarker discovery, drug development, digital medicine, and aging research. Insilico pioneered the applications of the generative adversarial networks (GANs) and reinforcement learning for generation of novel molecular structures for the diseases with a known target and with no known targets.

Cloudpharm

Cloudpharm[7] is a bio-pharmaceutical R&D Company. Its core business focuses on the discovery of bioactive compounds with pharmacological interest, emphasizing on natural products. Moreover, Cloudpharm provides services for drug identification protocols, as well as in silico services for drug design and discovery and drug repositioning.

[5] http://www.feops.com
[6] http://www.insilico.com/#rec41455834
[7] http://cloudpharm.eu

4. The Requirements Capturing Process

4.1 Requirements types and definition process

Among the key objectives of the SILICOFCM Work Package 1 is to collect and analyse requirements from the stakeholders being part of the SILICOFCM ecosystem. Especially in the case of the SILICOFCM project high complexity, a variety of stakeholders exists with specific requirements and expectations from the SILICOFCM platform. Within the Tasks 1-3 of WP1, requirements are defined as:

- Functional (F), which are associated with the capability or application needed to directly support the users' accomplishment of their mission and tasks, and
- Non-functional (NF), which are mainly general requirements, typically implicit and technical in nature and emerge as system requirements to satisfy the users' functional needs, e.g., availability, quality of service, timeliness, and accuracy.

4.2 Characteristics of a good requirements statement

A good statement of requirements can typically be characterized as follows [49]:

- A requirement must be *traceable* to an operational need and attributable to an authoritative source, e.g. a person or a document. Once defined, it receives a unique identifier allowing the software design, code, and test procedures to be precisely traced back to the requirement.
- Requirement definition should be *unambiguous*. A good practice is to test the wording of the requirement from the perspectives of different stakeholders and check whether it can be interpreted in multiple ways. Vague, general statements must be avoided. This will allow testing the requirements and demonstrating that they are satisfied by the end product or service. Descriptions need to be clear, specific and singular.
- Definitions need to be *measurable*, either quantitatively or qualitatively. Typical categories of measures are:
    - Measures of Effectiveness (MOEs), i.e. measures of mission success from stakeholders' point of view;
    - Measures of Performance (MOPs), used to determine whether the system meets performance requirements necessary to satisfy the MOE.
    - Key Performance Parameters (KPPs) or Indicators (KPIs) defined by stakeholders as measures of minimal and critical system or project performance and level of acceptance.
    - Requirements must be uniquely identified, consistent and compatible with each other.
    - Requirements need to be feasible, i.e. they are attainable in terms of technology, cost, and schedule. If a requirement cannot be implemented, it should be removed from the statement.
    - The specification of requirements should be design-free, reflecting what the system needs to accomplish.

4.3 Good practices in requirements definition

The top identified defects and the advices and preventive measures are given in Figure 6 [50].

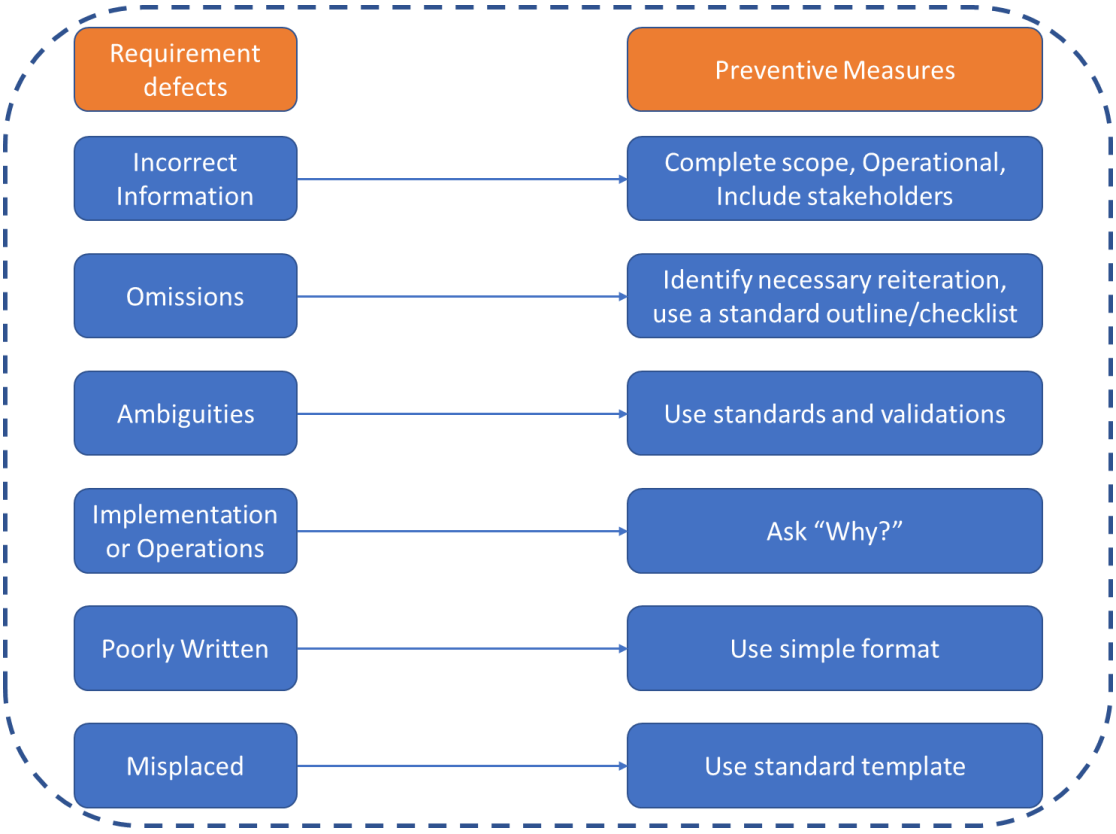


Figure 6. Defects and the preventive measures.

According to the analysis of MITRE systems engineers[8] among the most important best practices in requirements definition are the following:

- *Baseline and agree.* Developing requirements is usually a collaborative activity, involving users, developers, maintainers, integrators, etc., so avoid placing the responsibility of requirements analysis solely on one stakeholder. When all team members acknowledge a set of requirements is done, this is called a baseline (recognising that definitions will evolve).
- *Requirements analysis is an iterative process*. At each step, the results must be compared for traceability and consistency with stakeholders' requirements, and then verified with users, or go back into the process for further analysis, before being used to drive architecture and design.
- *Special attention is to be paid to interface requirements*. Requirements must clearly capture all the interactions with external systems and the external environment so that boundaries are clear.

8 www.mitre.org/work/systems_engineering/guide/se_lifecycle_building_blocks/requirements_engineering/analyzing_defining_requirements.html

- *Be flexible*. To balance out rigidness of baselining requirements, a development team should consider what constitutes a "change of requirements" as distinguished from a valid interpretation of requirements. The key is to find a balance between adherence to a baseline and sufficient flexibility.
- Use *templates* and *tools* that suit your needs.

A number of modalities are used in order to elicit the requirements:

1. Directly contacting with stakeholders;
2. Incorporating their own experience;
3. Reviewing related international scientific literature;
4. Introducing and analysing the experience of past projects and related ongoing ones where information is available;
5. Analysing official reports and documents, including EU documents.

The SILICOFCM requirements capturing and analysis process is graphically presented in the following figure:

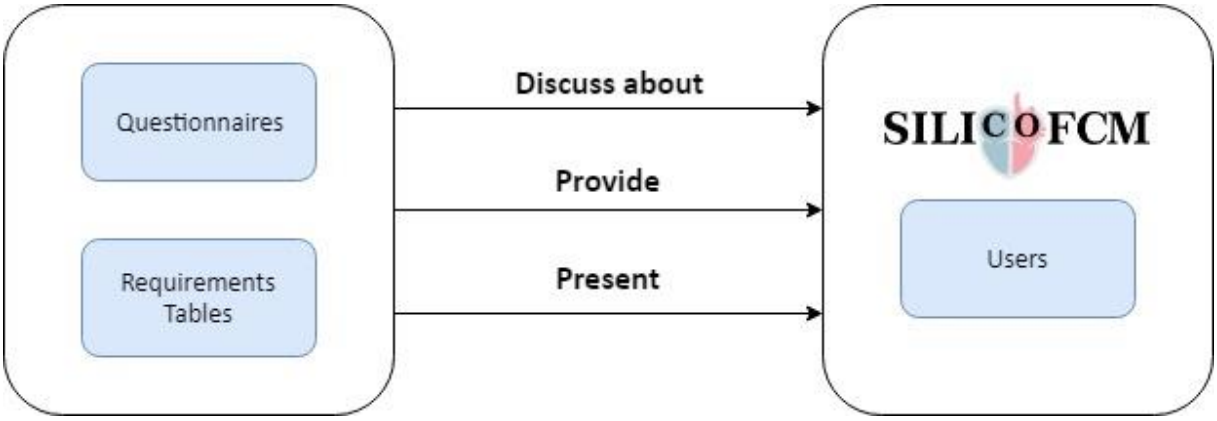


Figure 7. The SILICOFCM Requirements Capturing and Analysis Process.

As a result of these activities, we have developed, and present in the current deliverable, a coherent set of user requirements addressing all of the users' needs and corresponding expectations.

We nevertheless recognize, as stated previously, that requirements are bound to evolve from this initial set of agreed baselines and that requirement is an iterative process.

This iterative nature of requirements is necessary for several reasons, such as:

1. **The requirements change.** The period between the time point that the requirements are "finalized" to the time point that the system is actually deployed will often span months, if not years. During this timeframe changes will occur in the marketplace, legislation will change, and organization's strategy might change. All of these changes in turn will motivate true changes to our requirements.
2. **Users' understanding of the requirements change.** More often than not what we identify as a changed requirement is really just an improved understanding of the actual requirement. Users aren't very good at predicting what they want. They are good at indicating what they might want, and then once they see what it was actually built then can then provide specific and focused feedback as to how to get it closer to what is actually needed. Therefore, one needs an approach which easily enables this.

As a result, the project will systematically seek to capture user needs and requirements in every cycle of development. Nevertheless, the output of this initial "requirements gathering and elicitation process", documented in the present deliverable, provides for a robust starting point upon which subsequent activities, prototypical implementation of systems and services, and so on, will rely on.

5. User and regulatory requirement analysis

5.1 SILICOFCM platform end-users

Based on the answers on three Questionnaires, the SILICOFCM platform end-users are various, such as: Cardiologist; Pharmaceutical companies; Private Clinicians; Groups of clinicians (i.e. public or private bodies such as hospitals, healthcare institutes); Researchers/Healthcare Professionals Researchers/Biomedical Engineers; Postgraduate/Undergraduate Students. Based on the top ranked answers, we made three main groups of end-users: Cardiologists, Pharmaceutical companies, Researchers. In the later stage of SILICOFCM platform development, those groups can be changed depending on commercialization and dissemination activities.

On the other hand, the SILICOFCM platform support users are next: Data providers, Cloud providers (administrators) and developers (inner and outer). The schematic representation of SILICOFCM platform users and their main interaction with the platform is given in the Figure 8.

Figure 8. SILICOFCM platform users.

5.1.1 Cardiologists

The Cardiologists (User role hierarchy: High) will use the SILICOFCM platform for cardiomyopathy prognosis based on data mining algorithms and 3D imaging-based modelling of cardiomyopathy that can assist medical doctors by predicting the outcome of the disease for individual patients. We will perform exhaustive research in order to identify genotype-phenotype relationships associated with FCM. In order to train, test and validate data mining-based SILICOFCM for cardiomyopathy prognosis, the two databases will be used:

1. Clinical database,
2. Virtual database.

A broader and consistent utilization of SILICOFCM platform and its integration in drug development chain will help to improve health care quality, effectiveness and accuracy in the personalized diagnosis and treatment of FCM leading to better lifelong management of the FCM patients.

5.1.2 Researchers

Next user of SILICOFCM platform is an individual researcher (User role hierarchy: High). Those type of users will have access to virtual population and pool of heart models. Users may download the models for research only purposes. SILICOFCM project will collect a number of prospective data that will be

used for the extension of the SILICOFCM *in silico* modules and tools. However, those data are valuable and could be considered as a "benchmark" dataset for validating new modules for FCM monitoring or other and also for computational resources/methods. The SILICOFCM platform will provide the tools to validate new modules or computational resources/methods based on the prospective data of SILICOFCM or against existing SILICOFCM modules.

SILICOFCM consortium will investigate whether SILICOFCM platform could be open to 3rd party organizations to provide new modules and computational resources to SILICOFCM. In a potential business model, running a model or using computation resources of an institution could be charged and offered as a service. Specifically, a researcher may register a model/computational resource as an "under validation" model and use the SILICOFCM with supported solvers to run the simulation on a number of pre-validated models.

5.1.3 Pharmaceutical companies

The SILICOFCM platform will have the Pharmaceutical companies (User role hierarchy: High) as a target. The SILICOFCM integration in drug design and development chain is a highly complex, standardized process subject to numerous directives and regulations. SILICOFCM ambition is to provide a platform through which the pharmaceutical companies will be able to monitor effectiveness of pharmacological treatment and functional optimization of whole heart performance using state-of-the-art *in silico* models and resources made available by high profile research organizations. Moreover, SILICOFCM will provide a virtual case repository (virtual patients) annotated with specific anatomical and genetic criteria. The end-users will be able to apply the simulation modules to virtual cases of high interest.

Also, SILICOFCM platform provides tools for hierarchical testing of multiple compounds, predicting potency of each compound from the simplest and inexpensive experiments toward more complex and more expensive trails. The hierarchical process provides early elimination of less potent drugs that could reduce cost of drug development by an order of magnitude or more. Explicit modelling and tight coupling with experiments provides ability to reveal the reasons for failure in early stages of drug development and from gained information suggest alternative approaches and improvements.

5.2 SILICOFCM platform support users

As any platform, the SILICOFCM platform will have a support, such as Data providers, Cloud providers (administrators) and developers (inner and outer) who have privileges to monitor the platform's health and also develop and improve its performances. The Data provider can manage the user account, as well as the clinical data, while the Cloud provider (administrator) is responsible for a variety of functionalities concerning the cloud's infrastructure management.

The platform's inner developer is responsible for updating the core services of the SILICOFCM platform, while the registered developer (outer developer) is responsible for executing new workflow models. More details about SILICOFCM platform support users and their roles can be found in the D1.3 "SILICOFCM Reference Architecture".

5.3 User needs based on Questionnaires

In order to accomplish SILICOFCM architecture, the identification of the User's Needs (UNs) and expectations are imperative. The implementation of a User Requirements Analysis (URA) to collect and define the platforms performance is therefore critical for the success of the platform's applicability and adaptability. The objective of URA is dual: (i) collect the user needs and, (ii) specify the requirements that address the user needs. The collection of the user needs aims at achieving a better knowledge on the users' needs, while in parallel focuses on defining those set of requirements, which will be utilized as a basis for the design and the implementation phases. To accomplish this, three Questionnaires are created:

1. SILICOFCM User Requirements Questionnaire for Clinicians as end-users,
2. SILICOFCM User Requirements Questionnaire for Bioengineers and researchers.
3. SILICOFCM User Requirements Questionnaire for Pharmaceutical companies as end users

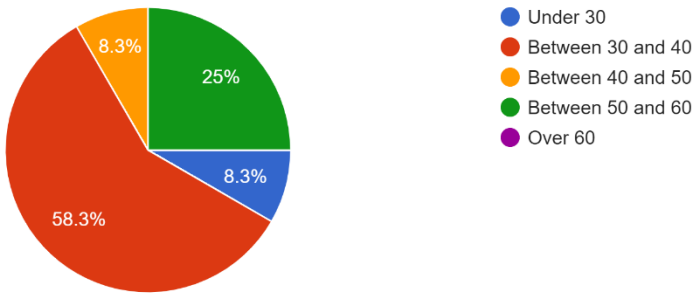
In this section, we present the results of the questionnaires provided to the users to gather their inputs for the system design. The Questionnaires contain some similar or the same questions, while majority of the questions is adjusted to target group.

As an iterative process, we have circulated a new version of the questionnaire intended for the end-users from industry i.e. pharmaceutical companies. The newly gathered feedback from pharmaceutical companies will have influence on further directions of SILICOFCM platform development.

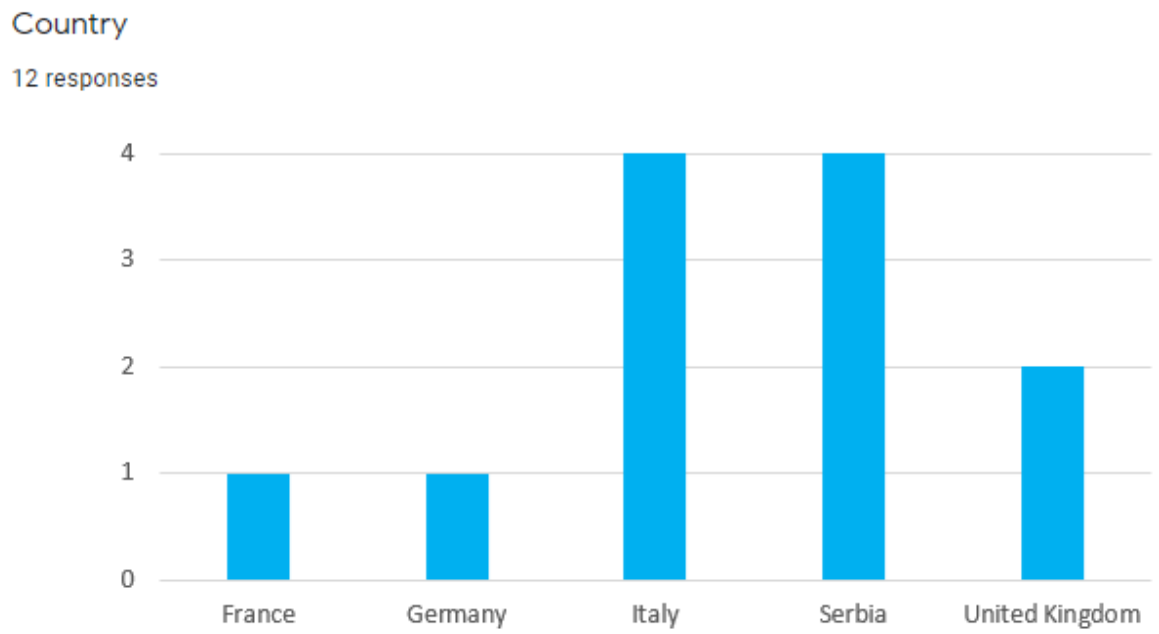
5.3.1 Questionnaire I - SILICOFCM User Requirements Questionnaire for clinicians as end-users

General information

Age
12 responses



Value	Count
Under 30	1
Between 30 and 40	7
Between 40 and 50	1
Between 50 and 60	3
Over 60	0



Value	Count
France	1
Germany	1
Italy	4
Serbia	4
United Kingdom	2

Organisation

12 responses

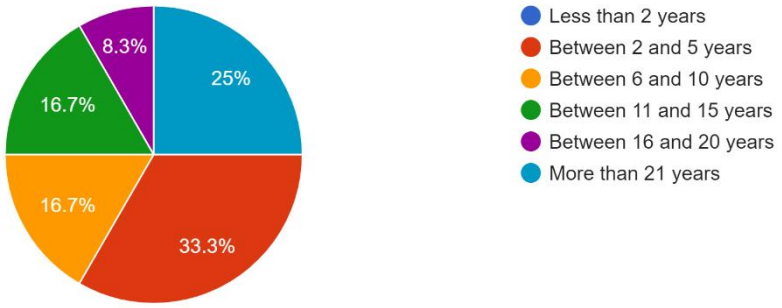
ICVDV
azienda ospedaliera universitaria careggi
Newcastle University and Newcastle Hospitals
Newcastle upon Tyne Hospitals
Pitié-Salpêtrière, APHP, Sorbonne Université
University Hospital
Careggi University Hospital
University of Florence
Institute for cardiovascular disease of Vojvodina
Careggi
Clinic for Cardiology, Clinical Center Kragujevac
Clinical Center of Serbia

Role in your organisation

12 responses

Principal investigator / cardiac surgeon
head, cardiomyopathy unit
Principal Investigator, Associate Professor
Consultant Cardiologist
Cardiologist
Medical Doctor
Senior Cardiologist
Post-doctoral research associate
clinical doctor
consultant in cardiology
Cardiologist
Medical Doctor

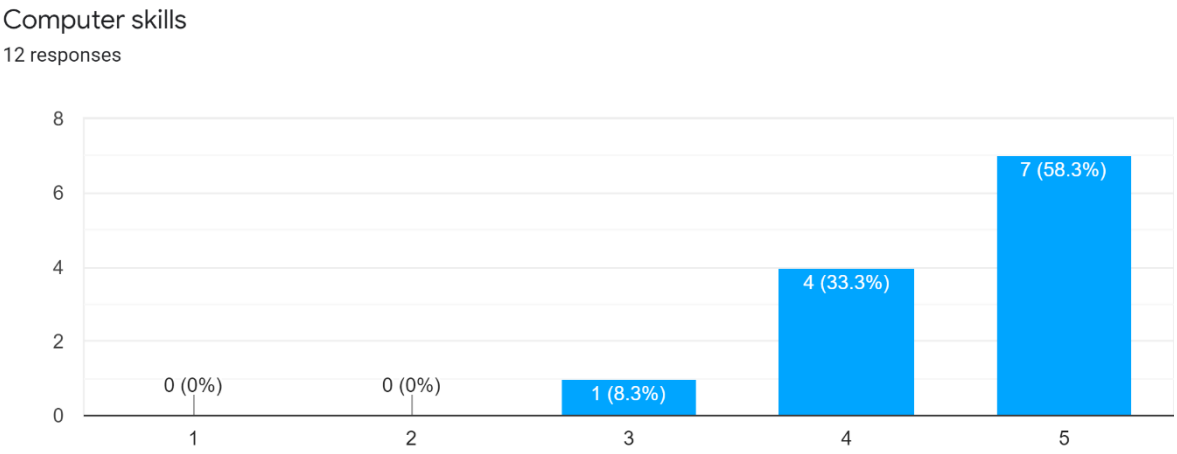
How many years of experience do you have in your profession?
12 responses



Value	Count
Less than 2 years	0
Between 2 and 5 years	4
Between 6 and 10 years	2
Between 11 and 15 years	2
Between 16 and 20 years	1
More than 21 years	3

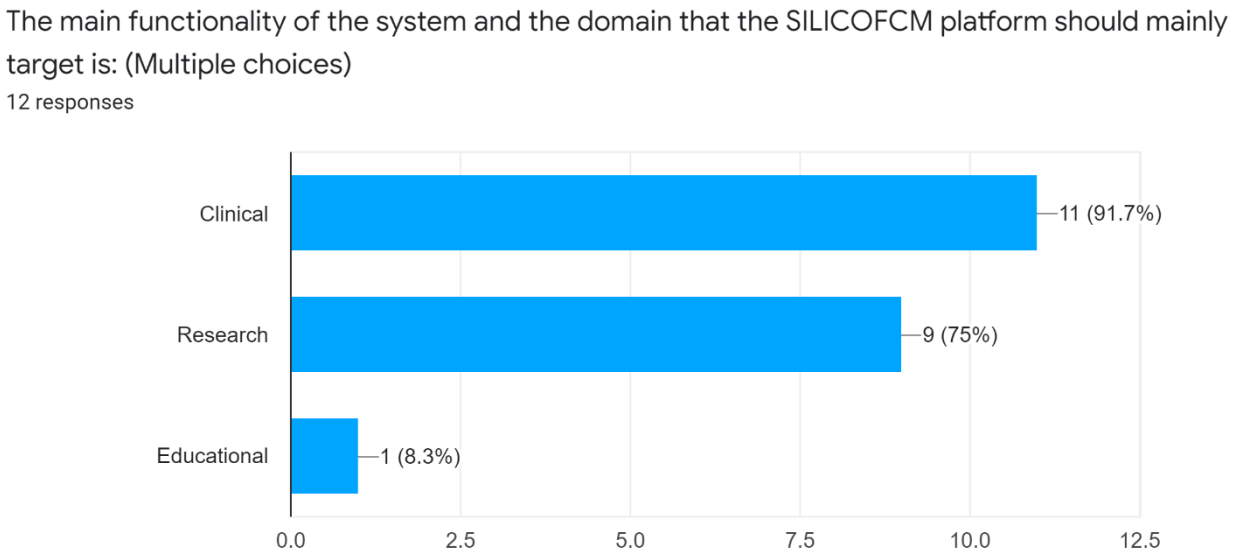
Computer use
12 responses

Value	Count
Everyday	12

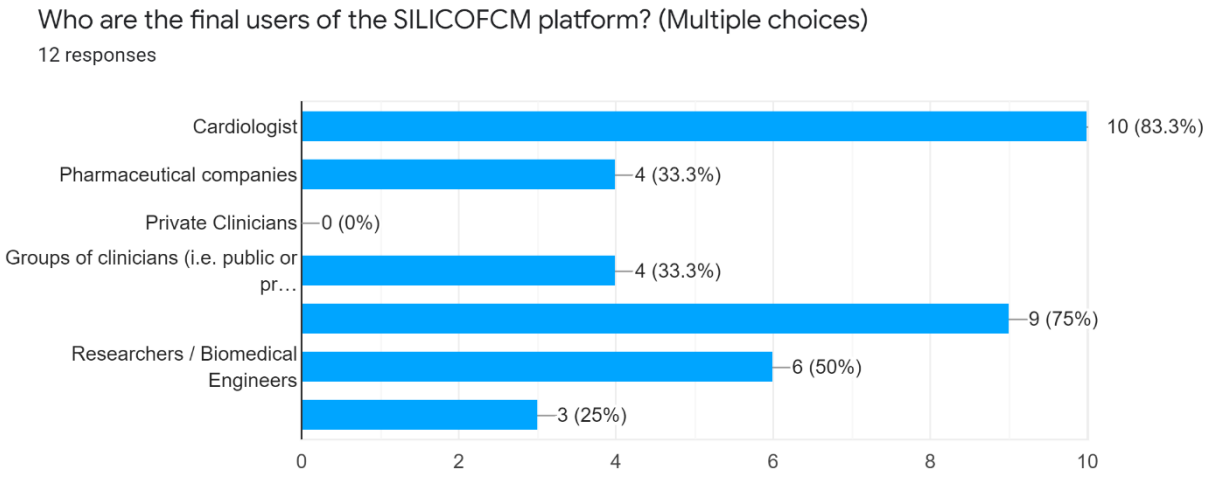


Value	Count
1 Insufficient	0
2	0
3	1
4	4
5 Excellent	7

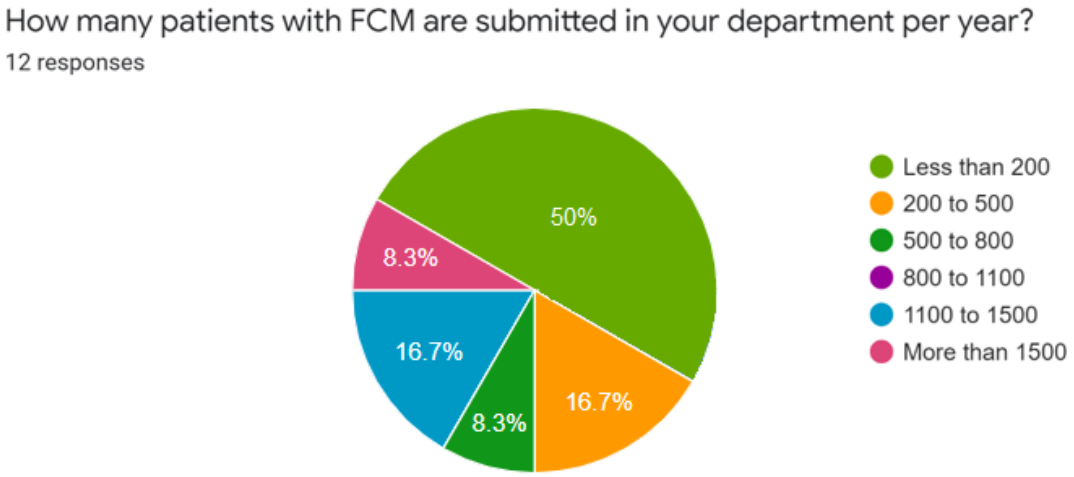
System usage scenarios



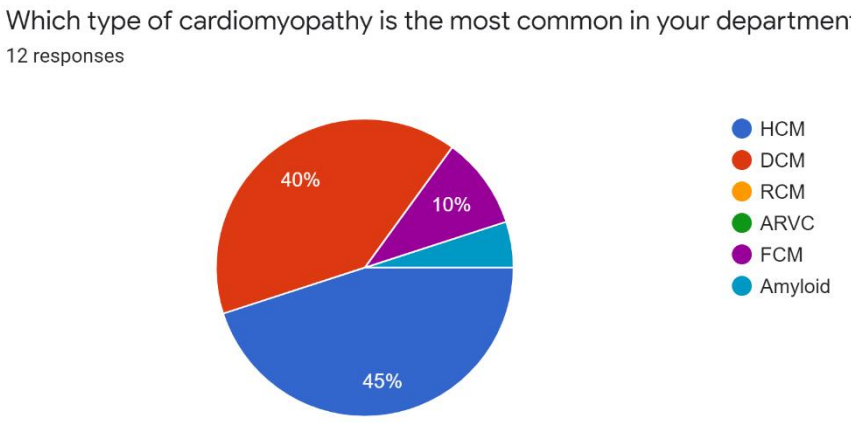
Value	Count
Clinical	11
Research	9
Educational	1



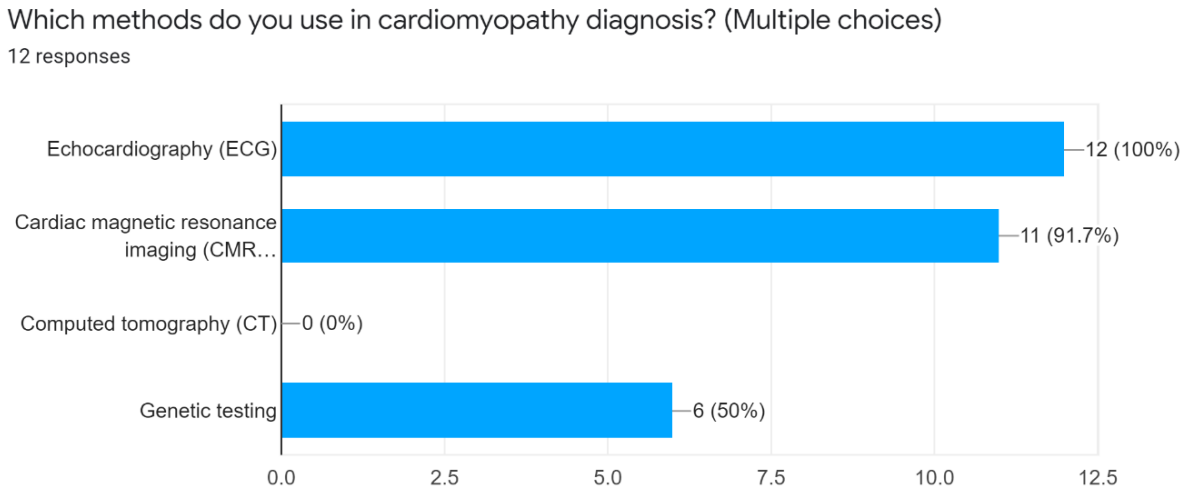
Value	Count
Cardiologist	10
Pharmaceutical companies	4
Private Clinicians	0
Groups of clinicians (i.e. public or private bodies such as hospitals, healthcare institutes)	4
Researchers/Healthcare Professionals	9
Researchers/Biomedical Engineers	6
Postgraduate/Undergraduate Students	3



Value	Count
Less than 200	6
200 to 500	2
500 to 800	1
800 to 1100	0
1100-1500	2
More than 1500	1



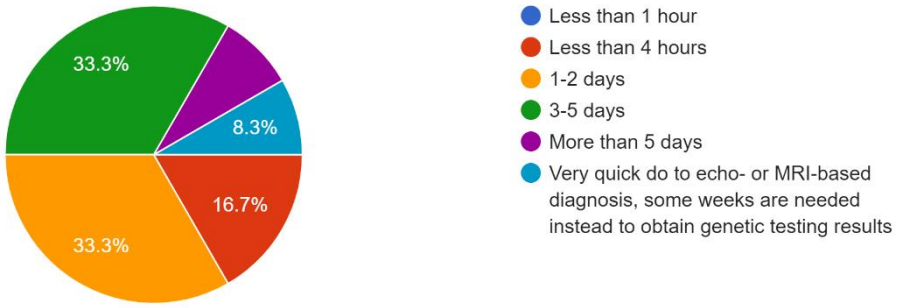
Value	Count
HCM	9
DCM	8
RCM	0
ARVC	0
FCM	2
Amyloid	1



Value	Count
Echocardiography	12
Cardiac magnetic resonance imaging (CMRI)	11
Computed tomography (CT)	0
Genetic testing	6

How much time do you need for diagnostic protocol per one patient?

