SILICOFCM

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Executive summary

Deliverable Scope

The scope of this documented titled in the project Description of the Action (DoA) as "D1.3 - SILICOFCM Reference Architecture'' is to define, design and present the proposed reference architecture of the in-silico clinical trial SILICOFCM cloud platform. The document presents the elicitation of User Requirements collected and analysed in D1.1 into functional and non-functional specifications, and the provided interfaces. The requirements were gathered through two type of questionnaires targeting different end user of the platform and interviews to experts. Moreover, it presents the multilayer structure of the platform, the integrated modules, the incorporated engines and services and the information flows between them. SILICOFCM proposed reference architecture is designed in such way to provide ease of use to the end user, automation through the simulation and tasks workflows and reliability and performance. The reference architecture is following the ISO 42010 standard.

SILICOFCM overall architecture

The SILICOFCM architecture integrates different functional modules, their corresponding engines and the advance computational and simulation project developed tools. More specifically the basic cloud modules are: User Access Management Module; Data Management Module; Workflow Manager Module; Visual Analytics Module. Moreover, the specific service engines are: Data quality control engine; Workflow engine; Docker engine; Visual analytics engine; REST API manager. The core simulation and in-silico modelling power of the SILICOFCM platform resides on the tools: MUSICO Tool; ALYA Solver Tool; PAK Solver Tool; Data Analytics Tool; Bioinformatics Tool; Virtual Population Tool and the Multiple Criteria Decision Making Tool.

SILICOFCM platform actors

The section 2 of the current document presents and analyse the platform stakeholders of SILICOFCM cloud platform which include: the Data providers; the Cloud providers (administrator); the inner and outer developers; and the platform end-users. The latter are analysed and their role described in detail in deliverable D1.1. Moreover, in the end-user group the following users are included: Pharmaceutical companies; Researchers and Cardiologists.

Cloud platform framework

The SILICOFCM framework will be realized in the form of a hierarchical multilayer schema which consists of five layers. At the bottom lies the hardware layer where the cloud resources along with any additional resources. Right above the hardware layer lies the security layer. The third layer includes the workflow manager with its core engines. Each one of these engines is directly involved with the SILICOFCM tools and modules that lie on the fourth layer, i.e., the back-end layer. Moreover, in section 6.2 is described in details with visual representation the distribution of the cloud computing services to the SILICOFCM users

Concluding the current document complies as a reference for the WP7 of the project where the cloud platform will be developed, deployed and fine-tuned in order to be fully operational and be characterized as a stable, high end and free of bugs in-silico platform. The final architecture of the SILICOFCM will be documented in details with the end of the corresponding tasks and WP.

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List of Abbreviations

Abbreviation	Explanation
3MDP	Multi-Modal Medical Data Analysis Platform
ADME	Absorption, Distribution, Metabolism and Excretion simulator
API	Application Programming Interface
AST	ALYA Solver Tool
BT	Bioinformatics Tool
DAT	Data Analytics Tool
DAT	Data Analytics Tool
DMM	Data Management Module
EMMA	Ex vivo Mathematical Myeloma Advisor
HTTP	Hypertext Transfer Protocol
IaaS	Infrastructure as a Service
ISCT	*In Silico* clinical trials
MCDMT	Multiple Criteria Decision Making Tool
MT	MUSICO Tool
PaaS	Provider as a Service
PBPK	Physiologically Based Pharmacokinetic
PK	PharmacoKinetic modelling
PST	PAK Solver Tool
REST	Representational State Transfer
SaaS	Software as a Service
SLA	Software License Agreement
SSL	Secure Sockets Layer
TCGA	The Cancer Genome Atlas
TLS	Transport Layer Security
UAMM	User Access Management Module
UI	User Interface
VAM	Visual Analytics Module
VM	Virtual Machine
WMM	Workflow Manager Module
UR	User Requirements

1. Introduction

1.1 Purpose and scope of the deliverable

This documents corresponds to "D1.3 - SILICOFCM Reference Architecture'', the third deliverable of "WP1 - Requirements & Conceptual Architecture" (M1-M6). This deliverable summarises and presents the work, the outcomes and results of "Task 1.3 - SILICOFCM Reference Architecture" that started on M1 and ended on M6. The objective of this task was to define, design and present the proposed SILICOFCM Reference Architecture following the ISO 42010 and based on the analysis and evaluation of the existing enabling and underlying technologies, the tools and modules of SILICOFCM and the functional and non-functional specifications.