12 responses

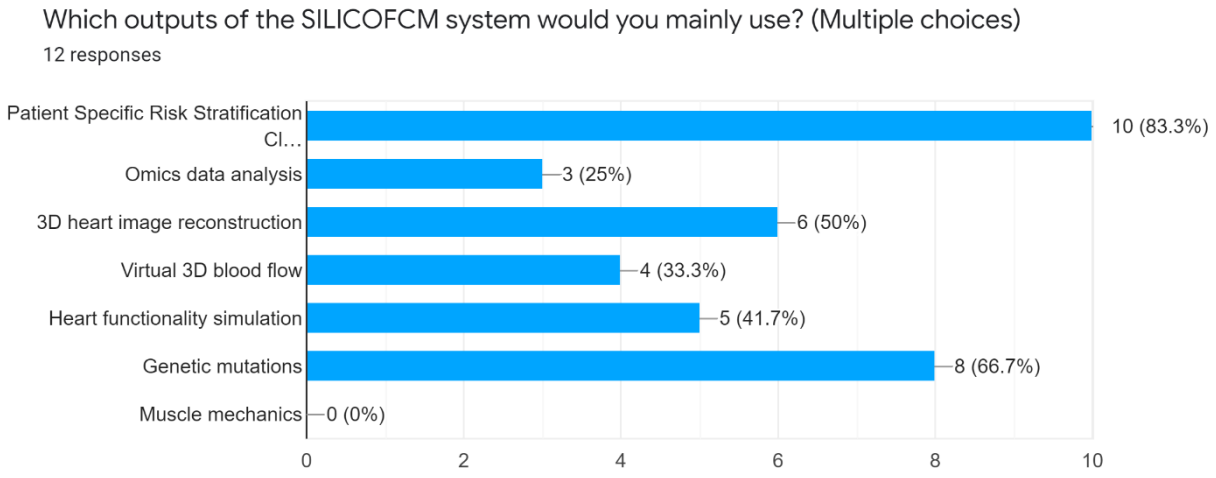


Value	Count
Less than 1 hour	0
Less than 4 hours	2
1-2 days	4
3-5 days	4
More than 5 days	1
Other: *Very quick do to echo- or MRI-based diagnosis, some weeks are needed instead to obtain genetic testing results*	1

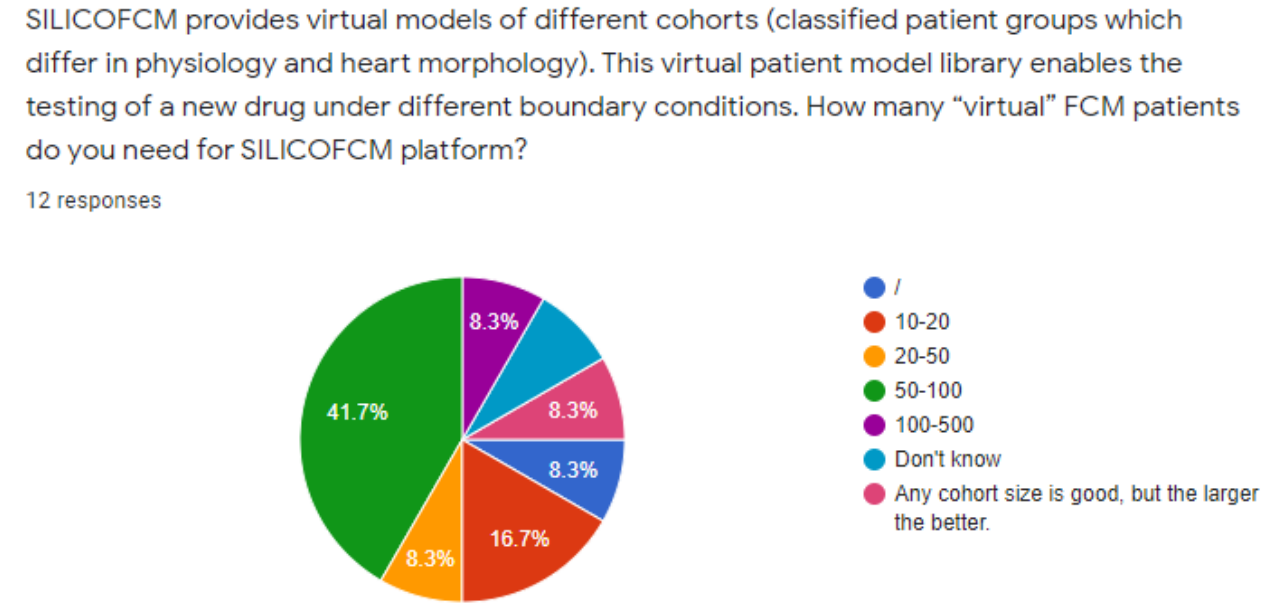
Which type of therapeutic intervention is the most common for FCM patients by your experience?

12 responses

- Optimal medical treatment
- drug treatment, ICD implantation
- Pharmacological (to ameliorate symptoms) and device (ICD)
- Medical therapy
- medical therapy of heart failure
- -
- Drug treatment
- I am not sure - as I work in research
- medical therapy
- drug therapy
- Implantation of implantable cardiac defibrilator
- Medical treatment

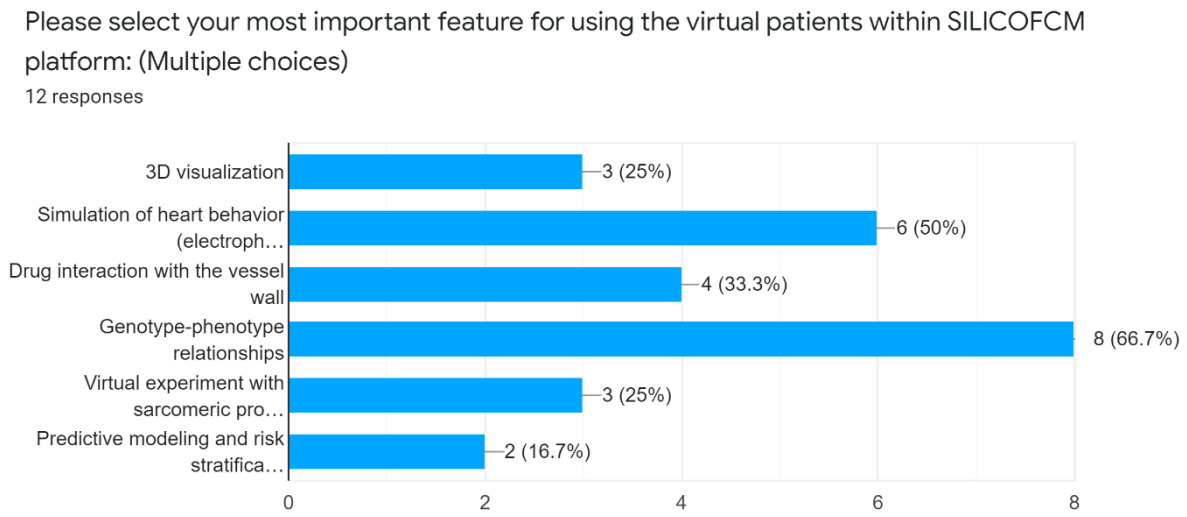


Value	Count
Patient Specific Risk Stratification Clinical Decision Support System (CDSS)	10
Omics data analysis	3
3D heart reconstruction	6
Virtual 3D blood flow	4
Heart functionality simulation	5
Genetic mutations	8
Muscle mechanics	0

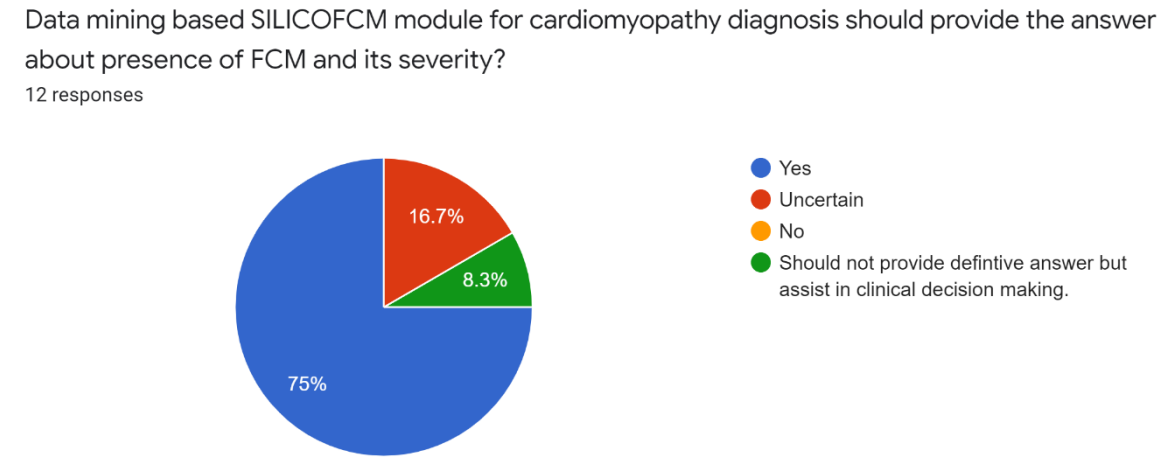


Value	Count
/	1
10-20	2
20-50	1
50-100	5
100-500	1

Other: *Don't know*	1
Other: *Any cohort size is good, but the larger the better*	1



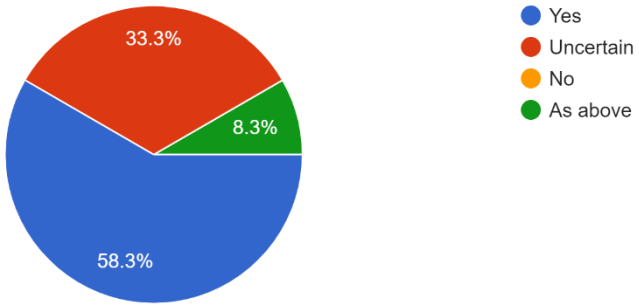
Value	Count
3D visualization	3
Simulation of a heart behaviour (electrophisiology)	6
Drug interaction with the vessel wall	4
Genotype-phenotype relationships	8
Virtual experiment with sarcomeric proteins on muscle functions	3
Predictive modeling and risk stratification	2



Value	Count
Yes	9
Uncertain	2
No	0
Other: *Should not provide definitive answer, but assist in clinical decision making*	*1*

Data mining based SILICOFCM module should provide the answer about type of cardiomyopathy treatment?

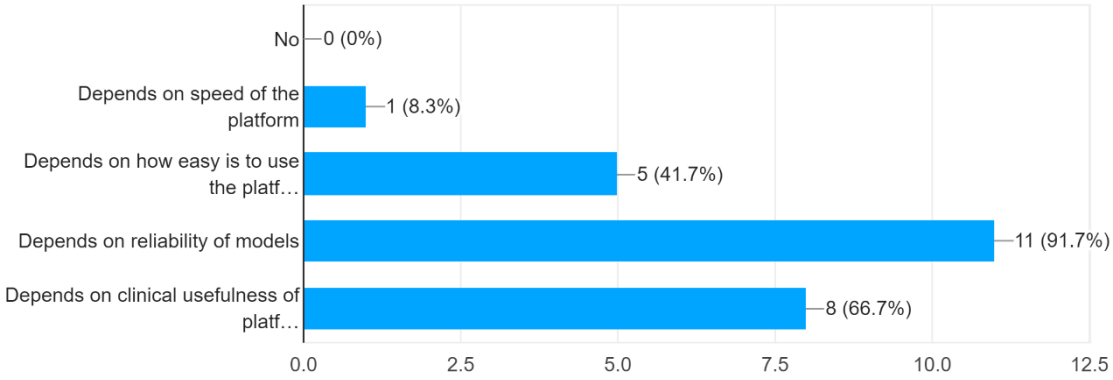
12 responses



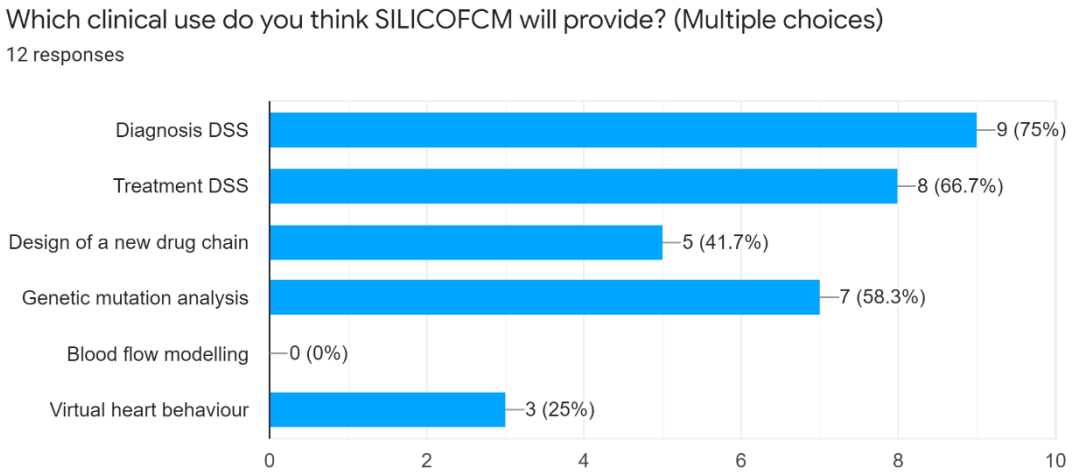
Value	Count
Yes	7
Uncertain	4
No	0
Other: *As above, i.e. should not provide definitive answer, but assist in clinical decision making*	*1*

Would you intend to use the SILICOFCM as a personalized clinical tool for individual patients? (Multiple choices)

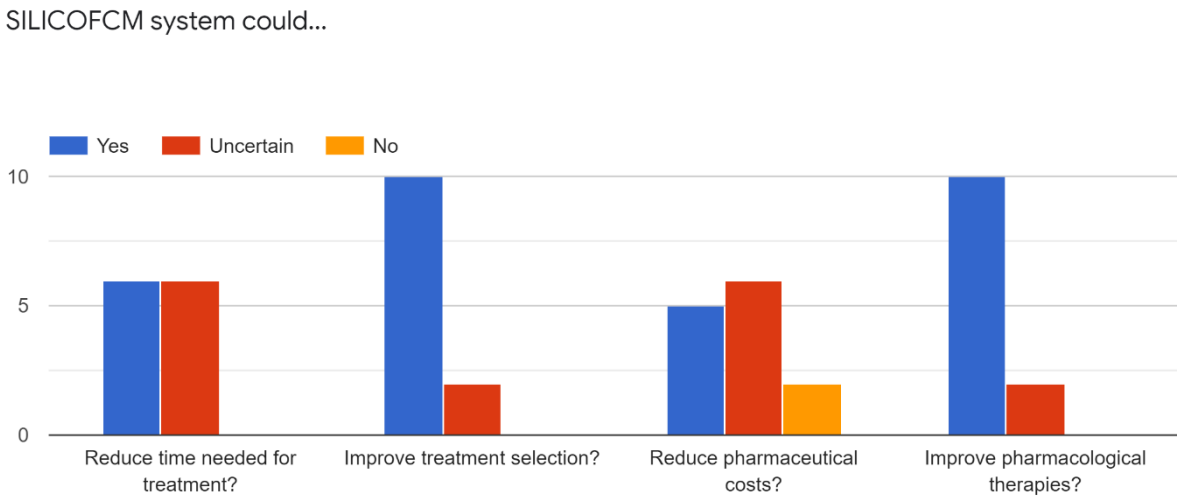
12 responses



Value	Count
No	0
Depends on speed of the platform	1
Depends on how easy is to use the platform	5
Depends on reliability of models	11
Depends on clinical usefulness of the platform	8



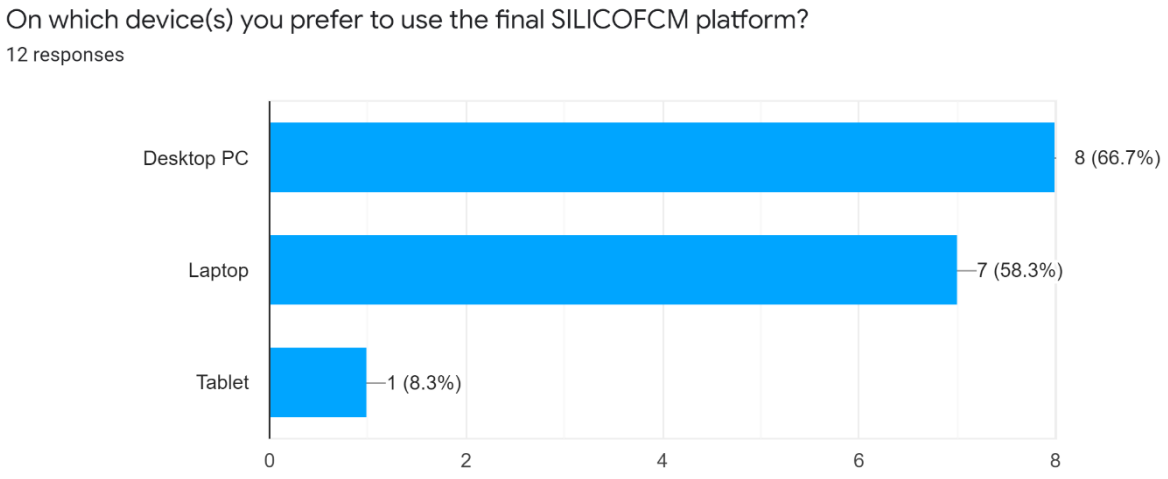
Value	Count
Diagnosis DSS	9
Treatment DSS	8
Design of a new drug chain	5
Genetic mutation analysis	7
Blood flow modelling	0
Virtual heart behaviour	3



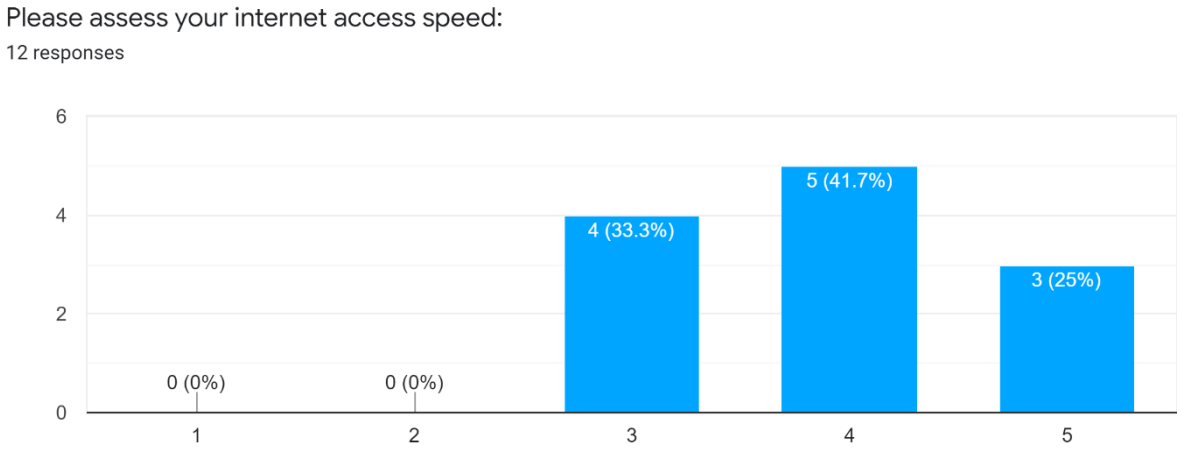
Value	Count		
	Yes	Uncertain	No
Reduce time needed for treatment?	6	6	0
Improve treatment selection?	10	2	0
Reduce pharmaceutical costs?	5	6	2

Improve pharmacological therapies?	10	2	0

Functional aspects



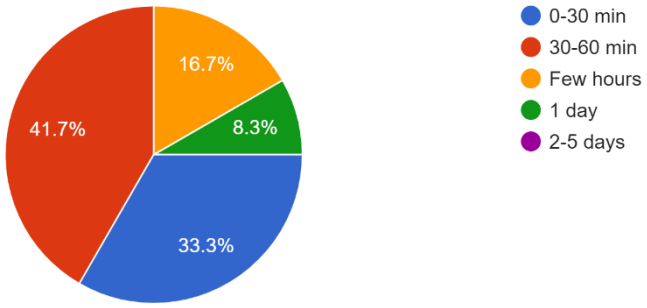
Value	Count
Desktop PC	8
Laptop	7
Tablet	1



Value	Count
1 Very slow	0
2	0
3	4
4	5
5 Very fast	3

Please select the maximum acceptable response time of the SILICOFCM modules:

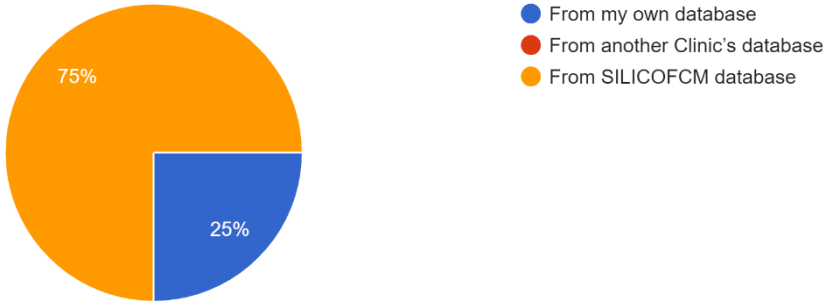
12 responses



Value	Count
0-30 min	4
30-60 min	5
Few hours	2
1 day	1
2-5 days	0

The final SILICOFCM platform will have to use the patients' data:

12 responses



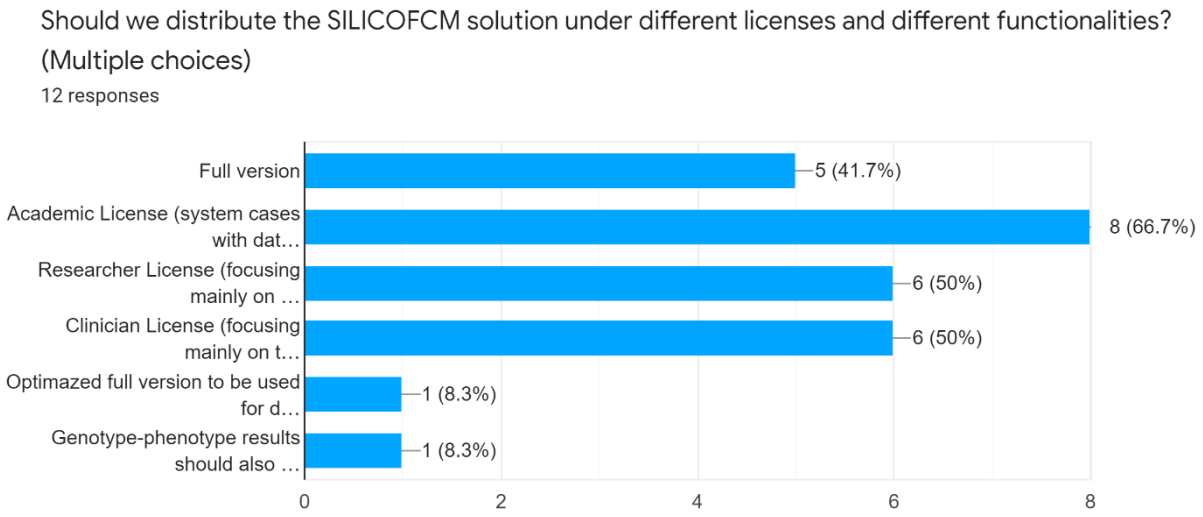
Value	Count
From my own database	3
From another Clinic's database	0
From SILICOFCM database	9

Which additional functionalities are necessary to be included in the final product? (optional)

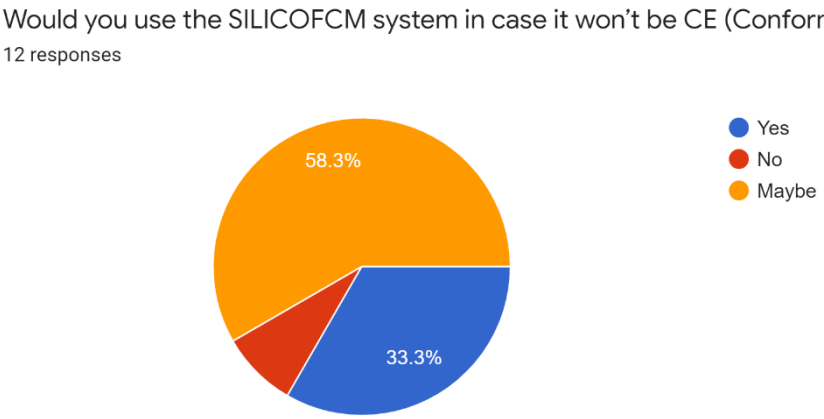
1 response

Validity/accuracy, reliability/reproducibility, accessibility, speed.