1.2 Deliverable structure

The structure of the deliverable is as follows:

Section 1 presents the purpose and the objective of this deliverable and the relation to the work performed in relation to the DoA.

Section 2 presents an overview of the platform users and user requirements, several use cases that have been created in order to serve as a basis for the SILICOFCM architecture definition and development, an overall information flow of the SILICOFCM architecture as well as detailed information flows of the different users with SILICOFCM modules.

Section 3 presents the conceptual architecture and the detailed SILICOFCM architecture, including the different modules (User Access Management Module, Data Management Module, Workflow Manager Module, Visual Analytics Module), the SILICOFCM engines (Data quality control engine, Workflow engine, Docker engine, Visual analytics engine, REST API manager), the state of the art in *in silico* clinical trials similar platforms and the methodological approach that was followed.

Section 4 presents in detail the SILICOFCM modules. More specifically, for each module the following information is provided: (i) overall description and objective, (ii) actors that will have access to the specific module, (iii) input and output info, (iv) potential dependencies and with the rest SILICOFCM modules.

Section 5 presents the SILICOFCM tools. More specifically, for each tool, the following information is provided: (i) description and objective, (ii) actors involved, (iii) input and output data, (iv) dependencies and interactions with rest SILICOFCM tools, and (v) related workflows.

Section 6 presents a conceptual hierarchical multilayer approach of the SILICOFCM framework, the distribution of the cloud computing services to the SILICOFCM users, the functional and non-functional specifications of the system, hardware specifications and User Interface analysis and first estimation of the UI mockups and UML sequence diagram for the services of the SILICOFCM platform.

Section 7, Section 8 and Section 9 present the deviations from the workplan, the conclusions and the references of the current document.

Section 10 is an Appendix including the models used for architecture description and Section 11 the detailed listing of D1.1 user requirements.

1.3 Relation with the SILICOFCM DoA

The following table presents the DoA description of Task 1.3 and how this deliverable addresses the description of the Task.

DoA Task Description	Addressed By D1.3
Based on the comparative analysis of the existing, enabling and underlying technologies on the analysis of algorithms and data mining strategies, the SILICOFCM consortium will define, design and document an innovative, generic approach and reference architecture that will facilitate the deployment of a system for effectiveness in critically ill patients. The SILICOFCM Reference Architecture will be based on open and widely adopted standards.	A detailed analysis of the state of the art in general technologies related to SILICOFCM approach and *in silico* clinical trials similar platforms has been performed (Section 3.4). The design of the overall conceptual SILICOFCM architecture (Section 3.1) relies on the definition and analysis of the users (Section 2.1), their requirements (Section 2.2), the modules (Section 4), tools (Section 5), their dependencies and communications (Section 3.2) as well as the functional and non-functional specifications (Section 6.3, 6.4) accounting on open and widely adopted standards (Section 3.5), enabling the development and implementation of an effective Cloud-based system (Section 6) for an in silico clinical trial platform for Familial cardiomyopathies.

2. Overview of platform Users and User Requirements

2.1 SILICOFCM platform stakeholders

The identified actors for the SILICOFCM cloud platform are the:

- Data providers
- Cloud providers (administrator)
- Typical end-users
  - Cardiologists,
  - Researchers
  - Pharmaceutical companies.
- Inner and outer developers

2.2 SILICOFCM platform User Requirements

Table 1 depicts the user requirements for the SILICOFCM platform collected and analysed during T1.1 and presented in D1.1. In this document the extraction of functional and non-functional specifications is conducted.