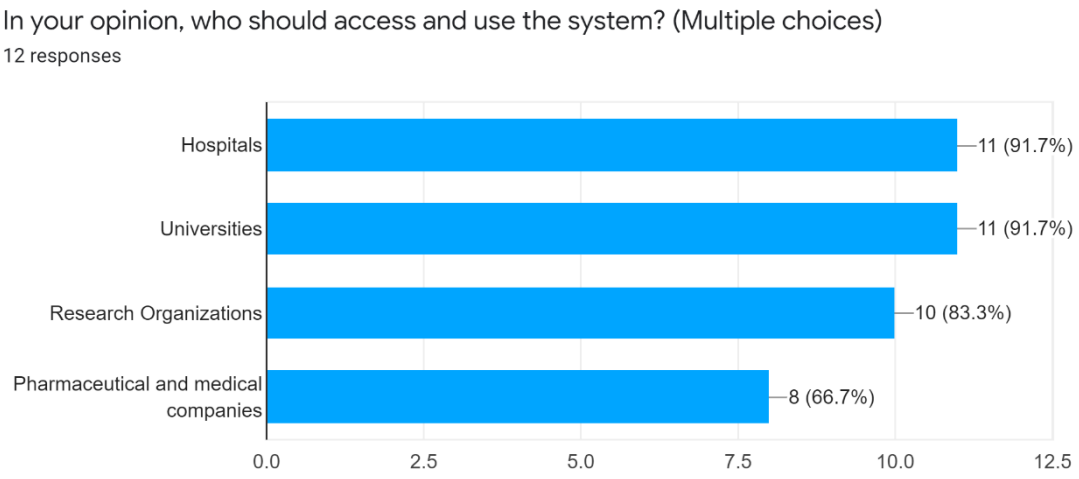
Exploitation aspects



Value	Count
Full version	5
Academic License (system cases with data for demonstration)	8
Researcher License (focusing mainly on the 3D geometry visualization and mechanical modelling)	6
Clinician License (focusing mainly on the 3D visualization and the pathologies	6
Other: *Optimized full version to be used for different purposes*	1
Other: Genotype-phenotype results should also be distributed	1



Value	Count
Yes	4
No	1
Maybe	7



Value	Count
Hospitals	11
Universities	11
Research Organizations	10
Pharmaceutical and medical companies	8

5.3.2 Analysis of Questionnaire I

The User Requirements Questionnaire for Clinicians as end-users contained following sections:

- General information;
- System usage scenarios;
- Functional aspects;
- Exploitation aspects and
- Clinician specific comments.

The questionnaire at the D1.1 v2.0 has the two participants more (12 in total), comparing with the v1.0, since the representative of new SILICOFCM partner (FMGB) answered the questions, as well as the representative from Clinical centre in Kragujevac (Serbia) who expressed the interest for SILICOFCM project and willingness to participate in the survey. In addition, the answer on question "Which cardiomyopathy is the most common in your department?" is changed from multiple answers (in v1.0) to only one answer (v2.0). Also, the question "Which methodology do you prefer to use in cardiomyopathy diagnosis" (in v1.0) has been replaced with "Which methods do you use in cardiomyopathy diagnosis?" (v2.0).

General information

The participants who filled out the questionnaire are less than sixty years old, with 58.3% between the age of 30 and 40. Four participants (40%) have 2-5 years of experience in clinical practice, 16.7% has 6-10 years of experience, 16.7% has 11-15 years of experience, 8.3% has 16-20 years of experience, while 25% has more than 21 years of clinical practice. All participants use their computers every day. Additionally, 58.3% of the participants consider having excellent computer skills.

System usage scenarios

The majority of participants think that main functionality of the SILICOFCM platform should be clinical and research. Cardiologists and Researchers/Healthcare Professionals are listed as the final users by 83.3% and 75% of the participants, respectively, while Researchers/Biomedical Engineers and Pharmaceutical companies should be final user according to the 50% and 33.3% of the participants, respectively.

One participant that filled out the Questionnaire has more than 1500 patients with FCM per year in the department. 50% of participants said that they have less than 200 patients, 16.7% of the participants have either 200 - 500 or 1100 - 1500 patients with FCM per year. 45% participants said that HCM is the most common type of the cardiomyopathy in their department, followed by DCM (40%). The total sum of answers corresponds to previously enabled multiple answers on this question (in v1.0). Every participant uses echocardiography (ECG) as a methodology for cardiomyopathy diagnosis. This is followed by Cardiac magnetic resonance imaging (CMRI) that is used by 91.7% and Genetic testing used by 50%. Currently, for 33.3% of the participants it takes 1-2 days for diagnostic protocol per patient. For smaller percent it takes less than 4 hours (16.7%) or 3-5 days (33.3%). For genetic testing results, several weeks are needed.

Majority of the participants (83.3%) would use mainly use Patient Specific Risk Stratification Clinical Decision Support System (CDSS), followed by Genetic mutations (66.7%). For 41.7% of the participants the number of virtual FCM patients needed for the SILICOFCM platform is 50-100. The most important feature for using the virtual patients within the SILICOFCM platform is the Genotype-phenotype relationships (66.7%). This feature is followed by Simulation of a heart behaviour (electrophysiology) (50%).

Majority of the participants (75%) think that data mining-based SILICOFCM tools should provide the answer about the presence of FCM and its severity, while one participant thinks that it should not provide definitive answer but assist in clinical decision making. More than half of the participants (58.3%) think that data mining-based SILICOFCM tool should provide the answer about the type of the cardiomyopathy treatment, one participant thinks that it should not provide definitive answer but assist in clinical decision making, while others are uncertain.

If the models prove to be reliable 91.7% participants would use SILICOFCM as a personalized clinical tool for individual patients. Participants think that clinical use of the SILICOFCM will provide Diagnosis DSS (75%), Treatment DSS (66.7%) and Genetic mutation analysis (58.3%).

Majority of the participants agree that SILICOFCM system should improve treatment selection and pharmacological therapies while they are uncertain about its use for reduction of pharmaceutical costs and time needed for treatment.

Functional aspects

Regarding the functional aspects of the SILICOFCM platform, 66.7% participants require to use the platform from their personal desktop computers, 58.3% from laptops, while 66.7% has access to fast/very fast internet speed. In terms of maximum acceptable time of the different SILICOFCM tools the results vary. According to the 33.3% results should be obtained in less than 30 minutes, 41.7% thinks that results should be obtained in less than 1h. Few hours are acceptable for 16.7%, while only 8.3% would wait 1 day for the results. Considering the use of the patient's data, 25% would use data from their database, while other 75% would use SILICOFCM database. The additional functionalities, which are necessary to be included in the final product are *Validity/accuracy, reliability/reproducibility, accessibility and speed;* according to the response of one participant.

Exploitation aspects

The SILICOFCM tools should be delivered under several different licenses and functionalities depending on the final users: academic, clinicians, researchers, industry. Having on mind this is the platform dedicated for in silico clinical trials, the final SILICOFCM platform should be used by hospitals, universities, research organization and pharmaceutical and medical companies.

Clinician specific comments

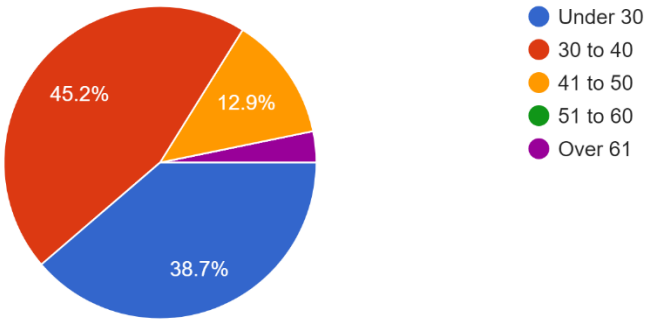
One participant commented that SILICOFCM platform should allow differentiation of different types of cardiomyopathies, and utilize the actual genetic, molecular and clinical data to accurately determine disease progression and identify / suggest appropriate treatment.

5.3.3 Questionnaire II - SILICOFCM User Requirements Questionnaire for bioengineers and researchers

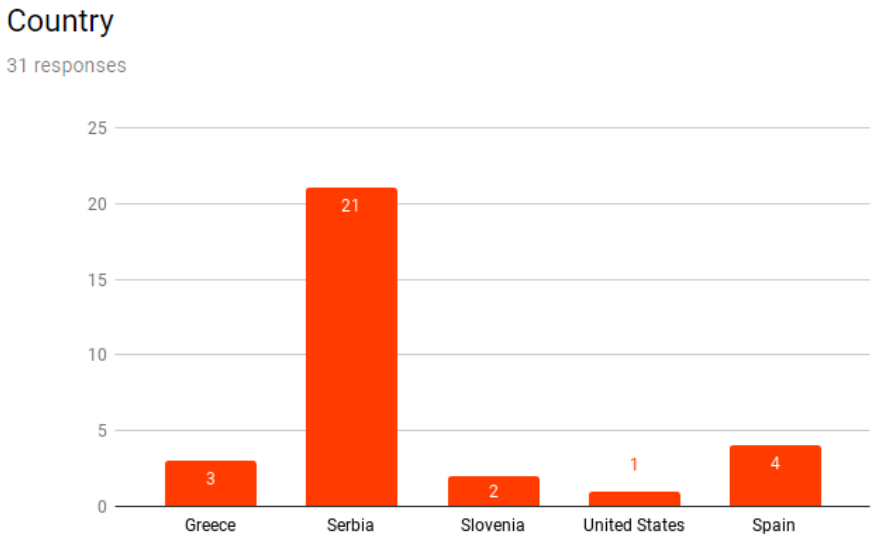
General information

Age

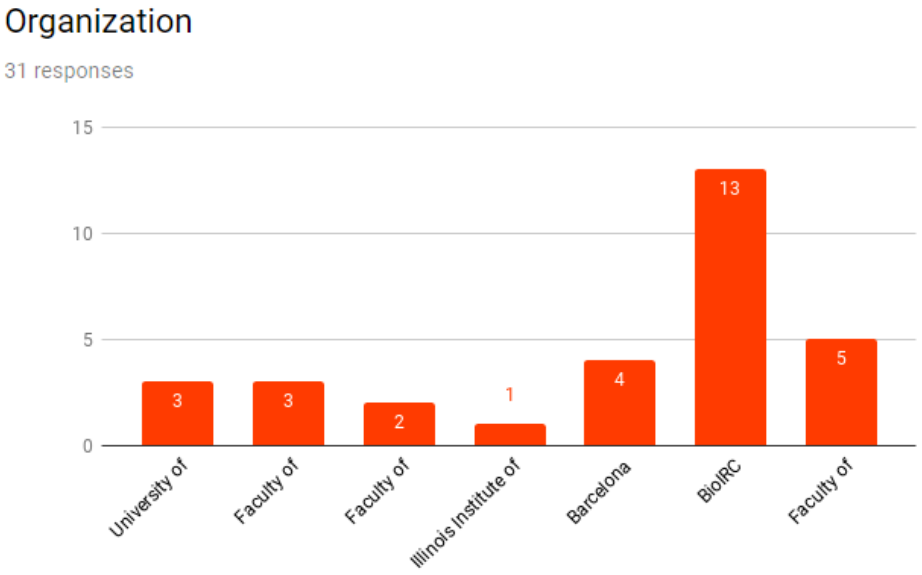
31 responses



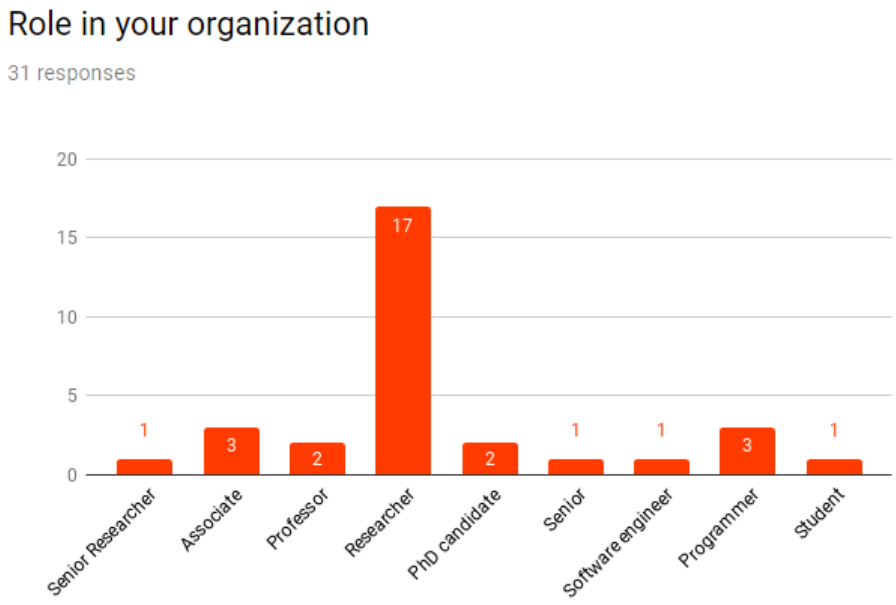
Value	Count
Under 30	12
30 to 40	14
41 to 50	4
51 to 60	0
Over 61	1



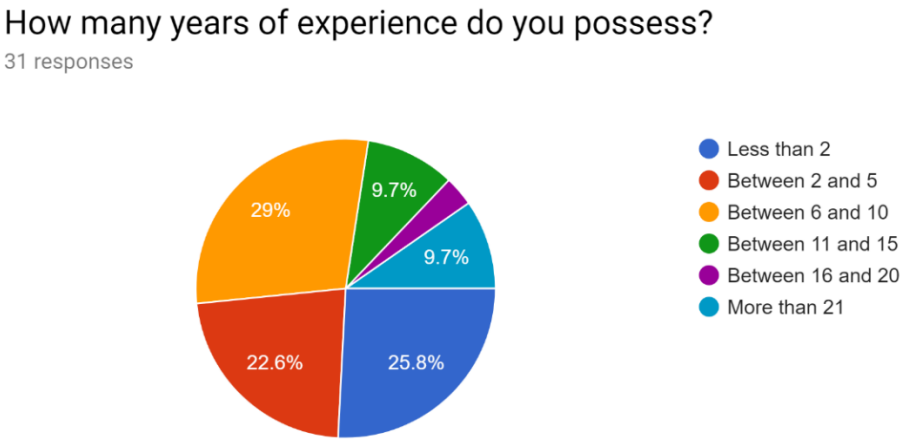
Value	Count
Greece	3
Serbia	21
Slovenia	2
United States	1
Spain	4



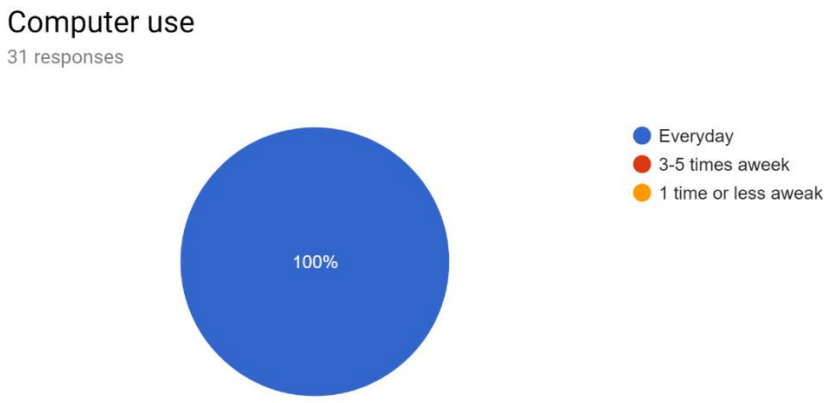
Value	Count
University of Ioannina	3
Faculty of Science, University of Kragujevac	3
Faculty of Computer and Information Science, University of Ljubljana	2
Illinois Institute of Technology	1
Barcelona Supercomputing Center	4
BioIRC, Bioengineering Research and Development Center	13
Faculty of Engineering, University of Kragujevac	5



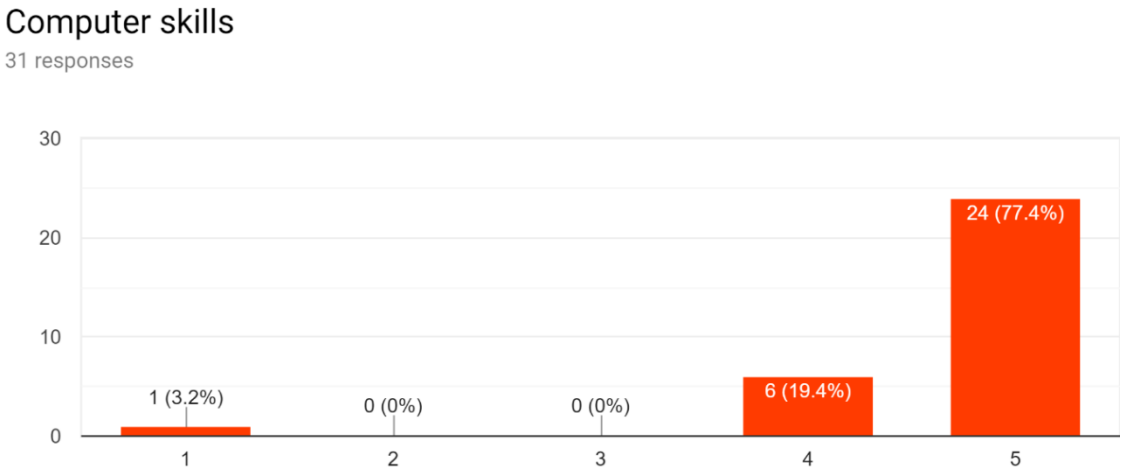
Value	Count
Senior Researcher	1
Associate Professor	3
Professor	2
Researcher	17
PhD candidate	2
Senior PostDoctoral Researcher	1
Software engineer	1
Programmer	3
Student	1



Value	Count
Less than 2	8
Between 2 and 5	7
Between 6 and 10	9
Between 11 and 15	3
Between 16 and 20	1
More than 21	3



Value	Count
Everyday	31

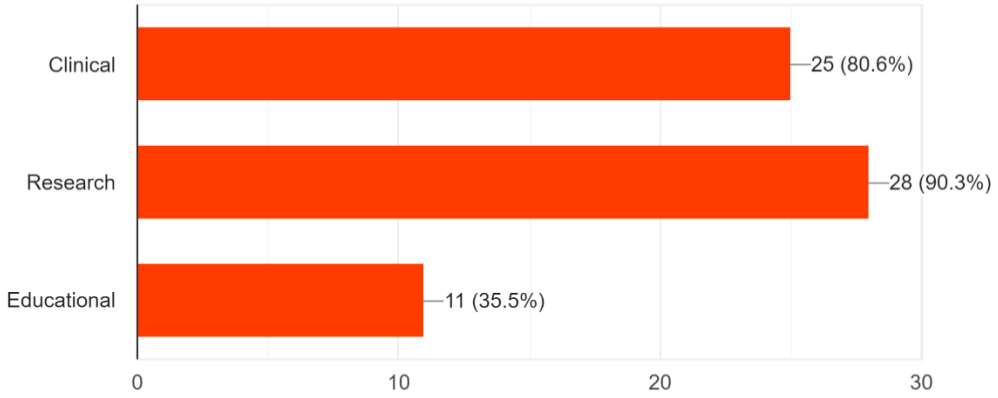


Value	Count
1 Insufficient	1
2	0
3	0
4	4
5 Excellent	24

System usage scenarios

The main functionality of the system and the domain that the SILICOFCM platform should mainly target is: (You can mark more than one answer)

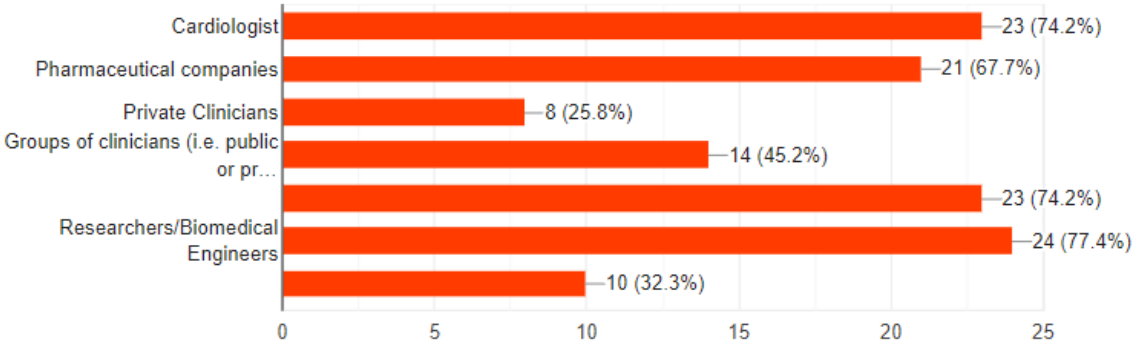
31 responses



Value	Count
Clinical	25
Research	28
Educational	11

Who are the final users of the SILICOFCM platform? (You can mark more than one answer)

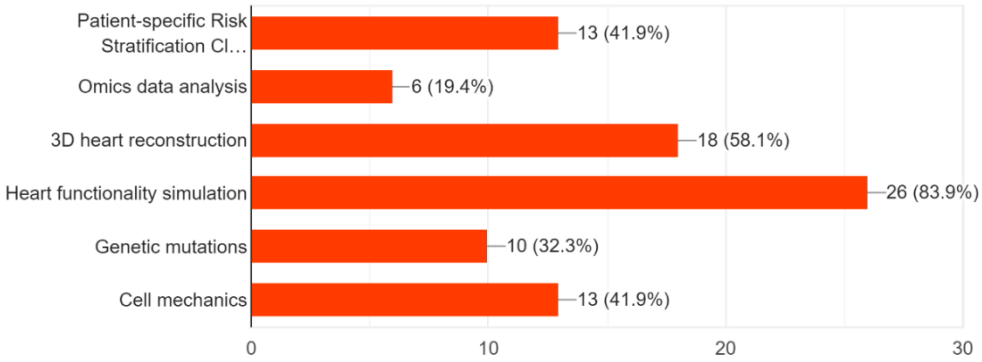
31 responses



Value	Count
Cardiologist	23
Pharmaceutical companies	21
Private Clinicians	8
Groups of clinicians (i.e. public or private bodies such as hospitals, healthcare institutes)	14
Researchers/Healthcare Professionals	23
Researchers/Biomedical Engineers	24
Postgraduate/Undergraduate Students	10

Which outputs of the SILICOFCM system would you mainly use? (You can mark more than one answer)

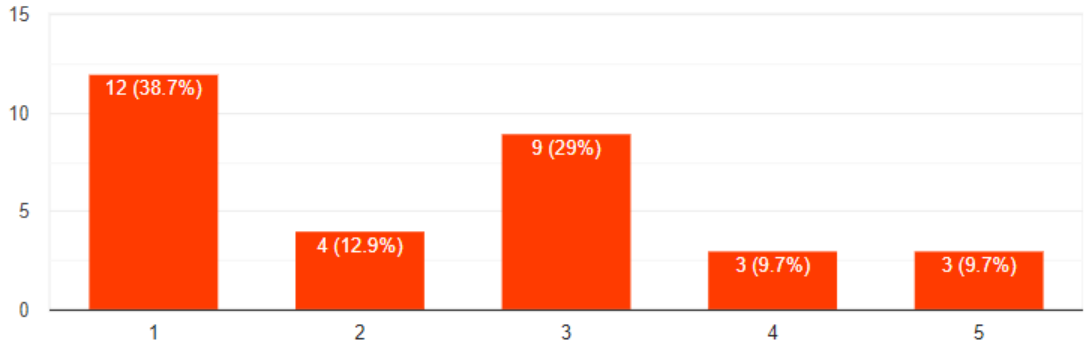
31 responses



Value	Count
Patient-Specific Risk Stratification Clinical Decision Support System (CDSS)	13
Omics data analysis	6
3D heart reconstruction	18
Heart functionality simulation	26
Genetic mutations	10
Cell mechanics	13

One of the SILICOFCM tools is MUSICO (MUscle SImulation COde), a computational platform which can link molecular interactions to the whole heart function. Please assess your familiarity with it or with a similar tool.

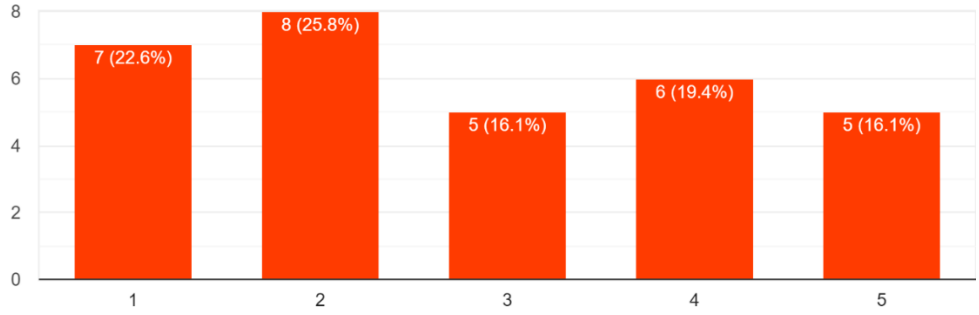
31 responses



Value	Count
1 Not familiar	12
2	4
3	9
4	3
5 Very experienced	3

Please assess your experience in computational simulations of experimental heart muscle behavior.

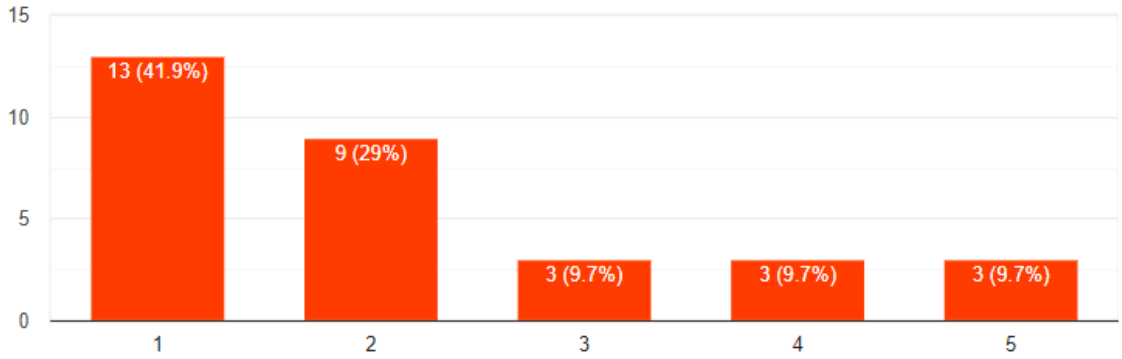
31 responses



Value	Count
1 Not familiar	7
2	8
3	5
4	6
5 Very experienced	5

One of the SILICOFCM tools is ALYA, Finite Element software, able to simulate electrophysiology and mechanics of the heart. Please assess your familiarity with it or with a similar tool.

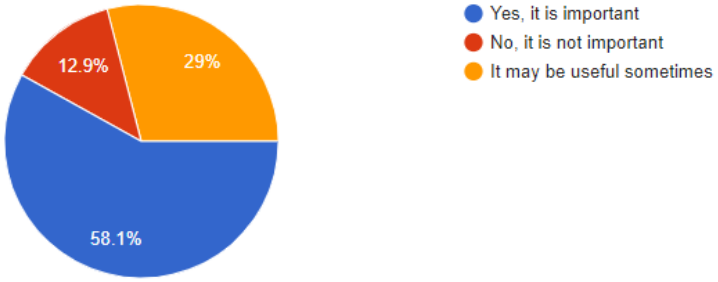
31 responses



Value	Count
1 Not familiar	13
2	9
3	3
4	3
5 Very experienced	3

How much important for your application do you consider accessing and modification of ionic currents that determine the human electrophysiology behavior?

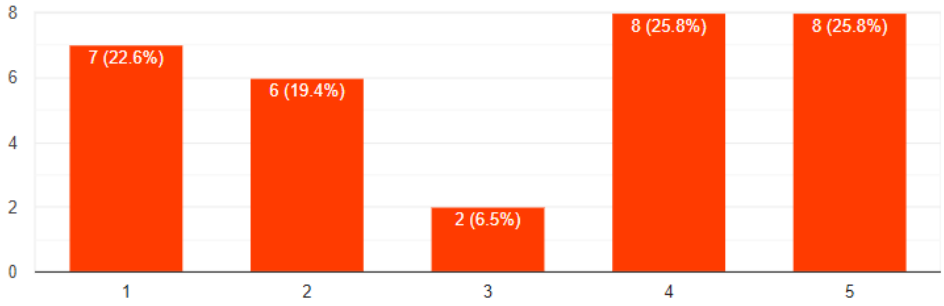
31 responses



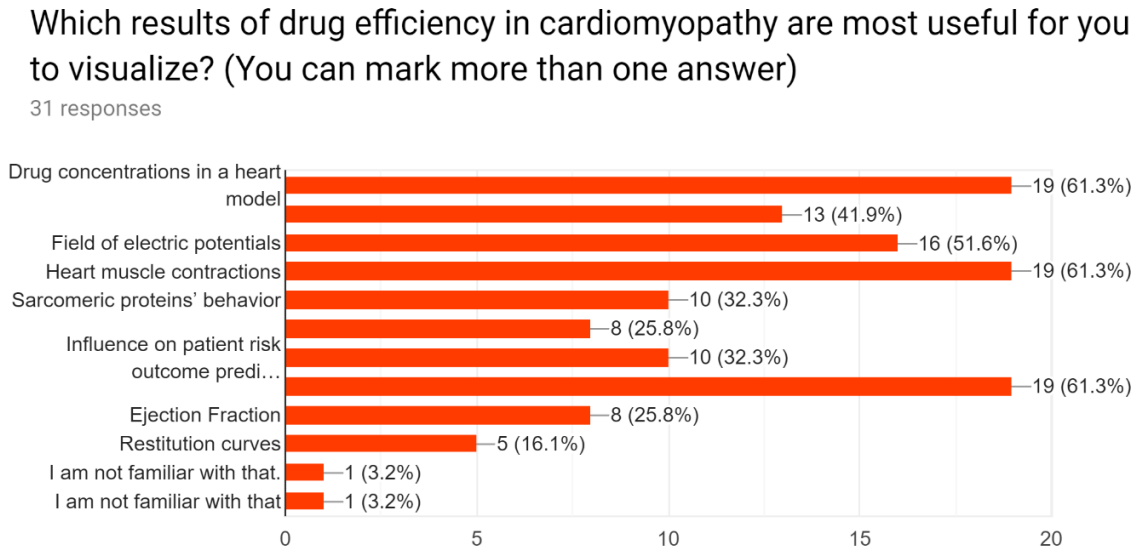
Value	Count
1 Yes, it is important	18
2 No, it is not important	9
3 It may be useful sometimes	4

One of the SILICOFCM tools is Finite Element software PAK, able to simulate electrophysiology and mechanics of the heart on multiscale level. Please assess your familiarity with it or with a similar tool.