Table 1 User Requirements as defined in D1.1

ID	D1.1 coding	Title of User Requirements	Priority (according to D1.1)
URNF1	NF_GUR_1	Ease of use	Mandatory
URNF2	NF_GUR_2	Ease of learning	Mandatory
URNF3	NF_GUR_3	Platform time response	Desirable
URNF4	NF_GUR_4	Simulation time acceptance	Desirable
URNF5	NF_GUR_5	Expandable Platform Storage	Mandatory
URNF6	NF_GUR_6	Reliable simulation results	Desirable
URNF7	NF_GUR_7	Available SILCOFCM platform service	Desirable
URNF8	NF_GUR_8	SILICOFCM model validation	Desirable
URNF9	NF_GUR_9	Notification messages	Mandatory
URNF10	NF_GUR_10	Data privacy	Mandatory
URNF11	NF_GUR_11	Different roles	Mandatory
URNF12	NF_GUR_12	Controlled Data access	Mandatory
URNF13	NF_GUR_13	OAUTH and API services for secure web user authentication and authorization	Mandatory
URNF14	NF_GUR_14	Https Communications	Mandatory
URNF15	NF_GUR_15	Big data management	Mandatory
URNF16	NF_GUR_16	System administration	Mandatory
URNF17	NF_GUR_17	IPR Protection	Mandatory

ID	D1.1 coding	Title of User Requirements	Priority (according to D1.1)
URNF18	NF_GUR_18	Capability for new services inclusion	Optional
URNF19	NF_GUR_19	Capability for new computational resources	Optional
URNF20	NF_GUR_20	Compliance of the SILICOFCM content and the scope with EU directives	Mandatory
URF1	F_DGR_1	Input/output Data Format	Mandatory
URF2	F_DGR_2	Data Vocabulary	Mandatory
URF3	F_DGR_3	Metadata	Mandatory
URF4	F_DGR_4	Data Anonymization	Mandatory
URF5	F_DGR_5	Upload of New Data	Mandatory
URF6	F_DGR_6	Data Consistence and Completeness	Mandatory
URF7	F_DGR_7	Data Updates	Mandatory
URF8	F_DGR_8	Scheduled Backup od SILICOFCM Data	Mandatory
URF9	F_DGR_9	Notification about Data Usage	Mandatory
URF10	F_DGR_10	Data Access Logging and Auditing	Mandatory
URF11	F_STUR_1	A list of available SILICOFCM tools	Mandatory
URF12	F_STUR_2	A list of available virtual patients/models and clinical/genetic data	Mandatory
URF13	F_STUR_3	A list of available computational resources per tool	Optional
URF14	F_STUR_4	UI which allows user to complete all needed tasks for running the simulation	Mandatory
URF15	F_STUR_5	Conversion of SILICOFCM simulation/experiment setup to a workflow	Mandatory
URF16	F_STUR_6	Workflows should be defined in a standard workflow definition language	Desirable
URF17	F_STUR_7	Validate the SILICOFCM tool workflow execution capability	Desirable
URF18	F_STUR_8	The task flowcharts should be handled and recovered from task failure	Desirable
URF19	F_STUR_9	Communication between remote-based tools	Mandatory
URF20	F_STUR_10	Communication between docker-based tools	Mandatory
URF21	F_STUR_11	Conversion of solvers' files	Mandatory
URF22	F_STUR_12	Incorporate convergence criteria per case	Desirable
URF23	F_STUR_13	Parallel execution of simulations	Mandatory
URF24	F_STUR_14	Estimation of simulation duration	Optional
URF25	F_STUR_15	Calculation of sarcomere mechanical response	Mandatory
URF26	F_STUR_16	Linking the MT with BT, ALT, PST	Mandatory

ID	D1.1 coding	Title of User Requirements	Priority (according to D1.1)
URF27	F_STUR_17	Mesh validation	Desirable
URF28	F_STUR_18	Imaging Data Processing	Optional
URF29	F_STUR_19	Set up the Boundary Conditions	Mandatory
URF30	F_STUR_20	Set up the Material Properties	Mandatory
URF31	F_STUR_21	Heart mechanics coupled with electric field and drug transport	Mandatory
URF32	F_STUR_22	Genetic Data Processing	Mandatory
URF33	F_STUR_23	Machine Learning Algorithms usage	Mandatory
URF34	F_STUR_24	Creation of virtual populations (cohort) of FCM patients	Mandatory
URF35	F_VAUI_1	Post-processing of results	Mandatory
URF36	F_VAUI_2	Visualization of 2D- and 3D-case results in browser	Mandatory
URF37	F_VAUI_3	Visualization of evaluation reports	Mandatory
URF38	F_VAUI_4	Browsing and filtering with an interactive visual access	Mandatory
URF39	F_VAUI_5	Visualization of Virtual Patients Cohort	Optional
URF40	F_VAUI_6	Visual and statistical comparison of sub-cohorts	Desirable
URF41	F_VAUI_7	Capability to Save/Load Working Progress	Desirable
URF42	F_VAUI_8	Data Download	Desirable
URF43	F_VAUI_9	Integration with other SILICOFCM services	Optional

2.3 SILICOFCM Use cases

According to user requirement identified in D1.1 the following list of use cases and usage scenarios is extracted.

Table 2 List of Usage scenarios described in D1.1

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

ID	Usage Scenarios	Dependencies
US_TU_4	Run the SULICOFCM 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

The following sections includes the use cases corresponding to the identified stakeholders of SILICOFCM platform.

2.3.1 Data provider

The data provider (Figure 1) is one of the four actors of the SILICOFCM platform. Through the SILICOFCM services, the data provider is able to manage his/her user account (e.g., user's credentials), as well as, manage his/her own clinical data. Data management involves first level functionalities which are related to: (i) view and edit the anonymized clinical data through an appropriate editor, based on its type/source, (ii) data quality assessment (i.e., data cleansing), (iii) metadata inspection, and (iv) examination of the data evaluation report which is related to the data quality assessment procedure. All these functionalities are supported by the workflow manager which lies in the heart of the SILICOFCM platform and serves as a module that directly affects all these operations.