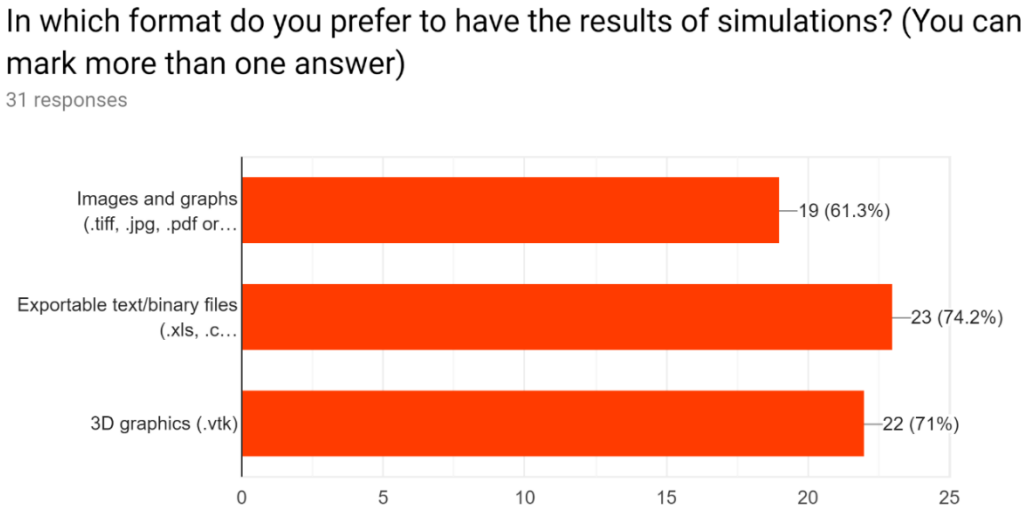
31 responses



Value	Count
1 Not familiar	7
2	6
3	2
4	8
5 Very experienced	8



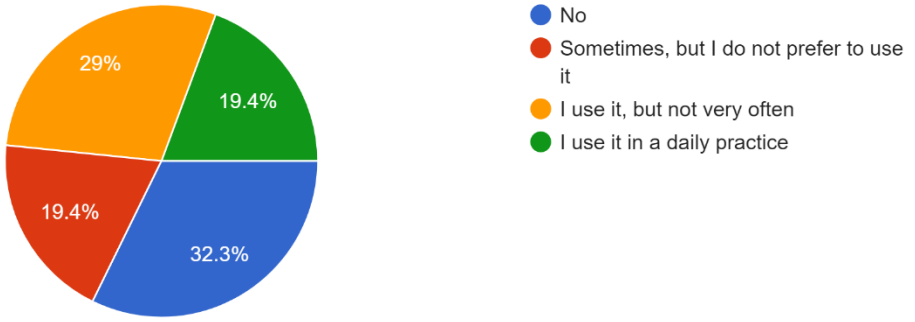
Value	Count
Drug concentrations in a heart model	19
Concentrations of ions in a heart model	13
Field of electric potentials	16
Heart muscle contractions	19
Sarcomeric proteins' behaviour	10
Displacements of key sarcomere points	8
Influence on patient risk outcome prediction	10
Stresses and strains in the cardiac muscle	19
Ejection Fraction	8
Restitution curves	5
Other: *Not familiar*	2



Value	Count
images and graphs (.tiff, .jpg, .pdf or similar)	19
exportable text/binary files (.xls, .csv, .arff, .RData)	23
3D graphics (.vtk)	22

Do you prefer to visualize results of simulations by using open source ParaView tool?

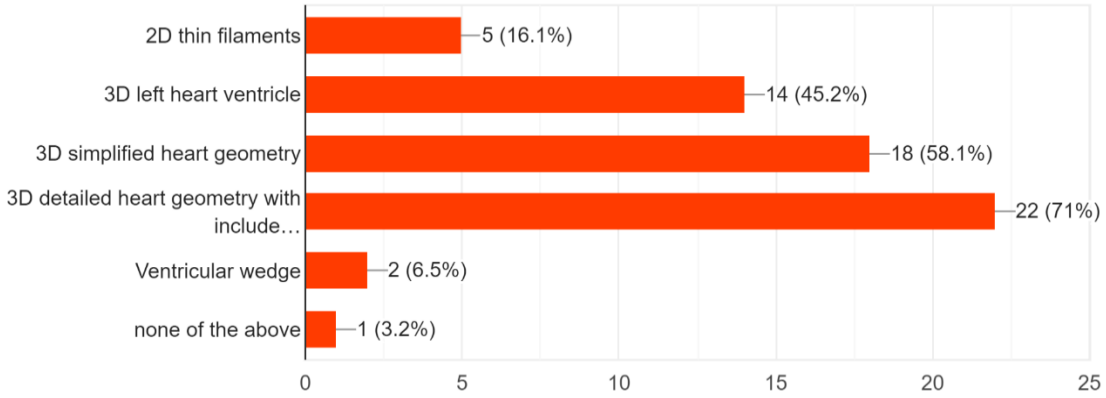
31 responses



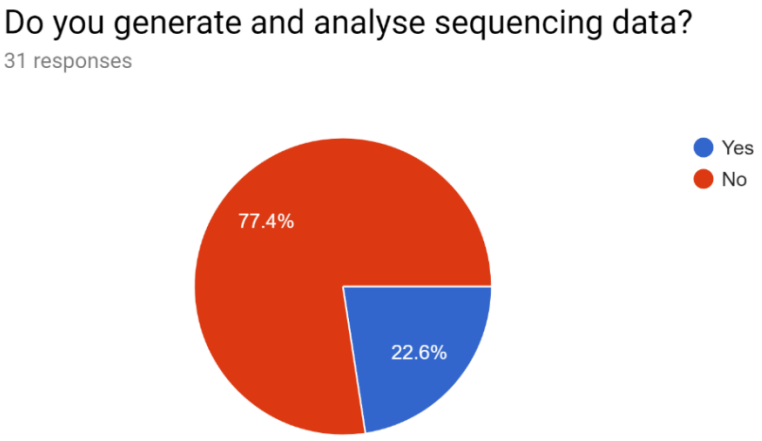
Value	Count
1 - No	10
2 - Sometimes, but I do not prefer to use it	6
3 - I use it, but not very often	9
4 - I use it in a daily practice	6

Which types of heart models are useful for you to have in the SILICOFCM library? (You can mark more than one answer)

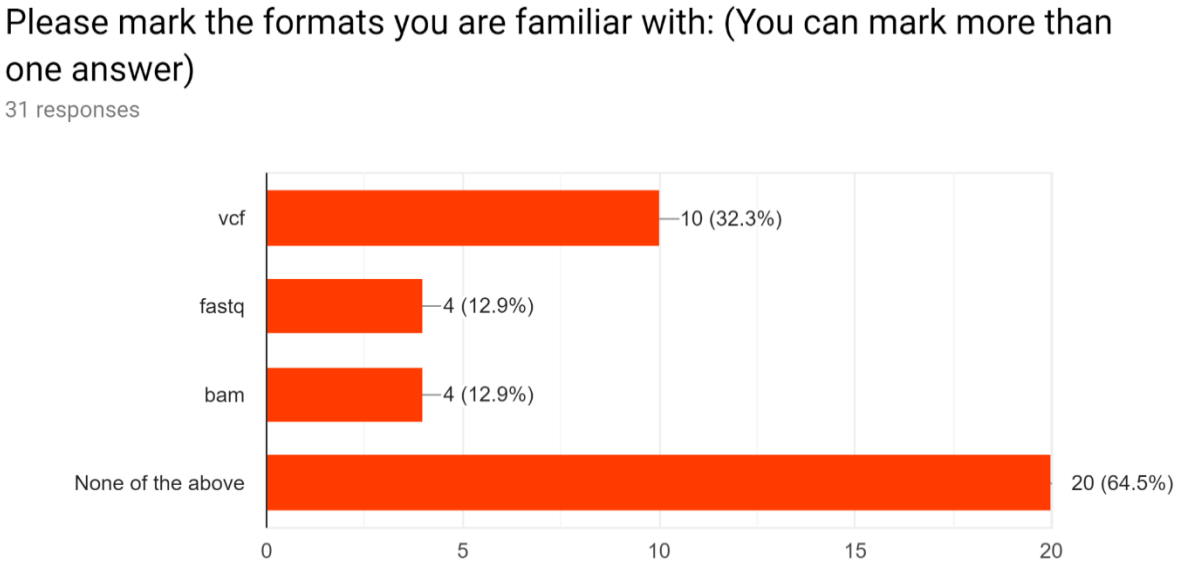
31 responses



Value	Count
2D thin filaments	5
3D Left heart ventricle	14
3D simplified heart geometry	18
3D detailed heart geometry with included fibres orientation	22
Ventricular wedge	2
Other: *None of the above*	1



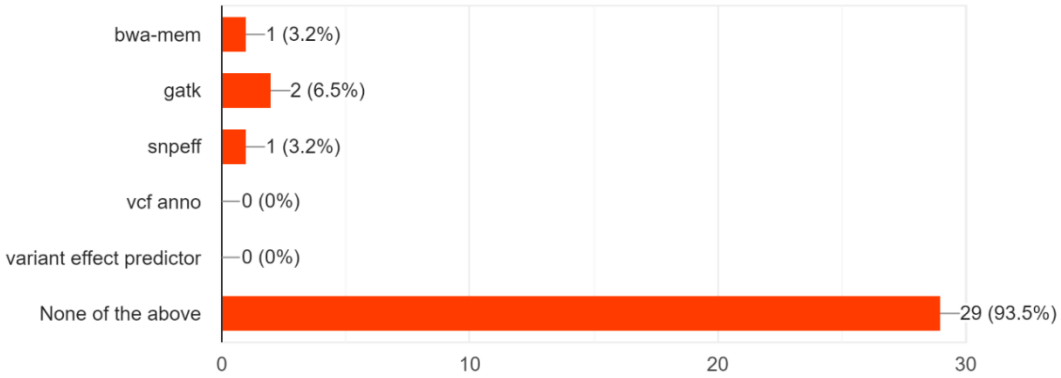
Value	Count
No	24
Yes	7



Value	Count
Vcf	10
Fastq	4
Bam	4
Other: *None of the above*	20

Please mark the following bioinformatics tools you are familiar with: (You can mark more than one answer)

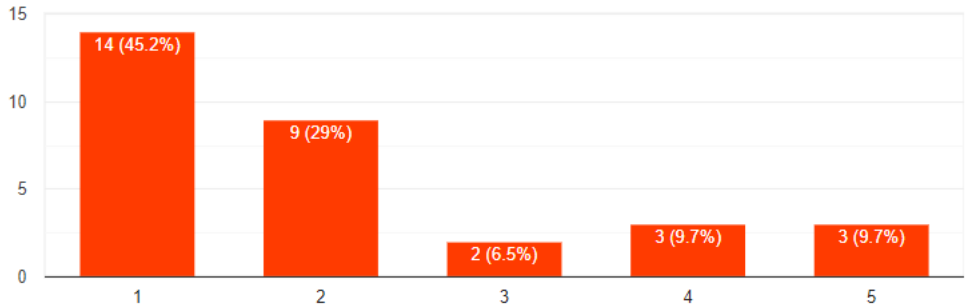
31 responses



Value	Count
bwa-mem	1
gatk	2
snpeff	1
vcf anno	0
variant effect predictor	0
Other: *None of the above*	29

One of the SILICOFCM tools is Machine learning/data mining framework, able to provide cardiomyopathy risk stratification of patients. Please assess your familiarity with this framework in risk stratification.

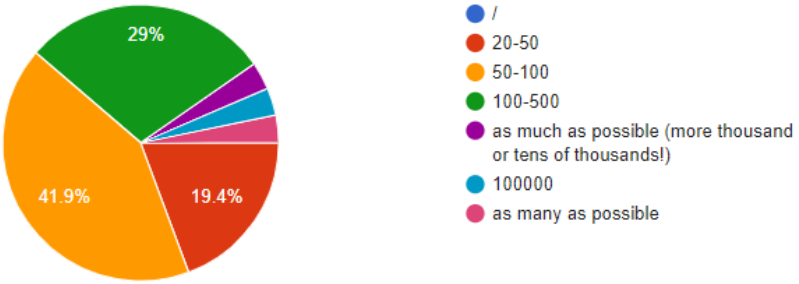
31 responses



Value	Count
1 Not familiar	14
2	9
3	2
4	3
5 Very experienced	3

SILICOFCM will provide virtual models of different cohorts (classified patient groups which differ in physiology and heart morphology). This virtual patient model library will enable testing of a new drug under different boundary conditions. How many "virtual" FCM patients do you consider relevant for the SILICOFCM platform?

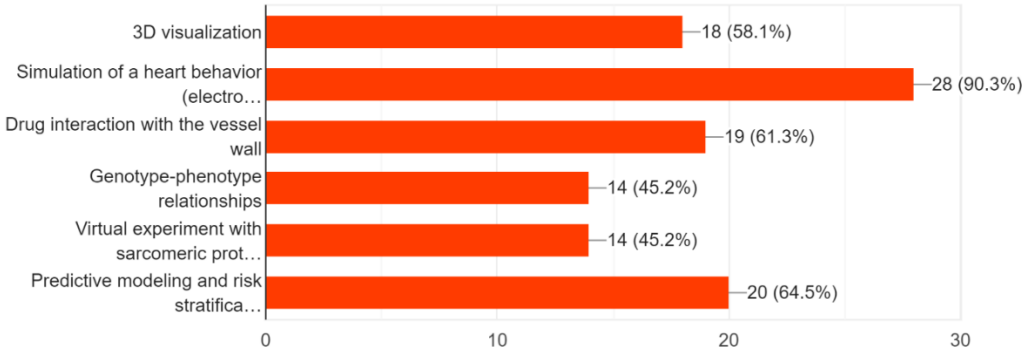
31 responses



Value	Count
/	0
20-50	6
50-100	13
100-500	9
Other: as many as possible	2

Please select the most important features for using virtual patients within the SILICOFCM platform: (You can mark more than one answer)

31 responses

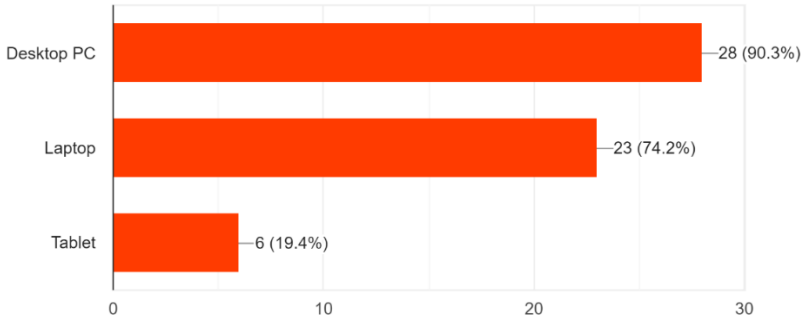


Value	Count
3D visualization	18
Simulation of a heart behaviour (electro-mechanics)	28
Drug interaction with the vessel wall	19
Genotype-phenotype relationships	14
Virtual experiment with sarcomeric proteins on muscle functions	14
Predictive modelling and risk stratification	20

Functional aspects

On which device(s) do you prefer to use the final SILICOFCM platform? (You can mark more than one answer)

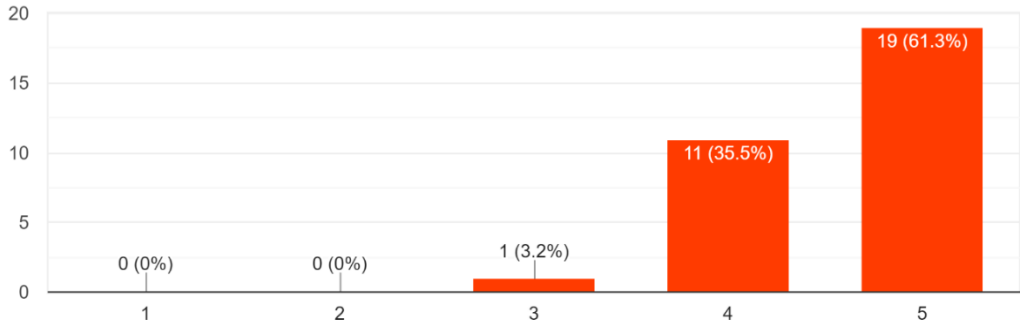
31 responses



Value	Count
Desktop PC	28
Laptop	23
Tablet	6

Please assess your internet access speed:

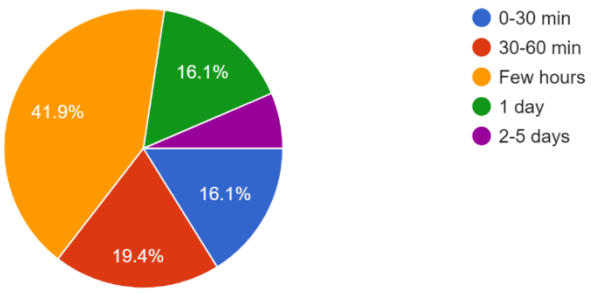
31 responses



Value	Count
1 Very slow	0
2	0
3	1
4	11
5 Very fast	19

Please select the maximum acceptable response time of the SILICOFCM tools:

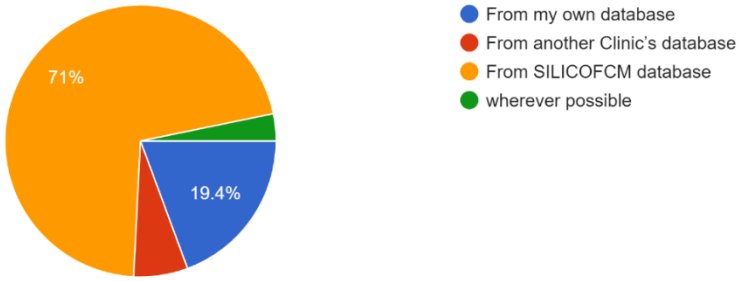
31 responses



Value	Count
0-30 min	5
30-60 min	6
Few hours	13
1 day	5
2-5 days	2

The final SILICOFCM platform will have to use the patients' data:

31 responses

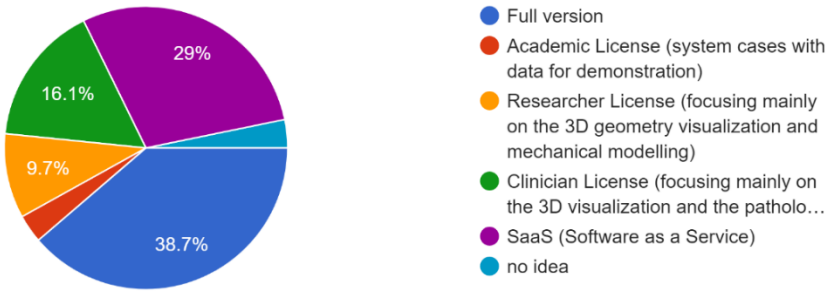


Value	Count
From my own database	6
From another Clinic's database	2
From SILICOFCM database	22
Other: *wherever possible*	1

Exploitation aspects

Should we distribute the SILICOFCM solution under different licenses and different functionalities?

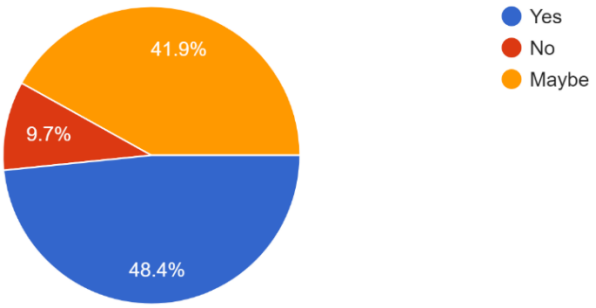
31 responses



Value	Count
Full version	12
Academic License (system cases with data for demonstration)	1
Researcher License (focusing mainly on the 3D geometry visualization and mechanical modelling)	3
Clinician License (focusing mainly on the 3D visualization and the pathologies)	5
SaaS (Software as a service)	9
Other: *no idea*	1

Would you use the SILICOFCM system in case it does not get CE certify?

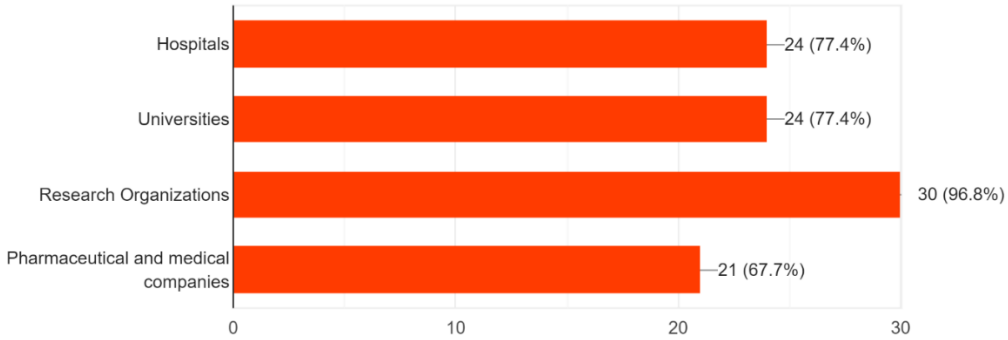
31 responses



Value	Count
Yes	15
No	3
Maybe	13

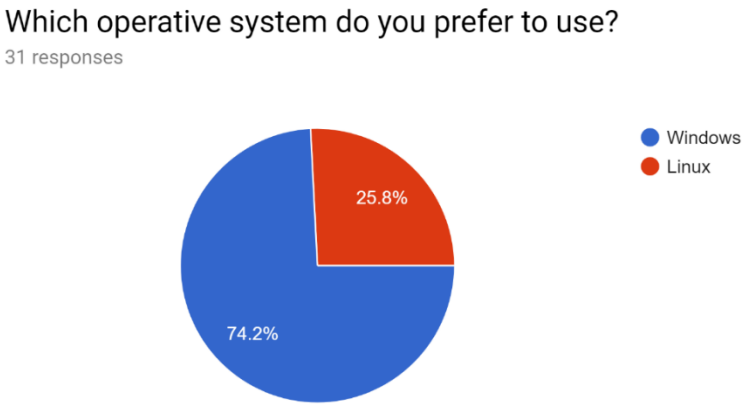
In your opinion, who should access and use the system? (You can mark more than one answer)

31 responses

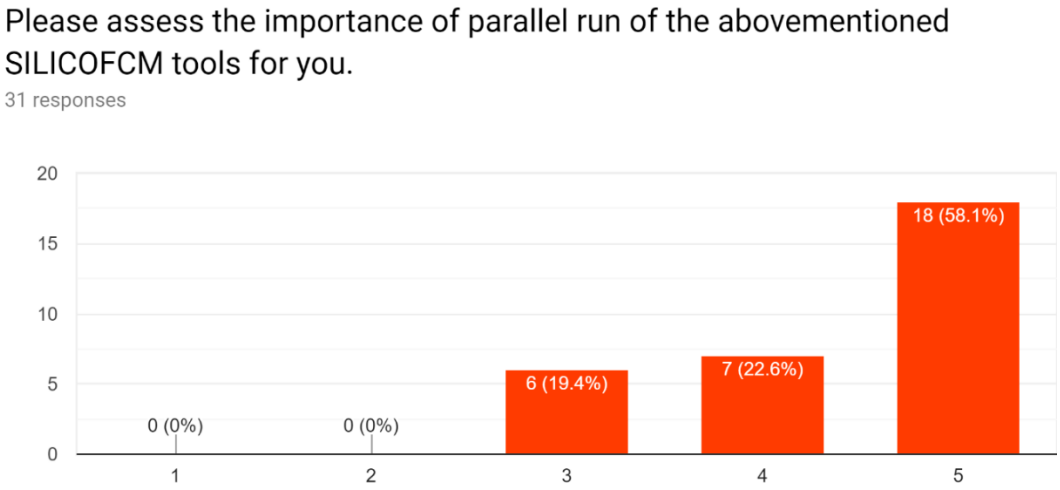


Value	Count
Hospitals	24
Universities	24
Research Organizations	30
Pharmaceutical and medical companies	21

Technical specific questions



Value	Count
Windows	23
Linux	8



Value	Count
1 Not important	0
2	0
3	6
4	7
5 Very important	18

5.3.4 Analysis of Questionnaire II

The User Requirements Questionnaire for Bioengineers and researchers contained following sections:

- General information;
- System usage scenarios;
- Functional aspects;
- Exploitation aspects and
- Technical specific questions.

General Information

The majority of the participants who filled out the questionnaire are either under 30 (38.7%) or from 30 to 40 years old (45.2%). The most common role of the participants is Researcher/Research Assistant

/Research Associate (61%). About 77% of participants have less than 10 years of work experience - less than 2 years (25.8%), between 2 and 5 (22.6%) and between 6 and 10 (29%). All participants use their computers every day. Additionally, 77.4% of the participants consider having excellent computer skills.

System usage scenarios

The majority of participants think that main functionality of the SILICOFCM platform should be clinical and research. Cardiologists, Researchers/Biomedical Engineers, Researchers/Healthcare Professionals and Pharmaceutical companies are listed as the final users by majority of the participants. The majority of the participants would use Heart functionality simulation (84%) and 3D heart reconstruction (58%).

Regarding SILICOFCM tools, almost 39% participants indicated that they are not familiar with MUSICO (MUscle SImulation COde) module. Almost 42% is not familiar with ALYA tool and 22% is not familiar with PAK tool. When asked to assess their experience with computational simulation of experimental heart muscle behaviour, only 16% is very experienced, while 22% has no experience in this area.

More than 58% of the participants think that access and modification of ionic currents that determine the human electrophysiology behaviour is important, while 29% think that it can be useful sometimes. The majority would like to visualize Drug concentrations in a heart model (61%), Heart muscle contractions (61%), Stresses and strains in the cardiac muscle (61%), Field of electric potentials (51%) after performed simulations of heart behaviour.

The most suitable formats for the results of the simulations are exportable text/binary files (.xls, .csv, .arff, .RData) and 3D graphics (.vtk). More than 50% of participants would not use ParaView tool as a way to visualize the obtained results. 3D detailed heart geometry with included fibres orientation or 3D simplified heart geometry is what the most participants think is useful to have in the SILICOFCM library.

The majority of the participants (77%) generate and analyses sequencing data. The majority is not familiar with formats: vcf, fastq and bam or bioinformatics tools: bwa-mem, gatk, snpeff, vcf anno, variant effect predictor.

About 45% of participants is not familiar with Machine learning/data mining framework, while almost 10% is very familiar with this framework. Similar to the results of the Questionnaire 1, about 40% think that 50-100 virtual FCM patients are needed. The majority indicated that the most important features for using virtual patients within the SILICOFCM platform are: Simulation of a heart behaviour (electro-mechanics) (90%), Predictive modelling and risk stratification (64%), Drug interaction with the vessel wall (61%) and 3D visualization (58%).

Functional aspects

Regarding the functional aspects of the SILICOFCM platform, almost all participants require to use the platform from their personal computers (desktop or laptop), while 95% have access to fast/very fast internet speed.

In terms of maximum acceptable time of the different SILICOFCM tools the results vary. According to about 40% results should be obtained in few hours, 16% think that results should be obtained in less than 30 minutes while 19% thinks that it should be less than an hour. One day is acceptable for 16%, while only 6% would wait 2-5 days for the results.

Considering the use of the patient's data, 71% would use data from the SILICOFCM database, while others would use date from their database/another Clinic's database.

Exploitation aspects

The SILICOFCM tools should be delivered under several different licenses and functionalities depending on the final users. Almost 40% of the participants think that SILICOFCM platform would be distributed as full version. This is followed by 29% who think that is should be distributed as SaaS (Software as a service).

Almost 50% would use, while 42% would potentially use the system without CE certification. Having on mind this is the platform dedicated for clinical medical trials, the final SILICOFCM platform should be used by hospitals, universities, research organization and pharmaceutical and medical companies.

Technical specific questions

The majority of the participants prefer Windows operative system (74%) compared to the 26% that prefer Linux OS. Everyone thinks that parallel run of the SILICOFCM tools should be possible, while 58% of the participants think that it is very important.

At the end of the questionnaire participants could give us their comments, and there was one comment regarding user-friendly interface. It is indicated that this type of platform is mainly for experts, and the user-friendly interface is needed both for them and wider range of end-users.

Based on the all filled in questionnaires, the user requirements are collected and given in the Section 5.5, while the Use Cases are provided both with Usage Scenarios (Section 5.6), which coupled with SILICOFCM hardware specification (Task 1.2) serve for detailed designed reference architecture (Task 1.3) of the SILICOFCM platform.