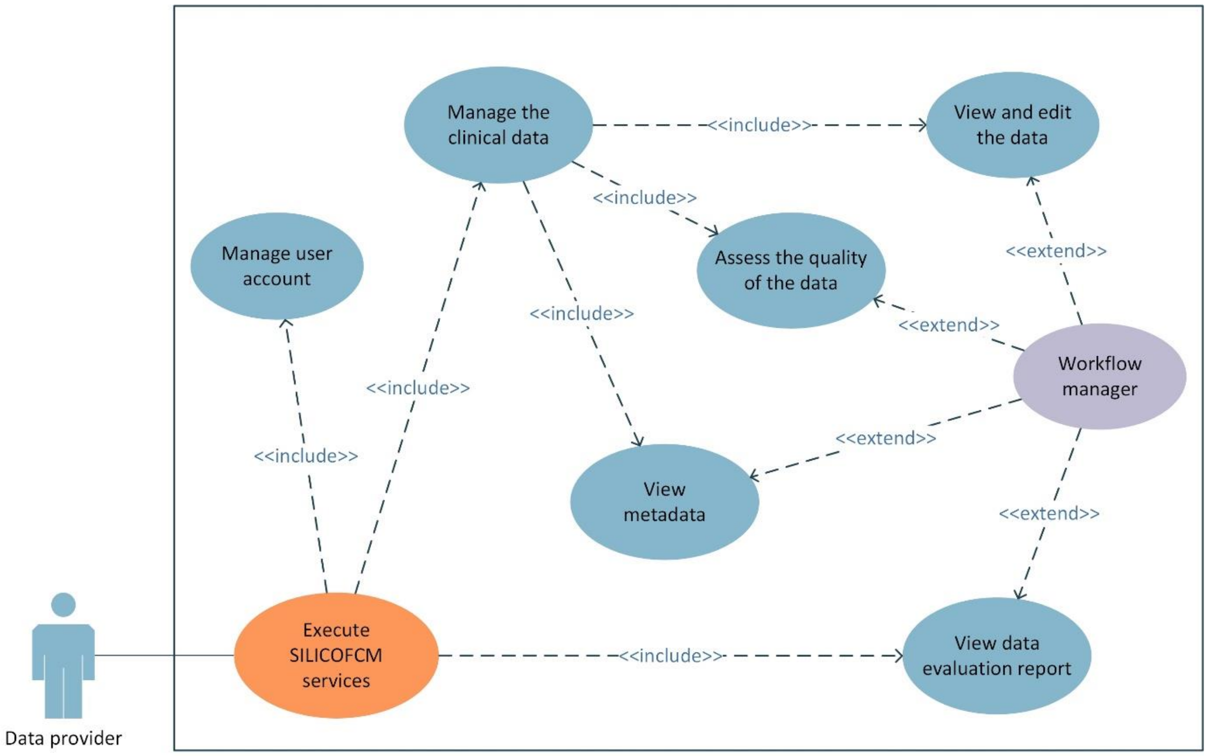

Figure 1: Use-case diagram for the Data provider.

2.3.2 Cloud provider (administrator)

The cloud provider, or administrator (Figure 2), is responsible for a variety of functionalities concerning the cloud's infrastructure management. More specifically, the cloud provider is able to:

- register or block users,
- configure virtual machines (VMs),
- create ordinary backups from the VMs,
- accept or reject extra cloud resources that have been requested by the users (e.g., hardware),
- define provisioning rules which determine the hierarchy of the operations within the cloud's services,
- create or update the services catalogue (descriptions concerning the services of the platform),
- monitor all the operations that are executed within the cloud,
- manage the cloud resources cost so as to increase the scalability of the platform,
- configure the firewall system parameters,
- manage the memory units and distribute them according to the needs of each service,
- accept or reject pending user access requests,
- manage the CPU cores and distribute them according to the needs of each service,
- define the specifications of the user interface for the front-end developers,
- manage all the network interfaces within the cloud, and finally
- view and analyze summary data (e.g., log files, records of processing).

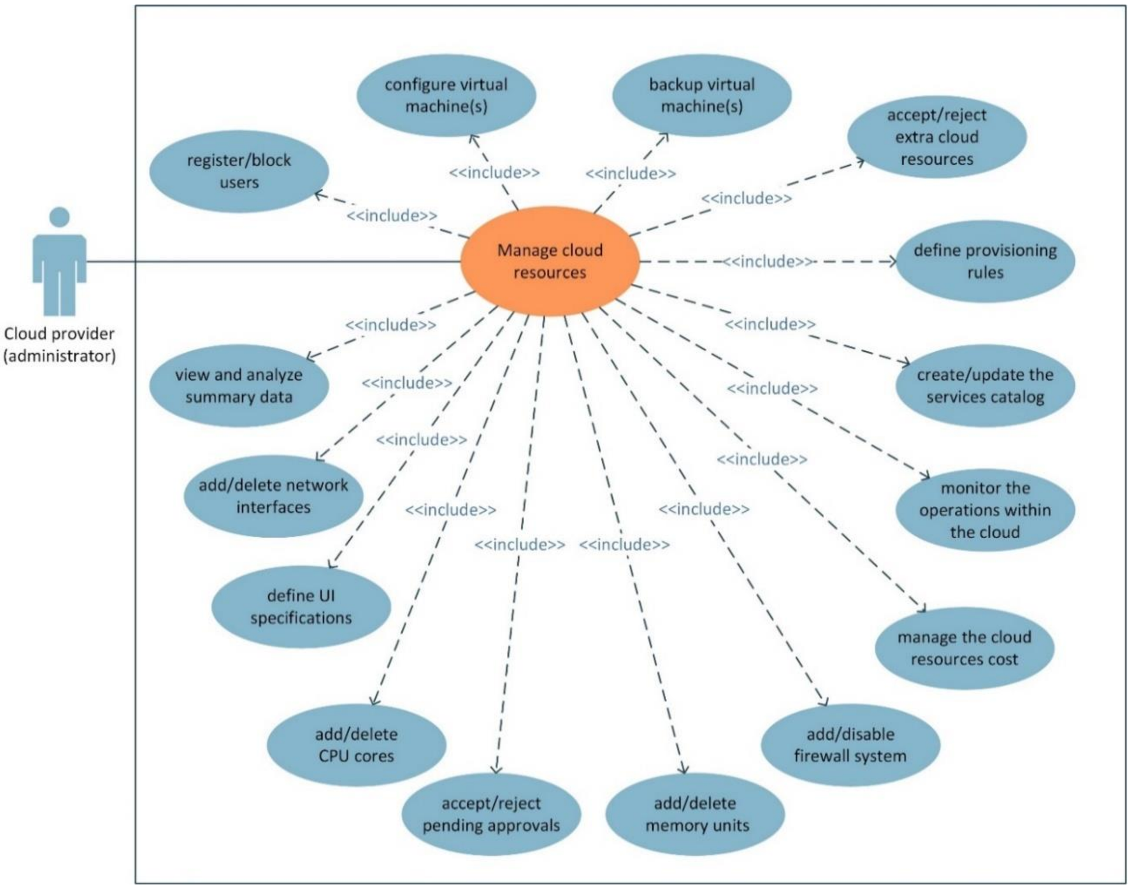

Figure 2: Use-case diagram for the Cloud provider (administrator).

2.3.3 Typical end-user

A typical end-user (Figure 3), is the fundamental actor of the platform. The identified typical end users (as defined in D1.1) of SILICOFCM platform are the: (i) the Cardiologists, (ii) the Researchers and, (iii) the Pharmaceutical companies. A detailed overview of their hierarchy and the expected use by the aforementioned users is provided in Table 3.

Table 3: SILICOFCM typical end-users and expected use.

Typical end user	Hierarchy	SILICOFCM platform use
Cardiologists	High	• Identification of genotype-phenotype relationships associated with FCM. • Prognosis of cardiomyopathy based on data mining algorithms. • Prediction of patient-specific disease outcome .
Researchers	Medium	• Access to virtual population and to a pool of heart models. • Utilization for research purposes for comparison with SILICOFCM modules and new models validation.
Pharmaceutical companies	Medium	• Monitoring of the effectiveness of pharmacological treatment. • Application of simulation modules in virtual cases of high interest. • Testing of multiple compounds, predicting potency of each compound from the simplest and inexpensive experiments toward more complex and more expensive trails. • Early elimination of less potent drugs, reveal of the reasons for failure in early stages of drug development.

Through the SILICOFCM services, the end-user is able to: (i) manage the user account (i.e., account credentials), (ii) select the type of analysis, and then (iii) define input parameters for the MUSICO Tool, the ALYA Solver Tool, the PAK Solver Tool, the Data Analytics Tool, the Bioinformatics Tool, the Virtual Population Tool and the Multiple Criteria Decision Making Tool, through appropriate front-end interfaces, according to the selected type of analysis. In addition, the typical user can visualize summary data as a result of the services execution, as well as, visualize the outcomes of the services through appropriate visualization panels. All these functionalities are supported by the workflow manager. In addition, the workflow manager can invoke the docker engine, i.e., a software which serves as an assemble workflow station.