5.3.5 Questionnaire III -SILICOFCM User Requirements Questionnaire for Pharmaceutical companies as end-users

General information

Name of the Pharmaceutical company

7 responses

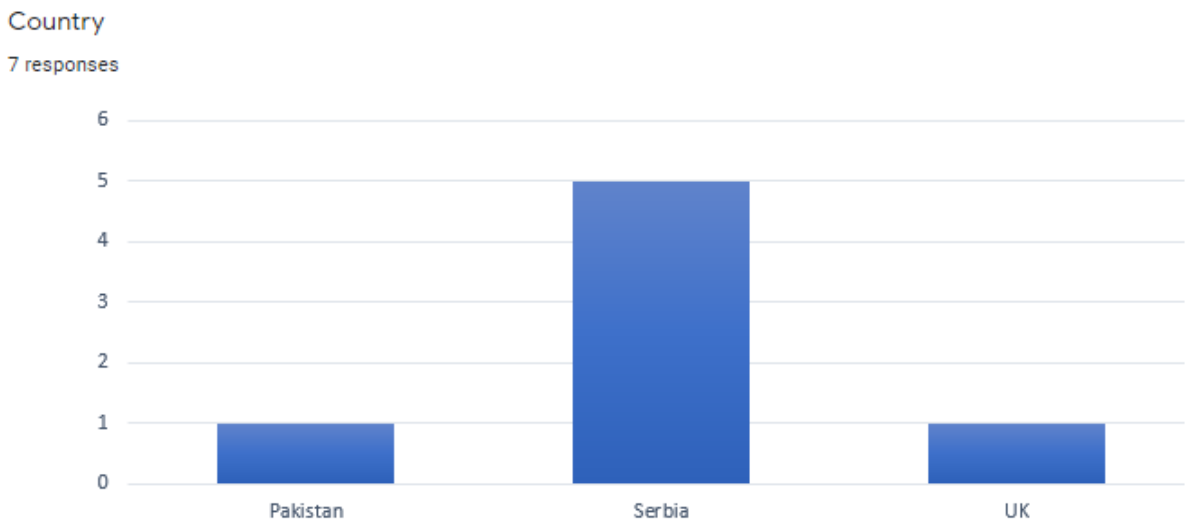
- Getz Pharma
- Pfizer
- Novartis
- Hemofarm AD
- FHI Zdravlje ad
- Pharmanova doo
- AstraZeneca

Your working position

7 responses

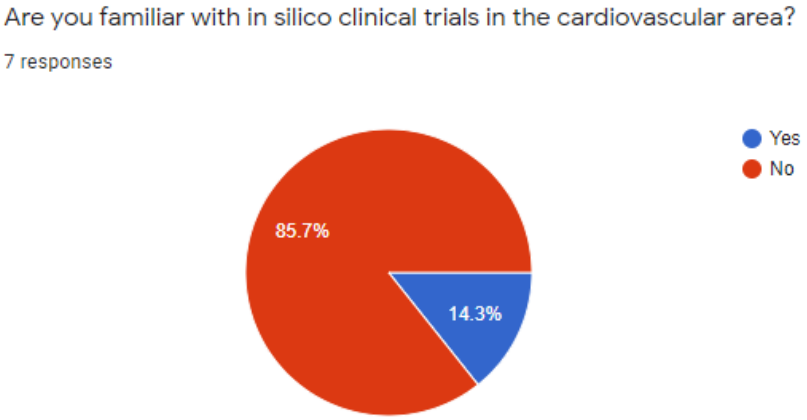
- Manager Institution
- Site Care Partner
- Medical Head
- Corporate Development Director
- Associate Director Ops
- Menadžer razvoja portfolija *
- Senior Scientist

* Translation: Portfolio development manager



Value	Count
Pakistan	1 (14.3%)
Serbia	5 (71.4%)
UK	1 (14.3%)

System usage scenarios



Value	Count
Yes	1 (14.3%)
No	6 (85.7%)

If the answer on previous question was YES, please specify in silico clinical trial.

3 responses

Not Applicable
sacubitril/valsartan in FCM
n/a

In your opinion, what are the main benefits of in silico clinical trials application in improvement of drug discovery, testing and efficacy for your company?

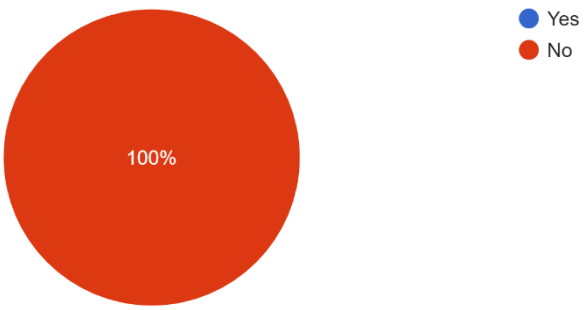
7 responses

Not Applicable
I do not have experince with silico trials
Innovative approach that would shorten time needed for data generation with the potential to minimize adverse events, lower the costs and maximize the outcomes
saving time, avoiding unnecessary clinical trials
I am not familiar with in silico clinical trials.
Mogućnost testiranja kardiovaskularne bezbednosti proizvoda kao i analiza uticaja na klinička stanja koja aplikacija pokriva *
Reduction of time and costs as well as on in vivo studies

* Translation: Possibility of testing the safety of cardiovascular products, as well as analysis of products' effect on clinical states

We are offering the cloud-based solutions – have you used these or similar services in the past?

7 responses



Value	Count
Yes	0 (0%)
No	7 (100%)

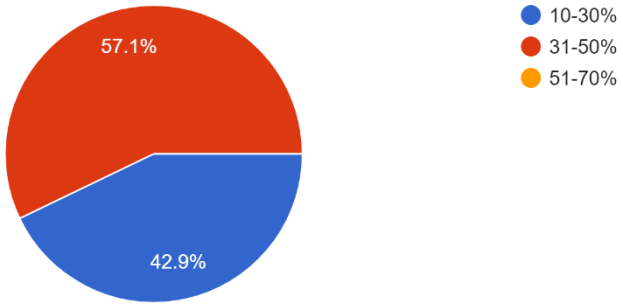
If the answer on previous question was YES, which cloud-based solutions / in silico clinical trials have you used before and for which purposes?

1 response

Not Applicable

In which percentage do you expect the time reduction of drug discovery and testing by using SILCIOFCM in silico clinical trial?

7 responses



Value	Count
10-30%	3 (42.9%)
31-50%	4 (57.1%)
51-70%	0 (0%)

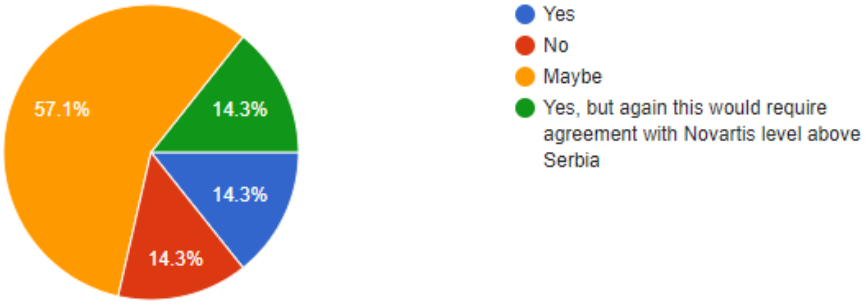
We are developing the platform capable to test the molecular compounds for treatment of HCM. In the SILICOFCM clinical trial we are examining the efficacy of Entresto®. Will you be willing to participate in validation of the SILICOFCM platform?

7 responses

Value	Count
Yes	1 (14.3%)
No	3 (42.9%)
Maybe	2 (28.6%)
Other	1 (14.3%)

In case Entresto© is not effective in HCM will you be willing to collaborate with us in development and validation of other interventions including the lifestyle interventions?

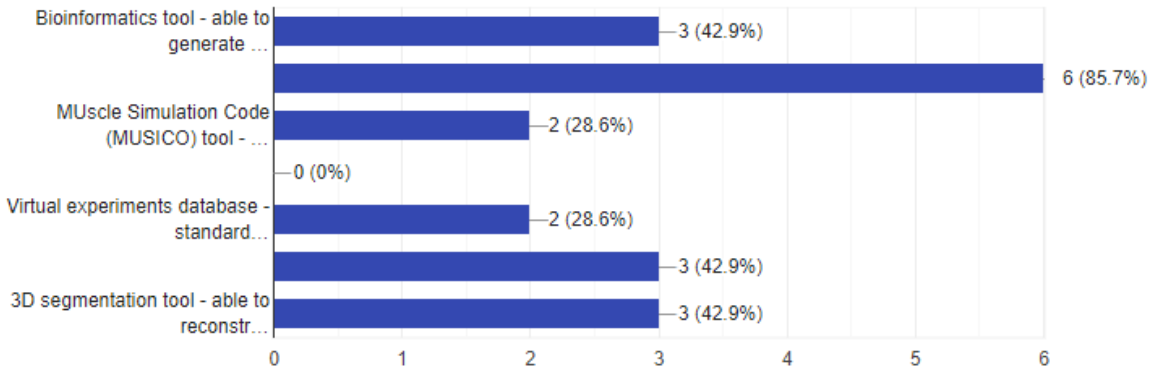
7 responses



Value	Count
Yes	1 (14.3%)
No	1 (14.3%)
Maybe	4 (57.1%)
Other	1 (14.3%)

We are developing several tools which integrated into SILICOFCM platform can examine drug efficacy, reduce time for drug discovery and testing, as well as predict the cardiomyopathy disease progression. Would you prefer to use some of the SILICOFCM tools as standalone for your research purposes? Multiple answers are possible.

7 responses

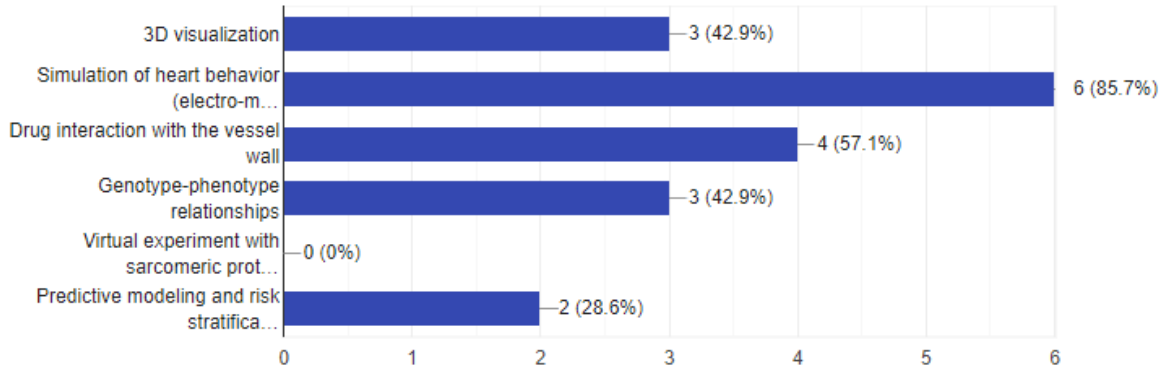


Value	Count
Bioinformatics tool - able to generate and analyse sequencing data	3 (42.9%)
Data analytics tool - able to provide cardiomyopathy risk stratification of patients	6 (85.7%)
MUscle Simulation Code (MUSICO) tool - a computational platform which can link molecular interactions to the whole heart function	2 (28.6%)

Finite element solvers - able to simulate electrophysiology and mechanics of the heart	0 (0%)
Virtual experiments database - standardized experiments for heart muscle twitch of mices/rats/human samples	2 (28.6%)
Virtual Population database - Virtual generated clinical data, Parametric LV/RV geometries, 3D reconstructed heart geometries, Virtual experimentation generated data, Virtual patient genome. This virtual patient model library will enable testing of a new drug under different boundary conditions	3 (42.9%)
3D segmentation tool - able to reconstruct the 3D heart model from US/CT/MRI data	3 (42.9%)

Please select the most important features for using virtual patients within the SILICOFCM platform: (Multiple answers are possible)

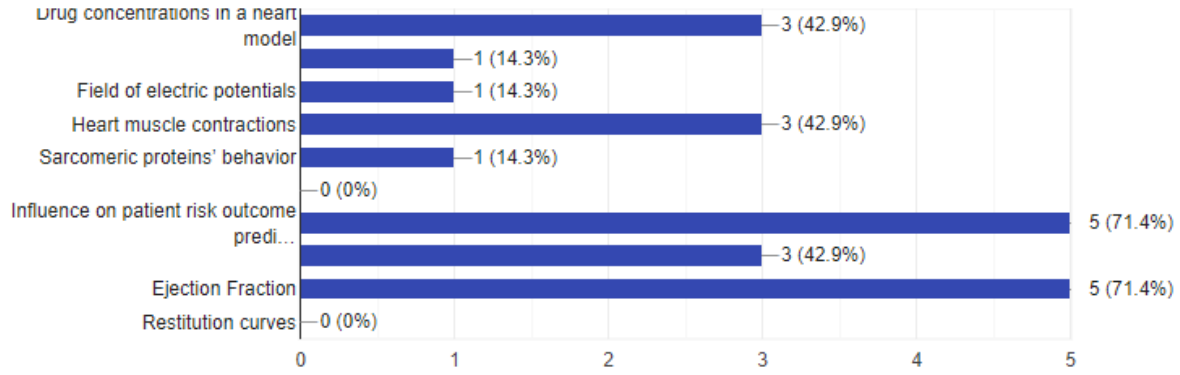
7 responses



Value	Count
3D visualization	3 (42.9%)
Simulation of heart behavior (electro-mechanics)	6 (85.7%)
Drug interaction with the vessel wall	4 (57.1%)
Genotype-phenotype relationships	3 (42.9%)
Virtual experiment with sarcomeric proteins on muscle functions	0 (0%)
Predictive modeling and risk stratification	2 (28.6%)

Which results of drug efficacy in cardiomyopathy are most useful for you to visualize? Multiple answers are possible.

7 responses



Value	Count
Drug concentrations in a heart model	3 (42.9%)
Concentrations of ions in a heart model	1 (14.3%)
Field of electric potentials	1 (14.3%)
Heart muscle contractions	3 (42.9%)
Sarcomeric proteins' behavior	1 (14.3%)
Displacements of key sarcomere points	0 (0%)
Influence on patient risk outcome prediction	5 (71.4%)
Stresses and strains in the cardiac muscle	3 (42.9%)
Ejection Fraction	5 (71.4%)
Restitution curves	0 (0%)

Beside HCM, SILICOFCM platform could be used also for other cardiac diseases like arrhythmia or cardiac failure. Would you like to use SILICOFCM platform for other cardiac disease and for which one?

7 responses

May be
do not have much experince in cardio clinical trials
Heart failure, myocardial infarction, atherosclerotic heart disease
maybe, cardiac failiure
NO
Da, posebno kod aritmija *
Arrhytmia

* Translation: Yes, especially for arrythmias.

5.3.6 Analysis of Questionnaire III

The User Requirements Questionnaire for Pharmaceutical companies was more concise comparing with the previous two questionnaires, containing the following sections:

- General information and
- System usage scenarios.

The questionnaire contained 15 questions in total, 3 general and 12 system usage scenarios questions and was created in collaboration of the SILICOFCM Coordinator (BioIRC) and Clinical manager (UNEW). Before the questions, the overview and main information about SILICOFCM project were provided, presenting the SILCIOFCM concept. The link to the project website and contact email were included in this information. The questionnaire was distributed twice to around 100 R&D Departments and Clinical Research units of pharmaceutical companies from Europe, US as well as from several other regions. Among all recipients, until M19 only seven pharmaceutical companies participated in the survey. The reason for low response might be the non-familiarity with the *in silico* trials, that's has been proved through answers of participants.

General Information

This section includes the general answers related to the name of participating pharmaceutical company, county and working position of the participants. The participating pharmaceutical companies were following: Getz Pharma, Pfizer, Novartis, Hemofarm AD, FHI Zdravlje AD, Pharmanova doo, AstraZeneca. The working positions of participants were following: manager (Getz Pharma), site care partner (Pfizer), medical head (Novartis), corporate development director (Hemofarm AD), associate director (FHI Zdravlje AD), portfolio development manager (Pharmanova doo), senior

scientist (AstraZeneca). The participants were from Pakistan (Getz Pharma), Serbia (Pfizer, Novartis, Hemofarm AD, FHI Zdravlje AD, Pharmanova doo) and UK (AstraZeneca), which is 7 participants in total.

System usage scenarios

In this section the responders provided information related to their familiarity with *in silico* clinical trials, as well as which SILICOFCM solutions they would use. Answering on their familiarity with the existence of *in silico* clinical trials in the cardiovascular area 6 (85.7%) were not familiar, while only 1 (14.3%), representative from Novartis, was familiar. It could be assumed that, even in case of larger number of surveyed persons, the number of non-familiar ones with *in silico* clinical trials would have the prevalence. It implies that consortium of SILICOFCM project, as well as the whole *in silico* community have to raise the awareness of the benefits which *in silico* applications bring with, that would lead to the mutually validation and verification of *in silico* solutions.

Analysing further questions, representative from Novartis was familiar with studies of sacubitril/valsartan in FCM which could be related to the SILICOFCM project knowing that Novartis was informed about the project in its early stage and interested for collaboration with SILICOFCM consortium. Novartis International AG, a Swiss multinational pharmaceutical company based in Basel, (Switzerland) is one of the largest pharmaceutical companies by both market capitalization and sales, which has the branches all over the Europe and world. The communication with the company has been established with branches in Serbia and UK, where SILICOFCM representatives had the meetings with the representatives of Novartis, setting the common goals and steps for further collaboration.

Answering on what are the main benefits of *in silico* clinical trials application in improvement of drug discovery, testing and efficacy for the pharmaceutical company 3 (42.9%) participants did not have any specific answer, while other 4 (57.1%) participants answered as following: i) *Innovative approach that would shorten time needed for data generation with the potential to minimize adverse events, lower the costs and maximize the outcomes*; ii) *Saving time, avoiding unnecessary clinical trials*; iii) *Possibility of testing the safety of cardiovascular products, as well as analysis of products' effect on clinical states*; iv) *Reduction of time and costs as well as in vivo studies*. In addition, no one participant had not used cloud-based solutions or similar services in the past. Thus, on the question which cloud-based solutions / *in silico* clinical trials had they used before and for which purposes there were no answers. On the other hand, all participants estimated the desired time reduction of drug discovery and testing by using SILCIOFCM *in silico* clinical trial, where 3 (42.9%) of them expect the time reduction of 10-30% and 4 (57.1%) expect the time reduction of 31-50%.

We informed the participants that we are developing the platform capable to test the molecular compounds for treatment of HCM and that in the SILICOFCM clinical trial we are examining the efficacy of Entresto©. On the question if they are willing to participate in validation of the SILICOFCM platform the answers were following: 1 (14.3%) – Yes; 1 (14.3%) – Yes, but validation would have to be done on a level above country (Novartis global level like Global Drug Development – GDD, or Novartis Institutes for BioMedical Research – NIBR); 2 (28.6%) – Maybe; 3 (42.9%) – No. On the following question if they are willing to collaborate with us in development and validation of other interventions including the lifestyle interventions, in case Entresto© is not effective in HCM, the answers were following: 1 (14.3%) – Yes; 1 (14.3%) – Yes, but validation would have to be done on a level above Serbia (Novartis global level like Global Drug Development – GDD, or Novartis Institutes for BioMedical Research – NIBR); 4 (57.1%) – Maybe; 1 (14.3%) – No.

In addition, the participants were informed we are developing several tools which integrated into SILICOFCM platform can examine drug efficacy, reduce time for drug discovery and testing, as well as

predict the cardiomyopathy disease progression. On the question if they prefer to use some of the SILICOFCM tools as standalone for the research purposes the answers were following: Data analytics tool, as the most favourable, would be used by 6 (85.7%) participants, Bioinformatics tool would be used by 3 (42.9%) participants, Virtual Population database would be used by 3 (42.9%) participants also, 3D segmentation tool would be used by 3 (42.9%) participants, MUscle Simulation Code (MUSICO) tool would be used by 2 (28.6%) participants, Virtual experiments database would be used by 2 (28.6%) participants also, while none of participants would use Finite element solvers. The relation between selected SILICOFCM tools is in accordance with the targeted group.

The most important features for using virtual patients within the SILICOFCM platform were selected in the following order: Simulation of heart behavior (electro-mechanics) – 6 (85.7%) participants; Drug interaction with the vessel wall – 4 (57.1%) participants; 3D visualization – 3 (42.9%) participants; Genotype-phenotype relationships – 3 (42.9%) participants; Predictive modeling and risk stratification – 2 (28.6%) participants, Virtual experiment with sarcomeric proteins on muscle functions – none.

On the question which results of drug efficacy in cardiomyopathy are most useful to visualize, the participants selected following: Influence on patient risk outcome prediction – 5 (71.4%) participants; Ejection Fraction – 5 (71.4%) participants; Drug concentrations in a heart model – 3 (42.9%) participants; Stresses and strains in the cardiac muscle – 3 (42.9%) participants; Heart muscle contractions – 3 (42.9%) participants; Concentrations of ions in a heart model – 1 (14.3%) participant; Field of electric potentials – 1 (14.3%) participant; Sarcomeric proteins' behaviour – 1 (14.3%) participant; Displacements of key sarcomere points – none; Restitution curves – none.

Finally, the participants were informed that beside HCM, SILICOFCM platform could be used also for other cardiac diseases like arrhythmia or cardiac failure. On question for which cardiac disease they would like to use SILICOFCM platform, the answers differed going from simple *yes/maybe/no*, to the pointing out the specific diseases such as heart/cardiac failure, myocardial infarction, atherosclerotic heart disease and cardiac arrhythmias.

Based on the answers, there are no specific and new user requirements that would affect the already created SILICOFCM reference architecture presented in D1.3. In summary, the presented feedback on distributed Questionnaire served as a good starting point for networking with nationally and internationally recognised pharmaceutical companies, their R&D departments and clinical research units. This process will continue during the next period of the project going towards creation of exploitation plan (M24), by when SILICOFCM consortium plans not only to distribute the questionnaires, but to have face-to-face meetings between SILICOFCM representatives and targeted pharmaceutical companies, as well as other stakeholders.

Jointly efforts of SILICOFCM consortium, as well as the whole *in silico* community will have to raise the awareness of *in silico* clinical trials, that will be hopefully enabled through newly established *In Silico* World on Slack community[9], where experts and different stakeholders can interact, get advices and share opinions on *in silico* sophisticated technologies, that would bring to the development of Good Simulation Practices and, through this, accelerates the adoption of *in silico* medicine and *in silico* trials.

[9] https://www.vph-institute.org/news/in-silico-world-on-slack.html

5.4 User needs based on similar systems

The analysis of the similar systems presented in the state-of-the-art has led to the definition of a number of the functional/non-functional requirements described in detail in Section 5.5.

5.5 User Requirements Analysis

This structured capturing and analysis of the requirements will significantly facilitate and boost the design and development processes as well as the platform further validation and evaluation activities.

A unique ID has been assigned to each one of user requirements, which is generated as follows: [F/NF]_[Initials of Requirement Title]_[Numbering], with F meaning Functional and NF standing for Non-Functional. Moreover, each requirement is labelled with a level of priority (Mandatory, Desirable, Optional), based on the users' views and the available resources. Each requirement description is also followed by the goal it serves, with means of verification and its dependencies.

5.5.1 General User Requirements

General User Requirements (GUR) cover aspects that are not related to specific functionalities, but they have strong relationship with all topics of the SILICOFCM work. The General User Requirements specify the SILICOFCM project's needs addressed to the following issues; usability, performance, reliability and availability, security and privacy, platform maintenance and expandability, ethical and legal issues.

Usability Requirements

Table 1. Ease of use (NF_GUR_1).

Requirement ID	**NF_GUR_1**	**Priority**[10]	Mandatory
Requirement title	Ease of use		
Description	The SILICOFCM platform functionalities should be easy to use for all types of users (researchers, cardiologists and clinicians in generally, pharmaceutical companies, etc). Different types of users will have different user interfaces, if a specialization offers an improvement in terms of usability.		
Rationale/Goal	A system or product that is easy to use for acceptability purposes and for reducing the required learning process for all types of users.		
Means of verification	A question asking specifically about the level of easiness of using in the system will be part of another questionnaire that will be launched during development phase of the SILICOFCM platform. The questionnaire will also ask for suggestions on how to make the system easier to interact with. Users will answer the questions in a scale from 0 to 5. However, a specific acceptance threshold, over which the system can be considered acceptable, cannot be easily defined, since making the system easy to use will be a continuous effort, covering the whole project duration.		
Dependencies	NF_GUR_2, NF_GUR_3, F_GUR_11		

Table 2. Ease of learning (NF_GUR_2).

Requirement ID	**NF_GUR_2**	**Priority**	Mandatory
Requirement title	Ease of learning		
Description	The functionalities and interfaces offered by the SILICOFCM platform should be easy to learn by all types of users. New users should be able to		

[10] *Mandatory requirement*: This feature must be built into the final system.
Desirable requirement: This feature should be built into the final system unless the cost is too high.
Optional requirement: This feature is 'nice to have'.

	learn all the functionalities offered with minimum supervision. Also, self-explanatory interfaces, and any other training material specifically oriented to the different type of users as well training lectures could support users on exploring and exploiting the SILICOFCM functionalities.
Rationale/Goal	To ensure the quick adoption of new platform's users, without need for extensive trainings.
Means of verification	A questionnaire launched during the platform development, will contain questions addressed to the users' opinion about easiness to learn using the platform will facilitate identification of platform's characteristics which are difficult to learn. Those characteristics will need further consideration by developers and users. Users will perform the evaluation in a scale from 0 to 5. However, a specific acceptance threshold, over which the system can be considered acceptable, cannot be easily defined, since making the system easy to learn will be a continuous effort, covering the whole project duration.
Dependencies	NF_GUR_1

Performance Requirements

Table 3. Platform time response (NF_GUR_3).

Requirement ID	**NF_GUR_3**	**Priority**	Desirable
Requirement title	Platform time response		
Description	All SILICOFCM functionalities should be without straggles between the user's request and the system response, i.e. responsive in real-time. The user should be informed with appropriate messages in case of time-consuming processes, and if possible, with an estimation of the time delay, in order to avoid user's confusion.		
Rationale/Goal	To raise user acceptance.		
Means of verification	A questionnaire (launched during platform development) about users' perception of the responsiveness of the platform will be provided through which users will facilitate the evaluation of the temporal aspects of system response in a scale of 0-5. Scores over 3 are considered acceptable.		
Dependencies	NF_GUR_4, NF_GUR_6, NF_GUR_7		

Table 4. Simulation time acceptance (NF_GUR_4).

Requirement ID	**NF_GUR_4**	**Priority**	Desirable
Requirement title	Simulation time acceptance		
Description	All SILICOFCM Tools and Modules should run in appropriate simulation time between the user's request and the system response. The user should be informed about the time needed for selected simulation, which depends on complexity of simulation. Also, the user should be informed with appropriate messages in case of time-consuming processes, and if possible, with an estimation of the time delay, in order to avoid user's confusion. In the previous launched Questionnaires, the mainly acceptable response time of SILICOFCM Tools is 0-30 min (clinicians' needs), and few hours (researchers' needs).		

Rationale/Goal	To raise user acceptance.
Means of verification	A questionnaire (launched during platform development) about users' perception of the responsiveness of the platform will be provided through which users will facilitate the evaluation of the temporal aspects of system response in a scale of 0-5. Scores over 3 are considered acceptable.
Dependencies	NF_GUR_6, NF_GUR_7

Table 5. Expandable Platform Storage (NF_GUR_5).

Requirement ID	**NF_GUR_5**	**Priority**	Mandatory
Requirement title	Expandable Platform Storage		
Description	The system should be able to handle constantly growing amount of data. The SILICOFCM platform will expand with more joined users and provided data. In case that firstly allocated storage resources are closed to the initial limit, additional resources should be provided.		
Rationale/Goal	To allow the growth of for the SILICOFCM platform in terms of stored data and enabled expandability of the platform storage.		
Means of verification	If needed, at least one extra dataset is successfully integrated into the system.		
Dependencies	NF_GUR_3, NF_GUR_7		

Reliability and Availability Requirements

Table 6. Reliable simulation results (NF_GUR_6).

Requirement ID	**NF_GUR_6**	**Priority**	Desirable
Requirement title	Reliable simulation results		
Description	The results produced by the SILICOFCM platform on user requests should be accurate and reliable.		
Rationale/Goal	A reliable simulation results should guarantee that the provided SILICOFCM services can be trusted.		
Means of verification	Results of simulations are validated and can be used and disseminated during and after the project lifetime. A questionnaire requesting evaluation of the reliability and accurate perception of SILICOFCM services will be launched during the project lifetime. Users will assess platform reliability with a score on a scale from 0 to 5. Scores over 3 are considered acceptable.		
Dependencies	NF_GUR_5, NF_GUR_7, NF_GUR_8		

Table 7. Available SILCOFCM platform service (NF_GUR_7).

Requirement ID	**NF_GUR_7**	**Priority**	Desirable
Requirement title	Available SILCOFCM platform service		
Description	The SILCOFCM project services should be always available to all types of users at any time. In case of system bugging, the users should be informed with estimation of time needed for re-available SILCOFCM services.		
Rationale/Goal	In order to accept the system by end users, it should not impose any time limit on the user whenever he/she wants to access the SILCOFCM services.		

Means of verification	The SILCOFCM platform service should be available mainly 24/7, taking into account occasional, unexpected failures.
Dependencies	NF_GUR_3, NF_GUR_4, NF_GUR_5

Table 8. SILICOFCM model validation (NF_GUR_8).

Requirement ID	**NF_GUR_8**	**Priority**	Desirable
Requirement title	SILICOFCM model validation		
Description	SILICOFCM project will collect a retrospective and prospective data that will be used within the SILICOFCM tools/modules (e.g. for creation of virtual patients), as well as for their refinement. Also, the SILICOFCM integrates data from each level of organisation (protein-protein interactions, motility assays, muscle cells and tissues) into a predictive comprehensive multiscale model. Each stage of the model will be validated by comparing model predictions with observation at higher level organization.		
Rationale/Goal	To ensure that the outputs of the offered SILICOFCM services are reliable and based on verified processes.		
Means of verification	Testing of the various platform components is applied throughout the development process.		
Dependencies	NF_GUR_6		

Table 9. Notification messages (NF_GUR_9).

Requirement ID	**NF_GUR_9**	**Priority**	Mandatory
Requirement title	Notification messages		
Description	The appropriate messages (warnings, notification, error messages etc.) are presented to the users in case of improper/unexpected functioning of the system.		
Rationale/Goal	In order to accept the system by end users, the user should be informed when the system is not functioning as expected. The communication between the user and system is priority.		
Means of verification	Notification messages appear when needed. The users can evaluate usefulness messages on scale from 0 to 5, addressing questions within Questionnaire in developing phase of the system. Scores over 3 are considered acceptable.		
Dependencies	NF_GUR_1, NF_GUR_2, NF_GUR_3, NF_GUR_4, NF_GUR_5, NF_GUR_6, NF_GUR_7		

Security and Privacy Requirements

Table 10. Data privacy (NF_GUR_10).

Requirement ID	**NF_GUR_10**	**Priority**	Mandatory
Requirement title	Data privacy		
Description	Any collected data must me anonymized on premise (before uploading) and protected from unauthorized access.		
Rationale/Goal	The data are protected against unauthorized users, considering the project involves sensitive personal data.		
Means of verification	Patients' data are anonymized on premise.		

	Patients data are protected against unauthorized access by system administrators. Only anonymized data are used. Security measures must provide access to data through secure channels.
Dependencies	NF_GUR_6, NF_GUR_17

Table 11. Different roles (F_GUR_11).

Requirement ID	**F_GUR _11**	**Priority**	Mandatory
Requirement title	Different roles		
Description	The SILICOFCM access control and security manager should provide different roles to the users. Different users of the platform should have access to different kinds of information.		
Rationale/Goal	Through the management the users could gain access to different UIs, to the cloud hardware infrastructure, to the services and the provided SILICOFCM simulation tools.		
Means of verification	The users have access to the set of services according to their roles. The SILICOFCM platform denies access for the user who has no permissions described for his role.		
Dependencies	NF_GUR_10, F_GUR_12, NF_GUR_17		

Table 12. Controlled Data access (F_GUR_12).

Requirement ID	**F_GUR_12**	**Priority**	Mandatory
Requirement title	Controlled Data access		
Description	Only authorized users should access the SILICOFCM platform integrated data. Different users should have access to different Platform's functionalities and data sets.		
Rationale/Goal	The data integrated within SILICOFCM platform should be accessible by users with specific access rights.		
Means of verification	All accesses to the Platform and the data are recorded during login-in. The log-in will be managed only by Administrators.		
Dependencies	NF_GUR_10, F_GUR _11, F_GUR_13, NF_GUR_17		

Table 13. OAUTH and API services for secure web user authentication and authorization (F_GUR_13).

Requirement ID	**F_GUR_13**	**Priority**	Mandatory
Requirement title	OAUTH and API services for secure web user authentication and authorization		
Description	The SILICOFCM platform should OAUTH and API services for secure web user authentication and authorization.		
Rationale/Goal	To ensure OAUTH and API services for secure web user authentication and authorization		
Means of verification	The data authorization and authentication process is executed.		
Dependencies:	NF_GUR_10, F_GUR _11, F_GUR_12, NF_GUR_17		

Table 14. Https Communications (F_GUR_14).

Requirement ID	**F_GUR_14**	**Priority**	Mandatory

Requirement title	Https Communications
Description	In order to ensure secure communication between users and SILICOFCM platform, all communications should be performed only in https with appropriate certificates.
Rationale/Goal	To ensure secure web communication between users and SILICOFCM platform
Means of verification	All SILICOFCM web services are performed via https.
Dependencies:	N/A

Table 15. Big data management (NF_GUR_15).

Requirement ID	NF_GUR_15	Priority	Mandatory
Requirement title	Big data management		
Description	Data stored within the platform are served as big data in an anonymised way in order to facilitate simulation in FCM research. Researchers should access a big database to use in order to perform proposed simulations. Simulations that require extra-long processes will warn users about the required time.		
Rationale/Goal	SILICOFCM should guarantee the analysis of big data.		
Means of verification	The SILICOFCM platform is able to manage with very large datasets. There are no unexpected processing delays or memory issues.		
Dependencies	NF_GUR_5, NF_GUR_7, F_DGR_4		

Table 16. System administration (NF_GUR_16).

Requirement ID	NF_GUR_16	Priority	Mandatory
Requirement title	System administration		
Description	Administrator should take actions regarding any security leak of the platform. Administrators must be able to inspect the data in an anonymized way to infer malicious behaviours.		
Rationale/Goal	Administrators should block/prevent a malicious or unauthorized access to the SILICOFCM platform. Some preventable measures could mean the necessity of inspecting the data. Authorized users accessing unauthorized data will be warned and requested to ask for permission.		
Means of verification	The data controller will setimate the capabiliteies for identification of malicious or unauthorized access. Score range is between 0 and 5. Scores over 3 are considered acceptable.		
Dependencies	NF_GUR_10, F_GUR_11, F_GUR _12, NF_GUR_17		

Table 17. IPR Protection (NF_GUR_17).

Requirement ID	NF_GUR_17	Priority	Mandatory
Requirement title	IPR Protection		
Description	IPRs related to SILICOFCM architecture, UI design, development, and implementation, as well as to created and shared data, should be ensured.		

Rationale/Goal	To provide fluent crossing from partners collaboration to product commercialization. To strength the trust of the data providers for sharing their data within the SILICOFCM integrated cohort.
Means of verification	A questionnaire containing questions about IPR Protection and how well platform deals with the management of sharing data is launched during platform development. Users will score from 0-5. Scores over 3 are considered acceptable.
Dependencies	N/A

Platform Maintenance and Expansion Requirements

Table 18. Capability for new services inclusion (F_GUR_18).

Requirement ID	**F_GUR _18**	**Priority**	Optional
Requirement title	Capability for new services inclusion		
Description	The platform should supply inclusion of new services, or update of existing ones.		
Rationale/Goal	To provide expandability of the SILICOFCM platform through either offering new or enhanced existing services. Upgrade of the existing services or inclusion of new services will satisfy expectations of SILICOFCM consortium members and final users.		
Means of verification	There are no SILICOFCM platform issues during upgrade of existing services or inclusion of new ones.		
Dependencies	NF_GUR_5, F_GUR _19		

Table 19. Capability for new computational resources (F_GUR_19).

Requirement ID	**F_GUR _19**	**Priority**	Optional
Requirement title	Capability for new computational resources		
Description	SILICOFCM consortium members (or final end users) may need to provide a new computational resource (i.e. HPC center or cloud infrastructure) to the SILICOFCM platform for future exploitation. The platform should supply inclusion of new computational resources.		
Rationale/Goal	To provide expandability of the SILICOFCM platform through additional computational resources. Expanded/improved computational resources will satisfy expectations of the consortium members and final users.		
Means of verification	There are no SILICOFCM platform issues during inclusion of new computational resources.		
Dependencies	NF_GUR_5, F_GUR _18		

Ethical and Legal Requirements

Table 20. Compliance of the SILICOFCM content and the scope with EU directives (NF_GUR_20).

Requirement ID	**NF_GUR_20**	**Priority**	Mandatory
Requirement title	Compliance of the SILICOFCM content and the scope with EU directives		

Description	All components and practices developed within SILICOFCM should be in accordance to the project's ethics and EU directives.
Rationale/Goal	The rights of the SILICOFCM users, and patients whose data are anonymous, are protected.
Means of verification	Supervision of the SILICOFCM platform components during their design and development. Legal issues and restrictions must be tested in order to ensure full compliance with project's ethics and EU directives.
Dependencies	All security and legal requirements.

5.5.2 Data Governance Requirements

The purpose of Data Governance Requirements (DGR) collection is to capture the needs of the SILICOFCM users in terms of data governance. Given that there are activities of the project focusing on data collection from retrospective and prospective clinical studies, as well as the storage of computational models and virtual population within the platform, providing a large amount of data for machine learning, a robust and efficient data governance framework is required.

The data governance framework will deal with a novel methodology for the *initialisation*, *maintenance* and *expansion* of this heterogeneous data infrastructure. *Different levels of* and *prerequisites for participation* will be specified in the data infrastructure on behalf of data providers. *Linkability* of the data sources will be in focus. Aspects of data *access*, General User Requirements (*availability* and *quality* including *completeness*, *validity*, *timeliness* and *accuracy*) will be covered by developing a well detailed evaluation framework.

In order to integrate all required data within the SILICOFCM platform, considering effective use and maintained, as well as the possibility for further expansion, series of requirements regarding the data, their storage, means of usage and accessibility have been collected and analysed. Also, requirements from the General User Requirements section are also applicable for this topic, but are not included in this section due to avoid duplication.

Table 21. Input/output Data Format (F_DGR_1).

Requirement ID	**F_DGR_1**	**Priority**	Mandatory
Requirement title	Input/output Data Format		
Description	The data Input/output format should follow predefined template. The SILICOFCM platform should support the most widely used file formats for solver input/output. This affects mainly the post-processing functionality of the platform.		
Rationale/Goal	To allow for the efficient and effective processing and interlinking of the data source with the SILICOFCM database.		
Means of verification	All the input/output data elements are represented in a predefined format. There are no issues with uploading and post-processing of data.		
Dependencies	N/A		

Table 22. Data Vocabulary (F_DGR_2).

Requirement ID	F_DGR_2	Priority	Mandatory
Requirement title	Data Vocabulary		
Description	The terminology for drugs, diseases, symptoms, clinical and genetic data, models, tests etc. should be international, as well as the classifications, vocabularies or coding systems. Description of those terms should be in the format which is understandable for users.		
Rationale/Goal	To allow the semantic interlinking of the data that can be used on the international level during and after the project lifetime.		
Means of verification	The used sets of terms correspond to the international classifications, vocabularies or coding systems.		
Dependencies	F_DGR_1		

Table 23. Metadata (F_DGR_3).

Requirement ID	F_DGR_3	Priority	Mandatory
Requirement title	Metadata		
Description	The data elements within SILICOFCM database should be accompanied by metadata, which would give a clear insight of the element they are linked with, such as its purpose, specific methods it has been based on, definition, if needed, etc.		
Rationale/Goal	Metadata are important for controlled sets of terms used so that the data recorded is well-understood and of specific meaning.		
Means of verification	Important information related to metadata (i.e. data structure and related vocabularies) are captured within the data management.		
Dependencies	F_DGR_1, F_DGR_2		

Table 24. Data Anonymization (F_DGR_4).

Requirement ID	F_DGR_4	Priority	Mandatory
Requirement title	Data Anonymization		
Description	The patients' data included in the SILICOFCM database should be anonymised. The privacy levels should be achieved, considering the need for precise and accurate data collection.		
Rationale/Goal	To insure the privacy of the patients whose data is stored within the SILICOFCM platform.		
Means of verification	All data is anonymised before entering to the SILICOFCM database. There is no IPR violation.		
Dependencies	F_DGR_1, F_DGR_2		

Table 25. Upload of New Data (F_DGR_5).

Requirement ID	F_DGR_5	Priority	Mandatory
Requirement title	Upload of New Data		
Description	Uploading of new anonymized data (clinical or/and genetic data), or geometrical models etc. to the SILICOFCM platform should be enabled. A safe way for uploading the data should be ensured due to their further store and processing.		
Rationale/Goal	To upload appropriate data on the SILICOFCM platform.		
Means of verification	Uploaded data in the adequate form through the appropriate UI.		

Dependencies	F_DGR_1, F_DGR_2, F_DGR_4

Table 26. Data Consistence and Completeness (F_DGR_6).

Requirement ID	F_DGR_6	Priority	Mandatory
Requirement title	Data Consistence and Completeness		
Description	The data within the SILICOFCM platform should be accurate and valid, as well as complete, i.e. predefined set of parameters must be included.		
Rationale/Goal	To ensure duality data that leads to reliability and consistency of the conclusions and results, obtained by using the provided data.		
Means of verification	The data include a predefined minimum of parameters. The data usage leads to valid conclusions and can serve for validation of results.		
Dependencies	F_DGR_1, F_DGR_2		

Table 27. Data Updates (F_DGR_7).

Requirement ID	F_DGR_7	Priority	Mandatory
Requirement title	Data Updates		
Description	Data in the SILICOFCM platform should be regularly updated, either through the incorporation of new models, material characteristics, patients, virtual population etc, or the introduction of new data for existing models, material characteristics, patients, virtual population etc. When existing data are updated, then the previous records of these data should remain intact.		
Rationale/Goal	To ensure improvement and refreshment of SILICOFCM database.		
Means of verification	The incorporation of new data within the SILICOFCM platform should follow the rules regarding data format, terminologies and metadata.		
Dependencies	F_DGR_1, F_DGR_2, F_DGR_5, F_DGR_6		

Table 28. Scheduled Backup of SILICOFCM Data (F_DGR_8).

Requirement ID	F_DGR_8	Priority	Mandatory
Requirement title	Scheduled Backup of SILICOFCM Data		
Description	The SILICOFCM database should have the backup. Models, material characteristics, patients, virtual population, simulation results and other critical data should be securely stored if not designated as publicly available.		
Rationale/Goal	To ensure data consistency and avoid loss of the data due to unexpected failure of SILICOFCM services.		
Means of verification	In case of improper/unexpected functioning of the SILICOFCM system, all critical data have backup and their loss is avoided.		
Dependencies	F_DGR_6		

Table 29. Notification about Data Usage (F_DGR_9).

Requirement ID	F_DGR_9	Priority	Mandatory
Requirement title	Notification about Data Usage		

Description	The data provider should receive notification when the SILICOFCM datasets accessed. This notification will be accompanied by information, including who accessed the datasets and through which service. Logs of the data usage should be available at any time for each data provider.
Rationale/Goal	To ensure the data provider's supervision on the data usage.
Means of verification	The notifications about data usage that each data provider receives should cover all accesses to the database.
Dependencies	F_DGR_10

Table 30. Data Access Logging and Auditing (F_DGR_10).

Requirement ID	**F_DGR_10**	**Priority**	Mandatory
Requirement title	Data Access Logging and Auditing		
Description	The access to the SILICOFCM services should be logged by recording information regarding which user had access, through which service and at which time point.		
Rationale/Goal	To follow the actions performed on the data for security purposes.		
Means of verification	All accesses to the SILICOFCM platform are logged and audited, including involved users and performed actions.		
Dependencies	NF_GUR_16		

5.5.3 SILICOFCM Tools Usage Requirements

The following sets of SILICOFCM Tools Usage Requirements (STUR) related to usage of existing SILICOFCM Tools: i) MUSICO Tool (MT), ii) ALYA Solver Tool (AST), iii) PAK Solver Tool (PST), iv) Data Analytics Tool (DAT), v) Bioinformatics Tool (BT), vi) Virtual Population Tool (VPT), vii) Multiple Criteria Decision Making Tool (MCDM), contain basic requirements to be considered during the SILICOFCM specification process (Task 1.2) and creation of the SILICOFCM reference architecture (Task 1.2).

Is should be noted that collected requirements serve as a reference point, and those which are omitted at this stage will be considered and integrated during the SILICOFCM platform development and refinement.

Table 31. A list of available SILICOFCM tools (F_STUR_1).

Requirement ID	**F_STUR_1**	**Priority**	Mandatory
Requirement title	A list of available SILICOFCM tools		
Description	The user should have a list of available tools and each tool should have all the required information to create and run a simulation. SILICOFCM platform should define indexes of tools that platform supports, as well as, inputs and output formats and specifications that those tools are going to produce.		
Rationale/Goal	To enable the user to have the list of available SILICOFCM tools with the required information to create and run a simulation.		
Means of verification	The user can overview and select a different SILICOFCM tools		

Dependencies	F_STUR_3, F_STUR_4

Table 32. A list of available virtual patients/models and clinical/genetic data (F_STUR_2).

Requirement ID	**F_STUR_2**	**Priority**	Mandatory
Requirement title	A list of available virtual patients/models and clinical/genetic data		
Description	SILICOFCM platform should provide a list of a virtual patients (cohorts or single patients)/models and clinical/genetic data. The user should be able to manage the information related to virtual patients/models and clinical/genetic data, depending on his/her interests and needs.		
Rationale/Goal	The list of a virtual patients/models and clinical/genetic data will enable user to use them within the given SILICOFCM functionalities.		
Means of verification	The user can overview and select a different virtual patients/models and clinical/genetic data.		
Dependencies	F_STUR_22, F_STUR_24 F_VAUI_4, F_VAUI_5, F_VAUI_6		

Table 33. A list of available computational resources per tool (F_STUR_3).

Requirement ID	**F_STUR_3**	**Priority**	Optional
Requirement title	A list of available computational resources per tool		
Description	Different models are associated with different solvers and computational resources. Also, computational resources may be the partner's HPC centre, or a cloud VM with parameterized CPU and memory.		
Rationale/Goal	To inform the user about available computational resources per tool.		
Means of verification	The list of available computational resources per tool is accurate and updated.		
Dependencies	NF_GUR_5, F_STUR_7		

Table 34. UI which allows user to complete all needed tasks for running the simulation (F_STUR_4).

Requirement ID	**F_STUR_4**	**Priority**	Mandatory
Requirement title	UI which allows user to complete all needed tasks for running the simulation		
Description	SILICOFCM should provide a UI for users to allow them to manually complete for running the simulation. The user should be able to enter all information related to the tasks' completion.		
Rationale/Goal	To provide user-friendly interface that enables the users to complete all needed tasks for running the simulation.		
Means of verification	The UI is created and satisfies the user's needs related to simulation execution.		
Dependencies	F_STUR_1, F_STUR_2, F_STUR_3 F_VAUI_1-11		

Table 35. Conversion of SILICOFCM simulation/experiment setup to predefined workflow (F_STUR_5).

Requirement ID	**F_STUR_5**	**Priority**	Mandatory
Requirement title	Conversion of SILICOFCM simulation/experiment setup to predefined workflow		
Description	A simulation setup consists of a virtual population, clinical and genetic data, boundary conditions and material properties, model (workflow definition) and specific computational resources. A simulation setup should be translated to a number of task flowcharts (predefined workflows). A task includes, meshing, data-conversion, simulation, post-processing, data-transfer etc.		
Rationale/Goal	To convert simulation/experiment setup to a workflow.		
Means of verification	The simulation/experiment setup is translated to appropriate number of task flowcharts.		
Dependencies	F_STUR_6		

Table 36. Workflows should be defined in a standard workflow definition language (F_STUR_6).

Requirement ID	**F_STUR_6**	**Priority**	Desirable
Requirement title	Workflows should be defined in a standard workflow definition language		
Description	The SILICOFCM workflows for tools/modules are core of the platform and should be defined in a standard workflow definition language.		
Rationale/Goal	To define all needed workflows responsible for correct execution and communication of SILICOFCM modules/tools.		
Means of verification	The communication between SILICOFCM modules/tools/ and their execution are performed without issues.		
Dependencies	F_STUR_5, F_STUR_7, F_STUR_9, F_STUR_10, F_STUR_22		

Table 37. Validate the SILICOFCM tool workflow execution capability (F_STUR_7).

Requirement ID	**F_STUR_7**	**Priority**	Desirable
Requirement title	Validate the SILICOFCM tool workflow execution capability		
Description	SILICOFCM platform should provide a functionality to verify that a given tool can be executed. There are cases when some functionalities may be offline or withdrawn. Therefore, some tool/module workflows may be not possible to be properly executed at a given time.		
Rationale/Goal	To verify that a given tool can be executed.		
Means of verification	The user receives verification notification related to SILICOFCM tool execution.		
Dependencies	F_STUR_6, F_STUR_13		

Table 38. The task flowcharts should be handled and recovered from task failure (F_STUR_8).

Requirement ID	**F_STUR_8**	**Priority**	Desirable
Requirement title	The task flowcharts should be handled and recovered from task failure		
Description	The SILICOFCM tasks may fail due to different reasons such as: resource insufficiency, wrong input etc. The workflow should handle those errors and try to recover from such an error. In case recovery is not possible, the end-user/support-user should be notified by appropriate notification.		
Rationale/Goal	To provide handling and recovery of task flowcharts from task failure using appropriate workflow/		
Means of verification	The workflow handles errors and tries to recover the tasks; the user is informed about output.		
Dependencies	F_STUR_6, F_STUR_7		

Table 39. Communication between remote-based tools (F_STUR_9).

Requirement ID	**F_STUR_9**	**Priority**	Mandatory
Requirement title	Communication between remote-based tools		
Description	The user should be able to execute three tools which could be located in remote sites, i.e., the MUSICO, the PAK solver, and the ALYA solver. The SILICOFCM system must provide appropriate secure communication tunnel.		
Rationale/Goal	To provide appropriate secure communication tunnel and enable communication between SILICOFCM remote solvers.		
Means of verification	The usage of SILICOFCM remote solvers (the MUSICO, the PAK solver, and the ALYA solver) is performed without issues.		
Dependencies	F_STUR_6, F_STUR_7, F_STUR_8		

Table 40. Communication between docker-based tools (F_STUR_10).

Requirement ID	**F_STUR_10**	**Priority**	Mandatory
Requirement title	Communication between docker-based tools		
Description	The user should be able to execute the SILICOFCM docker-based tools, i.e., the Bioinformatics Tool, the Data analytics Tool, the Virtual population tool, the Multiple Criteria Decision Making tool. The SILICOFCM system must provide appropriate docker engines.		
Rationale/Goal	To provide appropriate docker engines and enable communication between SILICOFCM docker solvers.		
Means of verification	The usage of SILICOFCM docker solvers (Bioinformatics Tool, the Data analytics Tool, the Virtual population tool, the Multiple Criteria Decision Making tool) is performed without issues.		
Dependencies	F_STUR_6, F_STUR_7, F_STUR_8		

Table 41. Conversion of solvers' files (F_STUR_11).

Requirement ID	**F_STUR_11**	**Priority**	Mandatory

Requirement title	Conversion of solvers' files
Description	The SILICOFCM will provide all needed tools in order to convert solvers' files. This is important for the SILICOFCM tools linking.
Rationale/Goal	To ensure communication between SILICOFCM tools and mutually usage of obtained filer (e.g. results) as inputs/outputs.
Means of verification	A given files are used as inputs/outputs for different SILICOFCM tools
Dependencies	F_STUR_16

Table 42. Incorporate convergence criteria per case (F_STUR_12).

Requirement ID	F_STUR_12	Priority	Desirable
Requirement title	Incorporate convergence criteria per case		
Description	The SILICOFCM platform should incorporate a default or user defined convergence acceptance criteria related to the SILICOFCM tools.		
Rationale/Goal	To provide a default or user defined convergence acceptance criteria for running a different SILICOFCM Tools.		
Means of verification	The default convergence acceptance criteria are defined, or user defines his/her own convergence acceptance criteria.		
Dependencies	F_STUR_21, F_STUR_15		

Table 43. Parallel execution of simulations (F_STUR_13).

Requirement ID	F_STUR_13	Priority	Mandatory
Requirement title	Parallel execution of simulations		
Description	The SILICOFCM platform should enable with parallelization of computational algorithms due to large models and time demanding simulations. Graphic Processing Units (GPUs) can be used to accelerate processing times of parallel problem		
Rationale/Goal	To speed-up the simulations.		
Means of verification	Real-time simulations are performed.		
Dependencies	F_STUR_14, F_STUR_15, F_STUR_16		

Table 44. Estimation of simulation duration (F_STUR_14).

Requirement ID	F_STUR_14	Priority	Optional
Requirement title	Estimation of simulation duration		
Description	The SILICOFCM platform should provide the estimation of time required to get results for given specific simulation.		
Rationale/Goal	To enable the user to have an insight into the duration of the simulation that may effect on disposing of his/her time.		
Means of verification	The user is informed about duration of the simulation.		
Dependencies	NF_GUR_4 F_STUR_13		

Table 45. Calculation of sarcomere mechanical response (F_STUR_15).

Requirement ID	F_STUR_15	Priority	Mandatory

Requirement title	Calculation of sarcomere mechanical response
Description	The current version of the MUSICO involves a number of sarcomere geometry models including the three-dimensional spatial models of multi-sarcomere geometry. Therefore, the MUSICO tool should enable calculation of sarcomere mechanical behaviour, employing appropriate protocol.
Rationale/Goal	To enable the end-user to test the influence of various diseases and therapies on muscle fibre functions using the SILICOFCM MUSICO Tool.
Means of verification	MUSICO results are not significantly different from the results of relevant models and experimental measurements.
Dependencies	F_STUR_2, F_STUR_13, F_STUR_5

Table 46. Linking the MT with BT, ALT, PST (F_STUR_16).

Requirement ID	F_STUR_16	Priority	Mandatory
Requirement title	Linking the MT with BT, ALT, PST		
Description	The SILICOFCM platform should enable the linking between MUSICO, Bioinformatics Tool and FE tools (ALYA and PAK solvers). The genetic data is linked with corresponding predictions of their functional impact on proteins (Task 4.3), and extracted data is subsequently prepared to allow fitting of the MUSICO muscle model. FE solvers coupled to the software MUSICO will create highly detailed multi-scale simulations of the sarcomere dynamics up to the whole heart behaviour in order to understand the effect of sarcomeric protein mutations leading to familial cardiomyopathies		
Rationale/Goal	To create highly detailed multi-scale simulations of the sarcomere dynamics up to the whole heart behaviour.		
Means of verification	The multi-scale models are validated.		
Dependencies	F_STUR_11, F_STUR_9, NF_GUR_8, F_STUR_5, F_STUR_22		

Table 47. Mesh validation (F_STUR_17).

Requirement ID	F_STUR_17	Priority	Desirable
Requirement title	Mesh validation		
Description	The SILICOFCM services should include the mesh validation of the models employed in FE (ALYA and PAK solvers) simulation. The specific acceptance criteria should be adopted.		
Rationale/Goal	To ensure quality of models within the SILICOFCM platform.		
Means of verification	Reliable results are obtained.		
Dependencies:	NF_GUR_6, NF_GUR_8, F_STUR_18		

Table 48. Imaging Data Processing (F_STUR_18).

Requirement ID	F_STUR_18	Priority	Optional
Requirement title	Imaging Data Processing		
Description	The SILICOFCM should enable usage and processing of imaging data (MRI, CT, DTMRI etc.) stored within SILICOFCM database. Those data will be		

	further used to create the geometrical models of cardiac anatomies needed for FE computational simulations. The segmented/processed data can be used for a surface mesh creation, fibres orientation, model parameterization, etc.
Rationale/Goal	To create detailed geometrical models.
Means of verification	Different models are successfully employed within FE simulations giving reliable and robust results.
Dependencies	F_STUR_2, F_STUR_17, F_STUR_19

Table 49. Set up the Boundary Conditions (F_STUR_19).

Requirement ID	**F_STUR_19**	**Priority**	Mandatory
Requirement title	Set up the Boundary Conditions		
Description	For mechanics simulations it is important to prescribe appropriate boundary conditions via labelling of surfaces, and regions. There are different sets of boundary conditions depending on employed simulation. The SILICOFCM should enable setting up of boundary conditions such as: prescribed entering drug concentration, ionic concentration, fluid flow velocities, pressures, forces, etc.) Also, the SILICOFCM system should define and offer default boundary conditions for appropriate type of simulation.		
Rationale/Goal	To perform different types of simulations.		
Means of verification	Adequate performance of simulation.		
Dependencies	F_STUR_5, F_STUR_21		

Table 50. Set up the Material Properties (F_STUR_20).

Requirement ID	**F_STUR_20**	**Priority**	Mandatory
Requirement title	Set up the Material Properties		
Description	The SILICOFCM services should enable setting up of material properties which are needed for simulation execution. Those material properties could be characteristics of drug transport, ionic transport and electric field, mechanical characteristics of heart tissue, etc. Also, the SILICOFCM system should define and offer default material properties for appropriate models and types of simulations.		
Rationale/Goal	To perform different types of simulations.		
Means of verification	Adequate performance of simulation.		
Dependencies	F_STUR_5, F_STUR_21		

Table 51. Heart mechanics coupled with electric field and drug transport (F_STUR_21).

Requirement ID	**F_STUR_21**	**Priority**	Mandatory
Requirement title	Heart mechanics coupled with electric field and drug transport		
Description	The SILICOFCM platform should allow execution of FE simulations which enable examination of the drug concentration in the SILICOFCM base-stored heart models, as well as the concentration of ions, field of electric		

	potentials in different compartments of heart models, and results of mechanical deformations of heart tissues.
Rationale/Goal	To examine and visualise outcomes of different therapies for identifying high risk individuals.
Means of verification	Adequate performance of simulation.
Dependencies	F_STUR_2, F_STUR_5, F_STUR_12, F_STUR_17, F_STUR_18, F_STUR_19, F_STUR_20

Table 52. Genetic Data Processing (F_STUR_22).

Requirement ID	**F_STUR_22**	**Priority**	Mandatory
Requirement title	Genetic Data Processing		
Description	The SILICOFCM platform should enable the user to run CWL (Common Workflow Language) workflows developed by SBG on the SILICOFCM platform using data stored on the platform. During implementation phase developers should be able to handle input/intermediary/output data on the platform. At final stages this should be done automatically by the platform.		
Rationale/Goal	Bioinformatics workflows described in CWL will be executed using Docker		
Means of verification	Successful completion of workflow run using a test dataset		
Dependencies	F_STUR_2, F_STUR_6, F_STUR_7, F_STUR_10, F_STUR_16		

Table 53. Machine Learning Algorithms usage (F_STUR_23).

Requirement ID	**F_STUR_23**	**Priority**	Mandatory
Requirement title	Machine Learning Algorithms usage		
Description	The SILICOFCM platform should provide Machine learning algorithms for Risk Stratification, Virtual Patients Repository Modelling, and mining of FCM clinical and genetic data stored within the SILICOFCM database. These various cases of ML algorithms usage will provide statistical overview of various cardiomyopathy patients risk groups, as well as predictive models that describe cardiomyopathy outcomes for virtual patients. They also can be applied for identifying the high-risk individuals.		
Rationale/Goal	To develop a cardiomyopathy risk stratification tool; to identify disease patterns from large amount of heterogeneous data.		
Means of verification	Adequate machine learning performance and classification. Acceptable to use by clinicians.		
Dependencies	F_STUR_2, F_STUR_22		

Table 54. Creation of virtual populations (cohort) of FCM patients (F_STUR_24).

Requirement ID	**F_STUR_24**	**Priority**	Mandatory
Requirement title	Creation of virtual populations (cohort) of FCM patients		
Description	The SILICOFCM platform should enable a creation of new virtual patients based on the prospective and retrospective data from SILICOFCM such as: clinical data, laboratory data (including genetic data), various heart geometries from the imaging clinical data, etc.		
Rationale/Goal	To create virtual FCM patients models repository.		

Means of verification	Provided the SILICOFCM database of virtual patients for re-use in pre- and post-competitive testing of drugs using data mining approach.
Dependencies	F_STUR_2, F_STUR_6, F_STUR_18, F_STUR_22

5.5.4 Visual Analytics and User Interfaces

SILICOFCM platform contains large amount of heterogeneous data (clinical, genetic data, etc.), and provides virtual models of different cohorts (classified patient groups which differ in physiology and heart morphology). This virtual patient model library of different cohorts will enable the testing of a new drug under different boundary conditions. In that order, the purpose of collection the Visual Analysis and User Interfaces requirements is to support the cohort discovery, as well as the other available data, which may contain meaningful information about patients during their re-use in pre- and post-competitive testing of drugs.

Table 55. Post-processing of results (F_VAUI_1).

Requirement ID	**F_VAUI_1**	**Priority**	Mandatory
Requirement title	Post-processing of results		
Description	The SILICOFCM platform should provide a solution that will be user-friendly and powerful enough in order to perform a number of required operations during the post-processing of simulations results.		
Rationale/Goal	Allow to the user to perform advanced 2D/3D operations and view of simulation results.		
Means of verification	The user can view the simulation results by performing advanced 2D/3D operations without issues.		
Dependencies	F_VAUI_2, F_VAUI_3, F_VAUI_7		

Table 56. Visualization of 2D- and 3D-case results in browser (F_VAUI_2).

Requirement ID	**F_VAUI_2**	**Priority**	Mandatory
Requirement title	Visualization of 2D- and 3D-case results in browser		
Description	The user will be able to view 3D geometries and related results, as well as 2D geometries and related graphs, by selecting specific cases. The SILICOFCM platform should ensure an efficient way to load and provide main navigation functionalities for the 2D/3D visualisation. Visualization of the results will depend on the various SILICOFCM tools used by the user.		
Rationale/Goal	To provide performing of advanced 2D/3D operations and view of simulation results.		
Means of verification	The user can view the results after performing the 2D/3D-case simulations.		
Dependencies	F_VAUI_1, F_VAUI_3		

Table 57. Visualization of evaluation reports (F_VAUI_3).

Requirement ID	**F_VAUI_3**	**Priority**	Mandatory
Requirement title	Visualization of evaluation reports		

Description	The user will be able to view the history of evaluation reports containing performance analysis of the developed predictive models (virtual patients). The reports will be used to iteratively improve prediction quality. The SILICOFCM platform should ensure an efficient way to load and provide main navigation functionalities for the visualization of evaluation reports.
Rationale/Goal	To ensure visualization of evaluation reports during predictive modelling and prediction evaluation for virtual patients.
Means of verification	The user can view the evaluation reports which contain performance analysis of the developed predictive models
Dependencies	F_VAUI_1

Table 58. Browsing and filtering with an interactive visual access (F_VAUI_4).

Requirement ID	**F_VAUI_4**	**Priority**	Mandatory
Requirement title	Browsing and filtering with an interactive visual access		
Description	The user can use a visual interface to gain an overview over models, results, the whole virtual cohort, and also can filter those data based on available attributes (geometries, mesh size, clinical/genetic properties etc.). It should be noted that any such action will be strictly bound to the data governance framework and will comply with the project's ethics.		
Rationale/Goal	To enable the data overview, browsing, filtering and comparing, that is an efficient way for users (researchers, medical experts) to explore subgroups of the available virtual patients, as well as results, models and other available data.		
Means of verification	Different types of data are accurately visualized.		
Dependencies	F_VAUI_5, F_VAUI_6, F_VAUI_7, F_VAUI_8, F_VAUI_9 NF_GUR_10, F_GUR_11, F_GUR_12, NF_GUR_20		

Table 59. Visualization of Virtual Patients Cohort (F_VAUI_5).

Requirement ID	**F_VAUI_5**	**Priority**	Optional
Requirement title	Visualization of Virtual Patients Cohort		
Description	The user should be able to choose between visualizing the cohort as a whole, or as a collection of its individual subjects (i.e. set of individual patients), depending on the user's needs. It should be noted that any such action will be strictly bound to the data governance framework and will comply with the project's ethics.		
Rationale/Goal	To provide a custom data presentation views for different visualization use cases, due to the heterogeneous data types within the database.		
Means of verification	Different types of virtual cohorts are accurately visualized.		
Dependencies	F_VAUI_4 NF_GUR_10, F_GUR_11, F_GUR_12, NF_GUR_20		

Table 60. Visual and statistical comparison of sub-cohorts (F_VAUI_6).

Requirement ID	**F_VAUI_6**	**Priority**	Desirable

Requirement title	Visual and statistical comparison of sub-cohorts
Description	In case of virtual sub-cohorts, the user should have a visual and statistical overview on the current cohort's data, and how it differs from the large integrated cohort (or a custom-defined one). Potentially, common statistical tests can be performed in order to compare sub-cohorts. Results can be visualized and exported as images (e.g. for publications). Also, it should be noted that any such action will be strictly bound to the data governance framework and will comply with the project's ethics.
Rationale/Goal	To ensure visual and statistical comparison of sub-cohorts during their re-use in pre- and post-competitive testing of drugs using data mining approach.
Means of verification	Accurate identification and statistical comparison of virtual patients' cohorts during pre- and post-competitive testing of drugs.
Dependencies	F_VAUI_4, F_VAUI_5, F_VAUI_7 NF_GUR_10, F_GUR_11, F_GUR_12, NF_GUR_20

Table 61. Capability to Save/Load Working Progress (F_VAUI_7).

Requirement ID	F_VAUI_7	Priority	Desirable
Requirement title	Capability to Save/Load Working Progress		
Description	The SILICOFCM system should enable the user to save and restore the configuration of custom-defined simulation analysis, or virtual sub-cohorts. Also, it should be noted that any such action will be strictly bound to the data governance framework and will comply with the project's ethics.		
Rationale/Goal	To ensure that user can save his/her work in progress, with possibility to re-load the obtained results during their later usage and comparison.		
Means of verification	The user can easily save/load his/her work.		
Dependencies	F_VAUI_1, F_VAUI_2, F_VAUI_3, F_VAUI_4, F_VAUI_5, F_VAUI_6, F_VAUI_8, F_VAUI_9		

Table 62. Data Download (F_VAUI_8).

Requirement ID	F_VAUI_8	Priority	Desirable
Requirement title	Data Download		
Description	The user can download the data (virtual patients/models, (sub)cohorts, simulation results, etc.) to his local file storage. Of course, it should be noted that any such action will be strictly bound to the data governance protocols. Usage of this function will be restricted, depending of final platform architecture and actors' roles.		
Rationale/Goal	To allow the users to analyse the data with their software tools.		
Means of verification	Data governance model regarding use / download of data.		
Dependencies	F_VAUI_4, F_VAUI_5 NF_GUR_10, F_GUR_11, F_GUR_12, NF_GUR_20		

Table 63. Integration with other SILICOFCM services (F_VAUI_9).

Requirement ID	F_VAUI_9	Priority	Optional

Requirement title	Integration with other SILICOFCM services
Description	If there is possibility, other SILICOFCM services are integrated in the user interface. It should be noted that any such action will be strictly bound to the data governance framework and will comply with the project's ethics.
Rationale/Goal	The user interface is supposed to be the primary access point for the users. Thus, it would be desirable to enable further analytics services.
Means of verification	Other SILICOFCM services are integrated in the visual interface.
Dependencies	F_VAUI_4 F_GUR_11, F_GUR_12

5.5.5 Overview of User Requirements and associated dependencies

A summary of all User Requirements and associated dependencies is given in the following table:

Table 64. Overview of User Requirements and associated dependencies.

ID	User Requirements	Dependencies
NF_GUR_1	Ease of use	NF_GUR_2, NF_GUR_3, F_GUR_11
NF_GUR_2	Ease of learning	NF_GUR_1
NF_GUR_3	Platform time response	NF_GUR_4, NF_GUR_6, NF_GUR_7
NF_GUR_4	Simulation time acceptance	NF_GUR_6, NF_GUR_
NF_GUR_5	Expandable Platform Storage	NF_GUR_3, NF_GUR_7
NF_GUR_6	Reliable simulation results	NF_GUR_5, NF_GUR_7, NF_GUR_8
NF_GUR_7	Available SILCOFCM platform service	NF_GUR_3, NF_GUR_4, NF_GUR_5
NF_GUR_8	SILICOFCM model validation	NF_GUR_6
NF_GUR_9	Notification messages	NF_GUR_1, NF_GUR_2, NF_GUR_3, NF_GUR_4, NF_GUR_5, NF_GUR_6, NF_GUR_7
NF_GUR_10	Patient privacy	NF_GUR_6, NF_GUR_17
NF_GUR_11	Different roles	NF_GUR_10, F_GUR_12, NF_GUR_17
NF_GUR_12	Controlled Data access	NF_GUR_10, F_GUR _11, F_GUR_13, NF_GUR_17
NF_GUR_13	OAUTH and API services for secure web user authentication and authorization	NF_GUR_10, F_GUR _11, F_GUR_12, NF_GUR_17
NF_GUR_14	Https Communications	N/A
NF_GUR_15	Big data management	NF_GUR_5, NF_GUR_7, F_DGR_4
NF_GUR_16	System administration	NF_GUR_10, F_GUR_11, F_GUR _12, NF_GUR_17
NF_GUR_17	IPR Protection	N/A
NF_GUR_18	Capability for new services inclusion	NF_GUR_5, F_GUR _19

NF_GUR_19	Capability for new computational resources	NF_GUR_5, F_GUR _18
NF_GUR_20	Compliance of the SILICOFCM content and the scope with EU directives	All security and legal requirements.
F_DGR_1	Input/output Data Format	N/A
F_DGR_2	Data Vocabulary	F_DGR_1
F_DGR_3	Metadata	F_DGR_1, F_DGR_2
F_DGR_4	Data Anonymization	F_DGR_1, F_DGR_2
F_DGR_5	Upload of New Data	F_DGR_1, F_DGR_2, F_DGR_4
F_DGR_6	Data Consistence and Completeness	F_DGR_1, F_DGR_2
F_DGR_7	Data Updates	F_DGR_1, F_DGR_2, F_DGR_5, F_DGR_6
F_DGR_8	Scheduled Backup of SILICOFCM Data	F_DGR_6
F_DGR_9	Notification about Data Usage	F_DGR_10
F_DGR_10	Data Access Logging and Auditing	NF_GUR_16
F_STUR_1	A list of available SILICOFCM tools	F_STUR_3, F_STUR_4
F_STUR_2	A list of available virtual patients/models and clinical/genetic data	F_STUR_22, F_STUR_24 F_VAUI_4, F_VAUI_5, F_VAUI_6
F_STUR_3	A list of available computational resources per tool	NF_GUR_5, F_STUR_7
F_STUR_4	UI which allows user to complete all needed tasks for running the simulation	F_STUR_1, F_STUR_2, F_STUR_3 F_VAUI_1-11
F_STUR_5	Conversion of SILICOFCM simulation/experiment setup to predefined workflow	F_STUR_6
F_STUR_6	Workflows should be defined in a standard workflow definition language	F_STUR_5, F_STUR_7, F_STUR_9, F_STUR_10, F_STUR_22
F_STUR_7	Validate the SILICOFCM tool workflow execution capability	F_STUR_6, F_STUR_13
F_STUR_8	The task flowcharts should be handled and recovered from task failure	F_STUR_6, F_STUR_7
F_STUR_9	Communication between remote-based tools	F_STUR_6, F_STUR_7, F_STUR_8
F_STUR_10	Communication between docker-based tools	F_STUR_6, F_STUR_7, F_STUR_8
F_STUR_11	Conversion of solvers' files	F_STUR_16
F_STUR_12	Incorporate convergence criteria per case	F_STUR_21, F_STUR_15
F_STUR_13	Parallel execution of simulations	F_STUR_14, F_STUR_15, F_STUR_16
F_STUR_14	Estimation of simulation duration	NF_GUR_4 F_STUR_13
F_STUR_15	Calculation of sarcomere mechanical response	F_STUR_2, F_STUR_13, F_STUR_5
F_STUR_16	Linking the MT with BT, ALT, PST	F_STUR_11, F_STUR_9, NF_GUR_8, F_STUR_5, F_STUR_22
F_STUR_17	Mesh validation	NF_GUR_6, NF_GUR_8, F_STUR_18

F_STUR_18	Imaging Data Processing	F_STUR_2, F_STUR_17, F_STUR_19
F_STUR_19	Set up the Boundary Conditions	F_STUR_5, F_STUR_21
F_STUR_20	Set up the Material Properties	F_STUR_5, F_STUR_21
F_STUR_21	Heart mechanics coupled with electric field and drug transport	F_STUR_2, F_STUR_5, F_STUR_12, F_STUR_17, F_STUR_18, F_STUR_19, F_STUR_20
F_STUR_22	Genetic Data Processing	F_STUR_2, F_STUR_6, F_STUR_7, F_STUR_10, F_STUR_16
F_STUR_23	Machine Learning Algorithms usage	F_STUR_2, F_STUR_22
F_STUR_24	Creation of virtual populations (cohort) of FCM patients	F_STUR_2, F_STUR_6, F_STUR_18, F_STUR_22
F_VAUI_1	Post-processing of results	F_VAUI_2, F_VAUI_3, F_VAUI_7
F_VAUI_2	Visualization of 2D- and 3D-case results in browser	F_VAUI_1, F_VAUI_3
F_VAUI_3	Visualization of evaluation reports	F_VAUI_1
F_VAUI_4	Browsing and filtering with an interactive visual access	F_VAUI_5, F_VAUI_6, F_VAUI_7, F_VAUI_8, F_VAUI_9, NF_GUR_10, F_GUR_11, F_GUR_12, NF_GUR_20
F_VAUI_5	Visualization of Virtual Patients Cohort	F_VAUI_4 NF_GUR_10, F_GUR_11, F_GUR_12, NF_GUR_20
F_VAUI_6	Visual and statistical comparison of sub-cohorts	F_VAUI_4, F_VAUI_5, F_VAUI_7 NF_GUR_10, F_GUR_11, F_GUR_12, NF_GUR_20
F_VAUI_7	Capability to Save/Load Working Progress	F_VAUI_1, F_VAUI_2, F_VAUI_3, F_VAUI_4, F_VAUI_5, F_VAUI_6, F_VAUI_8, F_VAUI_9
F_VAUI_8	Data Download	F_VAUI_4, F_VAUI_5 NF_GUR_10, F_GUR_11, F_GUR_12, NF_GUR_20
F_VAUI_9	Integration with other SILICOFCM services	F_VAUI_4 F_GUR_11, F_GUR_12

5.6 Use Cases and Usage Scenarios

The following section presents the Use Cases (UC) of SILICOFCM platform presented in UML diagrams (Figures 9-12) and the main usages scenarios (presented in Tables 65-84), related to main topics of the User Requirements Analysis (Sections 5.5.1-5.5.5). Through the Usage Scenarios (US) the stakeholders had the opportunity to describe how they envision the system in use.

5.6.1 General Use Cases and Usage Scenarios

General Use Cases

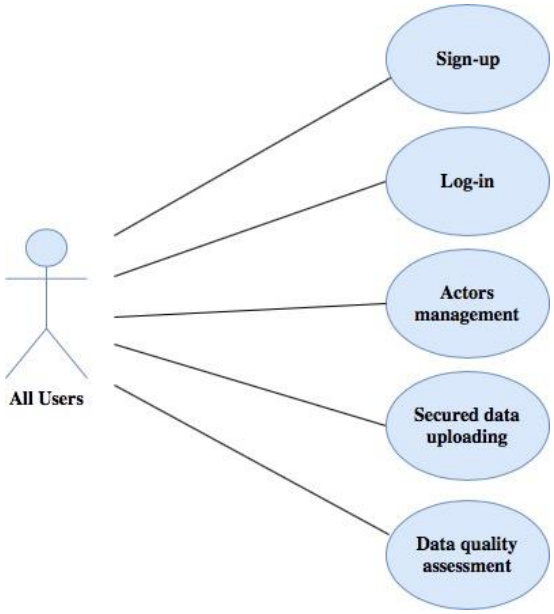


Figure 9. General Use Cases.

General Usage Scenarios

Table 65. User Sign-up (US_G_1).

ID	US_G_1
Title	User Sign-up
Purpose	User can sign-up to the SILICOFCM platform.
Primary Actor	All
Additional Actors	-
Description	The system, based on the user's profile and sign-up point, will demand from the user different types of information and different types of password level, in order to offer to the user different types of information and functionalities.
Pre-condition	None
Post-condition	The actor will be successfully signed-up.
Use Case Functionality	
Description	1. The system asks the user if he/she has already an account.

	2. If the user selects “No” then the system asks to select his/her role (Clinician, Researcher) and fill in his/her personal information, including his/her e-mail account. 3. A verification e-mail is sent to the user’s e-mail account. 4. Depending to the sign-up point of the user (Desktop PC, Laptop, Tablet) and his/her role, the system provides different types of security access levels. 5. When the user completes the Sign-up process, then he/she has the ability to access the corresponding information and functionalities provided to his/her role.
Alternatives	1a. If the user selects “Yes”, then s/he is redirected.
Dependencies	-
Non-Functional Requirements	
UI must provide interactive response.	

Table 66. User Log-in (US_G_2).

ID	US_G_2
Title	User Log-in
Purpose	The objective of this use case is to allow the user to log-in to the system using his/her credentials, enabling his/her access to different types of information and functionalities, according to his/her role.
Primary Actor	All
Additional Actors	-
Description	The user enters his/her credentials to the log-in prompt and the system introduces him/her to the provided functionalities.
Pre-condition	The user should already have an account in the SILICOFCM platform.
Post-condition	The user will successfully access the SILICOFCM platform based on access rights.
Use Case Functionality	
Description	1. The user enters the platform and views the Log-in screen of the system. 2. Depending to the log-in point of the user (Desktop PC, Laptop, Tablet) and his/her role, the system provides different types of security access levels (username + password, PIN, etc.). 3. The user fills in the requested authentication fields. 4. The system authenticates the user. 5. After successful authentication, the user enters the system’s functionalities provided to his/her role.
Alternatives	1. The user enters the platform and attempts to Log-in to the system. 2. The authentication fields that he/she enters are incorrect.

	3. The system identifies the error and through notification services, a pop-up message informs the user. 4. After the 3rd incorrect attempt, the *Help* button is activated and the user has the ability to request new credentials through e-mail.
Dependencies	US_G_1
Non-Functional Requirements	
The UI must provide interactive response.	

Table 67. Actors management (US_G_3).

ID	US_G_3
Title	Actors management
Purpose	To allow the administrator to manage the available roles of actors and their access to the various platform resources and functionalities.
Primary Actor	Administrator
Additional Actors	-
Description	The platform administrator views or makes changes to the available roles of actors (e.g. researcher, clinician, etc.) and their access rights to the various SILICOFCM data resources and analysis functionalities.
Pre-condition	The user has logged in to the platform and has the administrator privileges.
Post-condition	-
Use Case Functionality	
Description	1. The administrator opens the actors management control panel. 2. The list of available roles is presented. 3. The administrator selects a specific role and views its access rights to the various resources and functionalities. 4. The administrator performs changes in the access rights, e.g., gives access to a new dataset to the researcher role, or allows the clinicians to use a functionality previously available only to researchers. 5. The administrator stores the changes. 6. A notification e-mail is sent to those users having the altered roles, informing them about the changes.
Alternatives	-
Dependencies	US_G_2
Non-Functional Requirements	
The notification e-mails sent by the system to the users should be informative enough, so that the users understand the changes performed.	

Table 68. Secured data uploading (US_G_4).

ID	US_G_4
Title	Secured data uploading

Purpose	To allow the uploading of new data in the SILICOFCM platform through secure channels.
Primary Actor	Developers / End-Users
Additional Actors	-
Description	The SILICOFCM cloud platform provides a specific UI and service for uploading new data (genetic data; anonymized clinical data) through a secure channels to the platform in order to be stored and further processed.
Pre-condition	Appropriate format of new data; Enough storage capacities of the cloud-based platform; Provided secure protocol
Post-condition	-
Use Case Functionality	
Description	1. The Developers/End-Users log in to the platform 2. The Developers/End-Users proceed to the upload UI 3. The Developers/End-Users select the anonymized data, and upload it into the platform. 4. The SILICOFCM system opens a secure channel for the data transmission. 5. The data are securely transmitted to the SILICOFCM platform and ready for further use.
Alternatives	-
Dependencies	US_G_1, US_G_2
Non-Functional Requirements	
The UI must provide interactive response. There are no data leaks. Privacy is ensured. Any action is strictly bound to the data governance framework.	

Table 69. Data quality assessment (US_G_5).

ID	US_G_5
Title	Data quality assessment
Purpose	To allow the uploading of new data in the SILICOFCM platform through secure channels.
Primary Actor	Developers / End-Users
Additional Actors	-
Description	The SILICOFCM cloud platform provides a data quality control services for data curation in order to evaluate the quality of the uploaded data before any further processing. It uses a diagnostic tool which provides functionalities for incompatibilities check, outlier detection, and identification of duplicate terms.
Pre-condition	Provided diagnostic tool
Post-condition	-
Use Case Functionality	

Description	1. The Developers/ End-Users login to the platform. 2. The Developers/ End-Users proceed to the upload UI. 3. The Developers/ End-Users upload the anonymized data and proceed to data quality assessment. 4. Data quality report provides various metrics regarding the quality of the data. 5. After quality report, there is no duplicates, or other data incompatibilities existence.
Alternatives	-
Dependencies	US_G_1, US_G_2, US_G_4
Non-Functional Requirements	
The UI must provide interactive response.	

5.6.2 Data Governance

Use Cases

The Data Governance Use Cases are depicted in Figure 10. It should be noted that use cases from the general requirements are also applicable for data governance purposes, but duplication has been avoided.

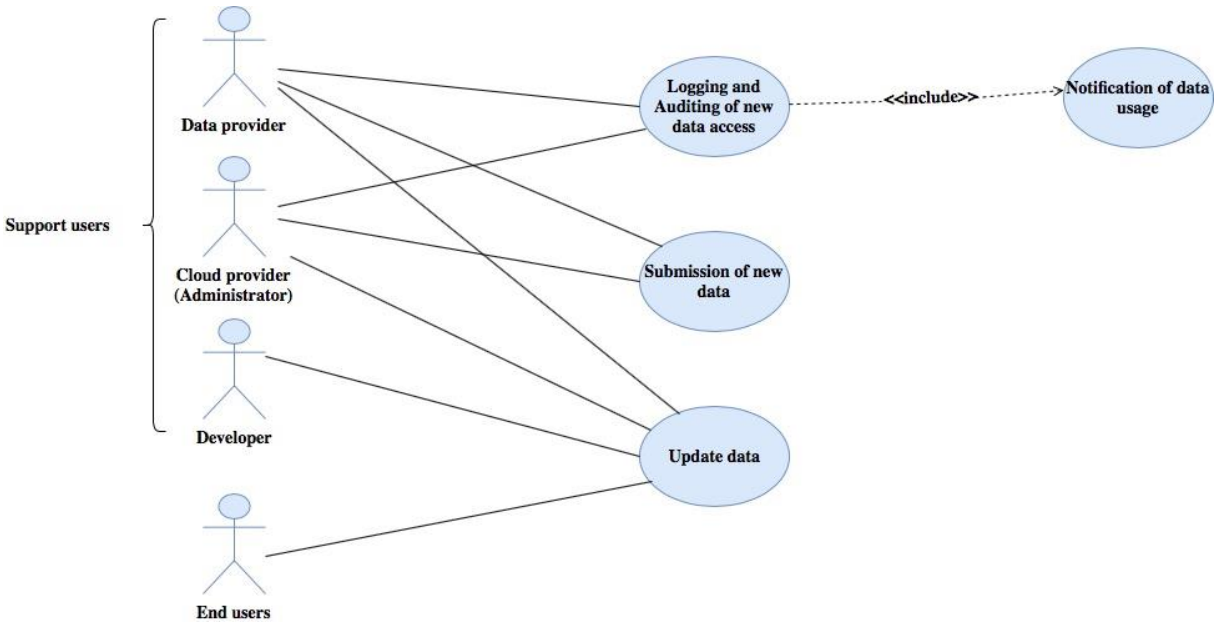


Figure 10. Use Cases for Data Governance.

Usage Scenarios

Table 70. Notification of Data Usage (US_DG_1).

ID	US_DG_1

Title	Notification of Data Usage
Purpose	To inform the data provider about the use of their datasets by the SILICOFCM platform services.
Primary Actor	Administrator / Data provider
Additional Actors	-
Description	The data provider receives notification when one of their datasets, part of the SILICOFCM integrated database. This notification is accompanied with relevant information, including who accessed it, through which service of the platform etc.
Pre-condition	The user is logged in the SILICOFCM platform and has the required access rights.
Post-condition	-
Use Case Functionality	
Description	1. The user receives a notification that their dataset within the SILICOFCM database has been accessed. 2. The user is presented with details, such as who accessed their datasets, through which service, etc.
Alternatives	Aggregated information can be provided on a periodic basis.
Dependencies	US_G_2
Non-Functional Requirements	
-	

Table 71. Submission of new data (US_DG_2).

ID	US_DG_2
Title	Submission of new data
Purpose	To upload and new anonymized data (clinical or/and genetic data), geometrical models, etc.
Primary Actor	Administrator / Data provider
Additional Actors	All
Description	The user, depending on his/her role, uploads the new anonymized data which will be stored within the SILICOFCM database and used for expanding and improving the existing database, as well as for simulations, comparison of results, etc. A safe way for uploading the data should be ensured due to their further store and processing.
Pre-condition	The user is logged in the SILICOFCM platform and has right to upload the data. There are available storage capacities The new data are anonymized and checked in term of quality.
Post-condition	-
Use Case Functionality	

Description	1. The user logs in the SILICOFCM platform and uploads the new anonymized data, depending on his/her role. 2. A safe protocol for uploading the data is performed. 3. The data are stored within the SILICOFCM database. 4. The data can be used improving the existing database, as well as for simulations, comparison of results, etc.
Alternatives	-
Dependencies	US_G_2
Non-Functional Requirements	
Expandable platform storage should be ensured.	

Table 72. Logging and Auditing of data access (US_DG_3).

ID	US_DG_3
Title	Logging and Auditing of data access
Purpose	To ensure that the access to the SILICOFCM platform and its datasets has been logged for administrative, security and accountability reasons.
Primary Actor	Administrator / Data provider
Additional Actors	-
Description	The access to the SILICOFCM services is be logged by recording information related to which user had access, through which service and at which time point.
Pre-condition	The user is logged in to the SILICOFCM platform and has the required access rights.
Post-condition	-
Use Case Functionality	
Description	1. The users view the log files for their own datasets. 2. The user is able to examine all the log files and actions along with additional information recorded for each one.
Alternatives	-
Dependencies	US_DG_1
Non-Functional Requirements	
Privacy is ensured.	

Table 73. Update data (US_DG_4).

ID	US_DG_4
Title	Update data
Purpose	To ensure improvement and refreshment of SILICOFCM database.
Primary Actor	End-users

Additional Actors	All
Description	Data in the SILICOFCM platform is regularly updated, either through the incorporation of new models, material characteristics, patients, virtual population etc., or the introduction of new data for existing models, material characteristics, patients, virtual population etc.
Pre-condition	The user is logged in to the SILICOFCM platform and has the required access rights.
Post-condition	-
Use Case Functionality	
Description	1. The user incorporates new models, material characteristics, patients, virtual population etc. 2. The user incorporates the new data for existing models, material characteristics, patients, virtual population etc.
Alternatives	-
Dependencies	US_G_2
Non-Functional Requirements	
-	

5.6.3 SILICOFCM Tools Usage

Use Cases

The basic Use Cases for SILICOFCM Tools are depicted in Figure 11. It should be noted that use cases from the general requirements and data governance are also applicable for SILICOFCM Tools usage purposes, but duplication has been avoided.

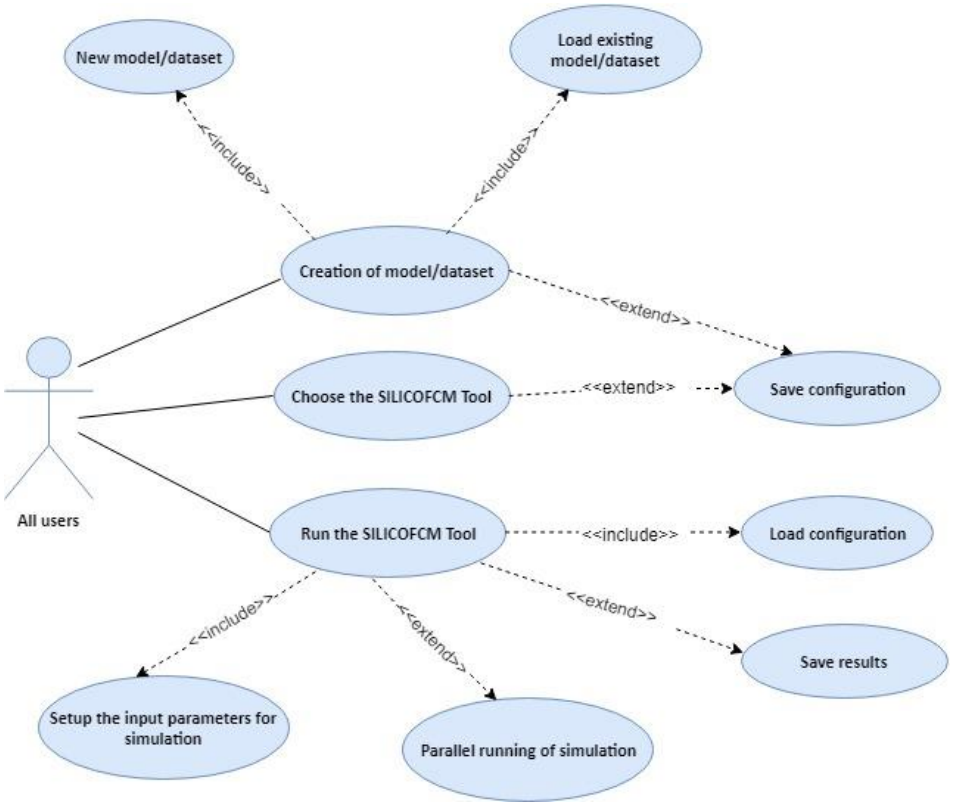


Figure 11. Use Cases for SILICOFCM Tools.

Usage Scenarios

Table 74. Choose the SILICOFCM Tool (US_TU_1).

ID	US_TU_1
Title	Choose the SILICOFCM Tool
Purpose	To choose the SILICOFCM Tool depending on simulation and research purposes.
Primary Actor	All
Additional Actors	-
Description	The user selects the SILICOFCM Tool depending on simulation and research purposes.
Pre-condition	-
Post-condition	-
Use Case Functionality	
Description	1. User selects the SILICOFCM Tool from drop-down menu, in accordance with type of simulation and research purposes.
Alternatives	-
Dependencies	US_G_2
Non-Functional Requirements	
The user should be able to save the configuration for later use.	

Table 75. Creation of model/dataset (US_TU_2).

ID	US_TU_2
Title	Creation of model/dataset
Purpose	To create the model or dataset needed for execution of appropriate simulations.
Primary Actor	All
Additional Actors	-
Description	The user can define the model or dataset needed for execution of appropriate simulations. It can be performed by selecting the existing virtual models or datasets (clinical/genetic data, etc) within the SILICOFCM database, or by creating the new ones. In both cases, the model/dataset can be used for comparison of obtained results and further simulations.
Pre-condition	-
Post-condition	-
Use Case Functionality	
Description	1. User selects the existing virtual models or datasets (clinical/genetic data, etc) from SILICOFCM database. 2. User creates the new model/dataset, depending on his/her role within the SILICOFCM ecosystem.
Alternatives	-
Dependencies	US_G_2
Non-Functional Requirements	
The user should be able to save the configuration for later use.	

Table 76. Setup the input parameters for simulation (US_TU_3).

ID	US_TU_3
Title	Setup the input parameters for simulation
Purpose	To prescribe different sets of input parameters in order to execute the calculations offered by SILICOFCM services.
Primary Actor	All
Additional Actors	-
Description	Depending on employed simulation, there are different sets of input parameters such as: prescribed boundary conditions, material properties, processed imaging data, genetic data, drugs concentration, etc. User should complete all needed tasks in order to successfully perform the desired simulation.
Pre-condition	
Post-condition	-
Use Case Functionality	

Description	1. User selects the SILICOFCM Tool. 2. User notes all input parameters needed for running the Tool. 3. User prescribes input parameters (prescribed boundary conditions, material properties, processed imaging data, genetic data, drugs concentration, etc.).
Alternatives	-
Dependencies	US_G_2, US_TU_4
Non-Functional Requirements	
The user should be able to save the configuration for later use.	

Table 77. Run the SILICOFCM Tool (US_TU_4).

ID	US_TU_4
Title	Run the SILICOFCM Tool
Purpose	To run a specific SILICOFCM Tool using a specific virtual model/database and input parameters, as those configured previously.
Primary Actor	All
Additional Actors	-
Description	The SILICOFCM cloud platform will enable a workflows engines and modules for execution of remote-based (MUSICO, the PAK solver, and the ALYA solver) and docker-based tools (Bioinformatics Tool, the Data analytics Tool, the Virtual population tool, the Multiple Criteria Decision Making tool). If needed, parallelization of computational algorithms due to large models and time demanding simulations, is performed.
Pre-condition	A configuration is previously stored.
Post-condition	-
Use Case Functionality	
Description	1. The user selects a stored configuration and applies the “run” option
Alternatives	-
Dependencies	US_G_2, US_TU_1, US_TU_2
Non-Functional Requirements	
-	

Table 78. Save results (US_TU_5).

ID	US_TU_5
Title	Save results
Purpose	To post-process the results, visualise, evaluate and store for later use.
Primary Actor	All

Additional Actors	-
Description	The user can save and restore the configuration of custom-defined simulation analysis, or virtual sub-cohorts. Also, visualization of 2D- and 3D-case results in browser, or saving the evaluation reports is possible.
Pre-condition	-
Post-condition	-
Use Case Functionality	
Description	1. User applies the “save” option.
Alternatives	-
Dependencies	US_TU_4
Non-Functional Requirements	
-	

5.6.4 Visual Analytics and User Interfaces

Use Cases

The basic Use Cases for Visual Analytics and User Interfaces are depicted in Figure 12. It should be noted that use cases from the general requirements, data governance and SILICOFCM Tools usage are also applicable for Visual Analytics and User Interfaces purposes, but duplication has been avoided.

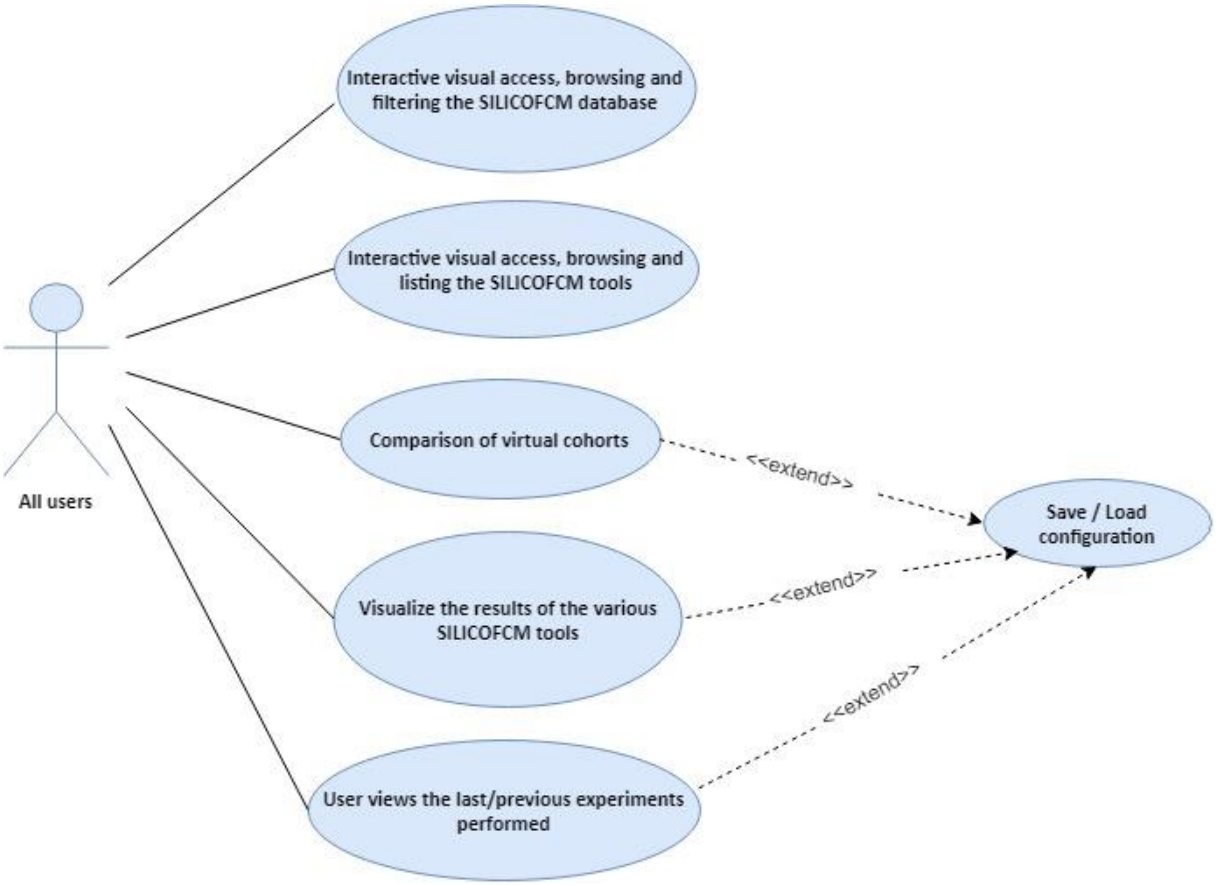


Figure 12. Use Cases for Visual Analytics and User Interfaces.

Usage Scenarios

Table 79. Interactive visual access, browsing and filtering the SILICOFCM database (US_UI_1).

ID	US_UI_1
Title	Interactive visual access, browsing and filtering the SILICOFCM database
Purpose	The use of visual interface enables the actor to get an interactive visual access, to browse and filter SILICOFCM database in order to get a deeper insight into the available dataset.
Primary Actor	All
Additional Actors	-
Description	The SILICOFCM platform provides a possibility for actor to get a deeper insight by using interactive visual access, browsing and filtering the available data.
Pre-condition	The user has been successfully authenticated.

Post-condition	-
Use Case Functionality	
Description	1. The actor gets a visual overview of the whole SILICOFCM database. 2. The actor browses or adds, modifies, or removes a filter. 3. Based on the browsing/filtering the system updates the visual overview. 4. The sequence continues with step 2.
Alternatives	-
Dependencies	US_G_2
Non-Functional Requirements	
-	

Table 80. Interactive visual access, browsing and listing the SILICOFCM tools (US_UI_2).

ID	**US_UI_2**
Title	Interactive visual access, browsing and listing the SILICOFCM tools
Purpose	The use of visual interface enables the actor to get an interactive visual access, to browse and filter SILICOFCM database in order to get familiarized with available tools and their possibilities.
Primary Actor	All
Additional Actors	-
Description	The SILICOFCM platform consists of several tools. Interactive visual access provides a possibility for actor to get familiarized with these tools by browsing and filtering the available tools.
Pre-condition	The user has been successfully authenticated.
Post-condition	-
Use Case Functionality	
Description	1. The system presents a visual overview of the available SILICOFCM tools. 2. The actor can browse or add, modify or remove a filter constraint for SILICOFCM tools. 3. The system updates the visual overview, based on the previously defined filters. 4. The sequence continues with step 2.
Alternatives:	-
Dependencies:	US_G_2
Non-Functional Requirements	
-	

Table 81. Comparison of virtual cohorts (US_UI_3).

ID	US_UI_3
Title	Comparison of virtual cohorts
Purpose	To ensure visual and statistical comparison of sub-cohorts during their re-use in pre- and post-competitive testing of drugs using data mining approach.
Primary Actor	All
Additional Actors	-
Description	The user has a visual and statistical overview on the current cohort's data, and how it differs from the large integrated cohort (or a custom-defined one). Potentially, common statistical tests can be performed in order to compare sub-cohorts. Results can be visualized and exported as images (e.g. for publications).
Pre-condition	The user has been successfully authenticated.
Post-condition	-
Use Case Functionality	
Description	1. The user selects two previously defined sub-cohorts 2. The user selects a statistical method to apply 3. The results can be visualized and exported as images
Alternatives	-
Dependencies	US_G_2
Non-Functional Requirements	
The user should be able to load/save the configuration.	

Table 82. Visualize the results of the various SILICOFCM tools (US_UI_4).

ID	US_UI_4
Title	Visualize the results of the various SILICOFCM tools
Purpose	To navigate and select a 3D/2D view or evaluation report of a specific simulation result.
Primary Actor	All
Additional Actors	-
Description	The user has ability from the web browser to navigate and select a 3D/2D view or evaluation report of a specific simulation result. Then, a number of result visualizations (based on simulation configuration) will be available for the user to select.
Pre-condition	The user has been successfully authenticated.
Post-condition	-
Use Case Functionality	

Description	1. The user chooses the tool system presents a visual overview of the available SILICOFCM tools. 2. The actor can browse or add, modify or remove a filter constraint for SILICOFCM tools. 3. The system updates the visual overview, based on the previously defined filters. 4. The sequence continues with step 1.
Alternatives:	-
Dependencies:	US_G_2
Non-Functional Requirements	
The user should be able to load/save the configuration.	

Table 83. User views the last/previous experiments performed (US_UI_5).

ID	**US_UI_5**
Title	User views the last/previous experiments performed
Purpose	To gain insight into last/previous experiments performed.
Primary Actor	All
Additional Actors	-
Description	User in the SILICOFCM home page can see a widget with user's last experiments and their status. User can select a specific experiment and navigate to the Experiment Details page.
Pre-condition	A configuration is previously stored.
Post-condition	-
Use Case Functionality	
Description	1. User uses a widget for selection of a specific experiment and navigate to the Experiment Details page.
Alternatives	-
Dependencies	US_UI_1
Non-Functional Requirements	
The user should be able to load/save the configuration.	

Table 84. Save / Load configuration (US_UI_6).

ID	**US_UI_6**
Title	Save / Load configuration
Purpose	To save current or restore appropriate configuration. Also, user can later restore that configuration over long period of time.
Primary Actor	All

Additional Actors	-
Description	The SILICOFCM platform provides a possibility for actor to save the work current progress or to restore that configuration over long period of time.
Pre-condition	The user has been successfully authenticated.
Post-condition	-
Use Case Functionality	
Description	1. The user selects to save (or load) work configuration 2. The system updates the state accordingly
Alternatives	-
Dependencies	US_G_2
Non-Functional Requirements	
-	

5.6.5 Overview of SILICOFCM Usage Scenarios

A summary of all basic Usage Scenarios and associated dependencies is given in the following table:

Table 85. Overview of Usage Scenarios and associated dependencies.

ID	Usage Scenarios	Dependencies
US_G_1	User Sign-up	-
US_G_2	Log-in	US_G_1
US_G_3	Actors management	US_G_2
US_G_4	Secured data uploading	US_G_1, US_G_2
US_G_5	Data quality assessment	US_G_1, US_G_2, US_G_4
US_DG_1	Notification of Data Usage	US_G_2
US_DG_2	Submission of new data	US_G_2
US_DG_3	Logging and Auditing of data access	US_DG_1
US_DG_4	Update data	US_G_2
US_TU_1	Choose the SILICOFCM Tool	US_G_2
US_TU_2	Creation of model/dataset	US_G_2
US_TU_3	Setup the input parameters for simulation	US_G_2, US_TU_4
US_TU_4	Run the SILICOFCM Tool	US_G_2, US_TU_1, US_TU_2
US_TU_5	Save results	US_TU_4
US_UI_1	Interactive visual access, browsing and filtering the SILICOFCM database	US_G_2
US_UI_2	Interactive visual access, browsing and listing the SILICOFCM tools	US_G_2
US_UI_3	Comparison of virtual cohorts	US_G_2
US_UI_4	Visualize the results of the various SILICOFCM tools	US_G_2
US_UI_5	User views the last/previous experiments performed	US_G_2
US_UI_6	Save / Load configuration	US_G_2

5.7 Regulations

The General Data Protection Regulation (EU) 2016/679 (GDPR)[11] regulates the protection of the persons in relation to the processing of personal data.

The personal data of end users stored in the SILICOFCM cloud platform are user names and emails. The virtual population is fully anonymized and all organizations providing retrospective and prospective data are obliged to conform to GDPR.

The specific deliverable and the specifications of the user requirements (functional/non-functional) are related only to the main measures that any cloud platform should consider in terms of security and privacy measures imposed by GPDR.

5.8 Recommendations in regulatory processes

The current state of *in silico* clinical trials (ISCT) methodology and the related emerging regulatory framework, the description of what is available in terms of validated patient-specific modelling technologies and development directions for full-scale adoption of patient-specific modelling and simulation in the regulatory evaluation of biomedical products was recently reviewed by Pappalardo at al. [51] with contribution of EMA and FDA members Dr Flora Musuamba Tshinanu and Dr Tina Morrison. Also, the three phases of commonly classified four phases of clinical trials involving new drugs were described. In addition, the place of Computational Modelling and *in silico* trials in research, medical devices development and regulatory submission in the FDA was overviewed by Tina Morrison et al. [52]. Recently published paper by Marco Viceconti at al. [53] gave the deeper explanation of current credibility of *In Silico* Trial Technologies and proposed a theoretical framing for assessing the credibility of a predictive models for In Silico Trials, which accounts for the epistemic specificity of this research field and is general enough to be used for different type of models. This paper covered aspects and definitions of model's validation and verification, as well as the regulatory processes.

CompBioMed Conference

The SILICOFCM coordinator visited international meetings and conferences where he had the opportunity to talk with the leading experts and professionals from EMA and FDA. It was the initial step for further collaboration with EMA and FDA in the approval processes, exchanging the experience and raising awareness of the SILICOFCM project. Prof. Filipovic participated at the CompBioMed Conference (London, UK, 25-27 September, 2019) and presented the project at the *Symposium Regulatory Science and in silico Trials*[12]. The goal of this special symposium was to bring together key stakeholders in the current development of *In-Silico Trials* (ISTs), to highlight state-of-the-art developments, to discuss the challenges that ISTs are facing, and to contribute to next steps in successfully applying IST in actual (pre-)clinical settings. The invited speakers of this symposium were Dr Tina Morrison, the Chair of FDA's Agency-wide Modeling and Simulation working group and Regulatory Advisor of Computational Modelling for FDA's Office of Device Evaluation, and Dr Flora Musuamba, vice-chair of the EMA Modelling and Simulation Working Party (EMA MSWP) and an alternate member of the EMA Scientific Advice Working Party (SAWP), who shared their experiences and overview of the current *In silico* trials and drug approval process and challenges that ISTs are facing. The main summary is given below.

[11] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32016R0679
[12] https://www.compbiomed-conference.org/symposia/regulatory-science-and-in-silico-clinical-trials/

Marketing approvals of (new) medical products (and combinations) generates large interests of both patients in need of new medicinal therapies and the sponsors (big pharmaceutical industry, SMEs, and academia). Before a new medical product can be used on humans in a country, it must be approved for that use by the relative Regulatory Authority of that country. In USA, this will be the remit of the FDA drugs and medical devices whereas in the European Union pharmaceuticals are approved by the EMA mostly and by national competent authorities to a lesser extent. The approval of medical devices is delegated to the member states, through selected notified bodies. Consequently, regulators have to find the appropriate balance between the need to ensure that decision-making is based on scientifically valid data and the need for access to the new medicines is considered. To obtain approval for a (new) medicinal product the sponsor must submit to the regulator evidences of a favourable risk/benefit balance based on available efficacy and safety data. Historically, the demonstration of drug's safety and efficacy was mostly based on evidences obtained experimentally, either *in vitro* (e.g. testing the efficacy of a new chemotherapy in a tumour cells culture, or the fatigue strength of a hip replacement in material testing machine), or *in vivo* on animals and on human volunteers or patients in controlled clinical trials and statistical analyse thereof; *in silico* methods were initially limitedly used.

However, a concerning issue has been acknowledged by almost all the stakeholders that, over the last decades, there has been a trend of rising research and development (R&D) expenditures, but no increase in the number of newly developed medicines submitted to regulatory agencies. One of the reasons put forward by pharmaceutical companies for the decrease in the efficiency of drug development and approval is that regulators are overly cautious, resulting in rising R&D expenditures and long drug development timelines. At the EMA, it has been acknowledged over the years that efficient drug approval process would benefit for early and frequent interactions with drugs' sponsors through establishment of formal procedures and offices for this purpose. To date, these interactions include Innovation Task Force (ITF) briefing meetings, scientific or qualification advice, qualification opinion and marketing authorization applications (including presubmission and explanatory meetings) as summarized below in Figure 13 [54]. These steps are part of the innovation in medicines, defined by EMA[13].

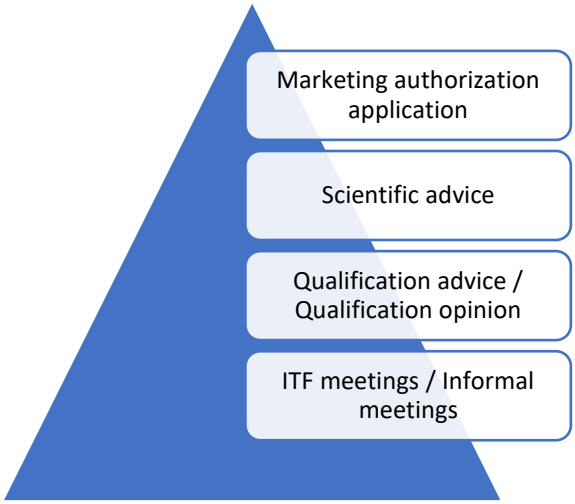


Figure 13. Interactions with drugs' sponsors for efficient drug approval process [54].

It is also acknowledged that clinical trials become increasingly complex, large, and expensive. The traditional approaches of drug development based on large randomized controlled trials faces big

[13] https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines

issues to be implemented in situations, despite a high unmet medical need, namely orphan indications, drugs for very young children and the elderly, and slowly evolving diseases, etc. Biomarkers, sophisticated imaging methods, patient-reported outcomes, combined with novel and innovative methodologies such as modelling and simulation (M&S) and *in silico* approaches play an increasingly important role in drug research and development and have the potential to deliver new medicines to the right patient faster and at a lower overall cost than today, also by ensuring that resources reserved for the drug-development programs are diverted. M&S and *in silico* approaches are now routinely used by pharmaceutical companies and drug sponsors for example for key decision making on the most promising drug development programs in their pipelines and for moving to key steps of their projects and to characterize some important features of their different studies. M&S are now also increasingly used to identify the most sensitive subgroups of patients for both drug efficacy and safety, thanks to systems medicines and systems pharmacology models. The above listed applications are contributing to faster access to better quality medicines for patients. Regulators therefore need not only to provide guidance, advices and recommendations on the acceptability of these methods for regulatory submissions but also to adequately use them in their decision-making process. Moreover, the fact that good standards for evaluation of some models in some particular context of use are currently lacking is also one of the current big challenges. Recently, EMA had a Multi-stakeholder workshop on draft 'Regulatory Science to 2025' strategy[14], where one session was dedicated to Clinical trials, digital therapeutics and modelling & simulation[15], where it was outlined that *In Silico* Trials should be at the core of the EMA strategy.

Webinar: Can Digital Evidence Replace Clinical Evidence? - A "Straight from the Source"

The Webinar Can Digital Evidence Replace Clinical Evidence? - A "Straight from the Source" was held 18th September 2019, organised by AXENDIA (analyst and advisory firm) and supported by FDA, where speakers were Tina Morrison (FDA) and Daniel Matlis (AXENDIA)[16]. It was discussed about FDA's perspective on:

- Shifting from traditional evidence sources to digital evidence;
- How to create virtual patients with digital evidence to replace clinical evidence;
- Examples of digital evidence in Pharma and Medical Devices used at FDA to initiate and augment clinical studies;
- Creating an in silico clinical trial playbook;
- Why data in PDF's are not sufficient.

The definition of disruptive technologies and *in silico* methods (i.e. Modeling & Simulation (M&S)) as well as its concept were presented, and followed with advices for Good Simulation Practices. In addition, the Total Product LifeCycle (TPLC approach) – closed loop approach for development and management for medical products was presented, asking the question can such a TPLC reduce the risk and improve quality and outcomes of medical products, and giving the answer that community is not there yet. In addition, the ISCT fits in TPLC is presented (Figure 14). Examples of how ISCT are used in health technology ecosystem (pharmaceutical, biology, medical devices, clinical diagnostics) were given also. The main conclusion was related to the validation and verification of medical devices

[14]https://www.ema.europa.eu/en/events/multi-stakeholder-workshop-draft-regulatory-science-2025-strategy-stakeholders-human-medicines#documents-section
[15]https://www.ema.europa.eu/en/documents/presentation/presentation-ema-regulatory-science-2025-optimise-capabilities-modelling-simulation-extrapolation_en.pdf
[16]http://axendia.com/blog/2019/09/05/can-digital-evidence-replace-clinical-evidence/

outlining that the review process will consist of access to the simulations, examining of performances, and experience of using it, not only looking into PDFs.

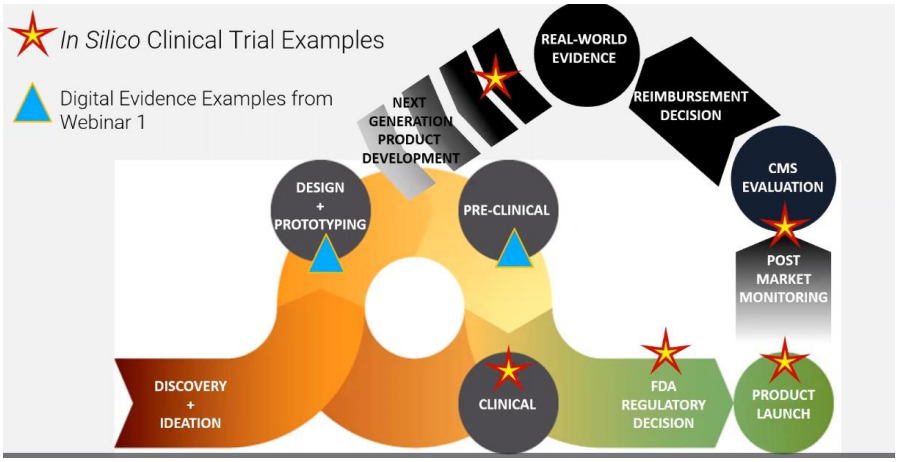


Figure 14. How ISCT fits in TPLC.

Standards

All parties from the regulatory bodies agree that before a new medical product can be sold in a country, evidence must be provided to the regulatory agency of that country supporting the claim that such new product, if used as expected and under properly controlled conditions, is *safe* (when it does not worsen the health of the recipient) and *effective* (when the product does improve the recipient's health). For the international commercialisation, wide recognised standards must be complied.

Following the recommendations of EMA's and FDA's representatives, the SILICOFCM project currently has two standards under consideration:

- IEC 62304:2006 Medical device software - Software life cycle processes[17]. A harmonised standard for software design in medical products adopted by the European Union and the United States[18];
- (American Society of Mechanical Engineers) ASME V&V 40-2018: Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices[19].

The content of standards will be elaborated in detail within the WP8.

[17] https://www.iso.org/standard/38421.html
[18] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/detail.cfm?standard__identification_no=38830
[19] https://www.asme.org/codes-standards/find-codes-standards/v-v-40-assessing-credibility-computational-modeling-verification-validation-application-medical-devices

6. Deviation from the work plan

According to the recommendations of the EC at the First review meeting in Luxembourg (6th June 2019), the D1.1 has been updated after received feedback from pharmaceutical companies and regulatory bodies.

7. Conclusions

D1.1 “Requirements Analysis” corresponds to the work performed within Task 1.1 “State-of-the-Art and Requirements Analysis” (M1-M6) of SILICOFCM project. Analysis of the state of-the-art technologies that SILICOFCM platform relies on has been performed, as well as the current trends in FCM monitoring. Version 2 of the D1.1 (submitted on M20) differs from the version 1 of the D1.1 (submitted on M7) in terms of newly added Sections 5.3.5-5.3.6 and Section 5.8, giving a more complete feedback from all three main SILICOFCM end-users, as well as recommendations in regulatory processes gathered from the international regulatory bodies.

This document provides the initial set of user requirements. Requirements were collected in terms of functionalities, usability, performance, availability and reliability, security and privacy, platform maintenance and expandability, legal and ethical issues. Obtaining the user requirements is the first step which is needed for SILICOFCM platform’s architecture specification. Those requirements are translated into non-functional and functional specifications of the SILICOFCM platform in D1.3 “SILICOFCM Reference Architecture”. These requirements will evolve with understanding of the SILICOFCM platform, and also will lead to improved capabilities of the platform. Based on the user requirements, a range of basic use cases and usage scenarios are described. This approach provides the opportunity for the stakeholders to describe how they conceive the use of the platform. The outcome of this process is summarised in the Section 5.5.5 and Section 5.6.5, where the number of requirements and usage scenarios are given.

This document serves as a basis for the creation and development of the SILICOFCM platform and together with the Task 1.2 „SILICOFCM Specification” contributes to the SILICOFCM architecture design which is included within Task 1.3 „SILICOFCM Reference Architecture”.

8. References

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