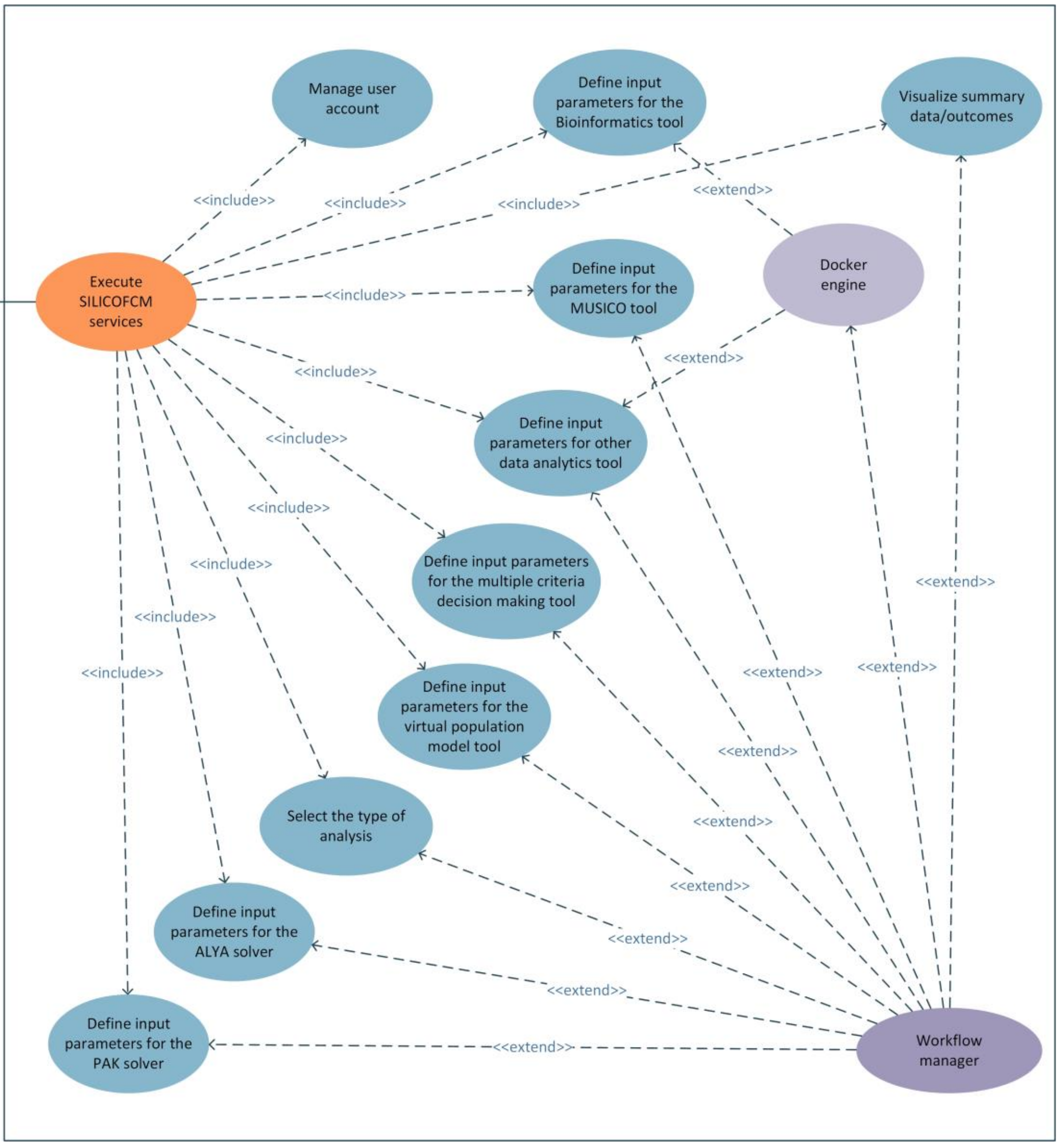

Figure 3: Use-case diagram for the typical end-user.

2.3.4 Inner and outer developer

The developers (Figure 4) are divided into two main categories: (i) the platform's developer (inner developer) who is responsible for updating the core services of the SILICOFCM platform, and (ii) the outer developer who is responsible for executing new workflow models. More specifically, the platform's developer is able to: (i) edit the VM settings (e.g., software libraries), and (ii) configure the workflow manager by adding new workflows, applying new workflows, deleting new workflows, and finally updating and deleting the core workflows which are directly related to the services of the platform. On the other hand, the outer developer does not have access to modify any of the core workflows but can only add and apply new workflows so as to test their efficacy on the SILICOFCM data. For example, the outer developer can upload a machine learning workflow in order to test its evaluation performance (e.g., accuracy, area under the curve) on the SILICOFCM data.

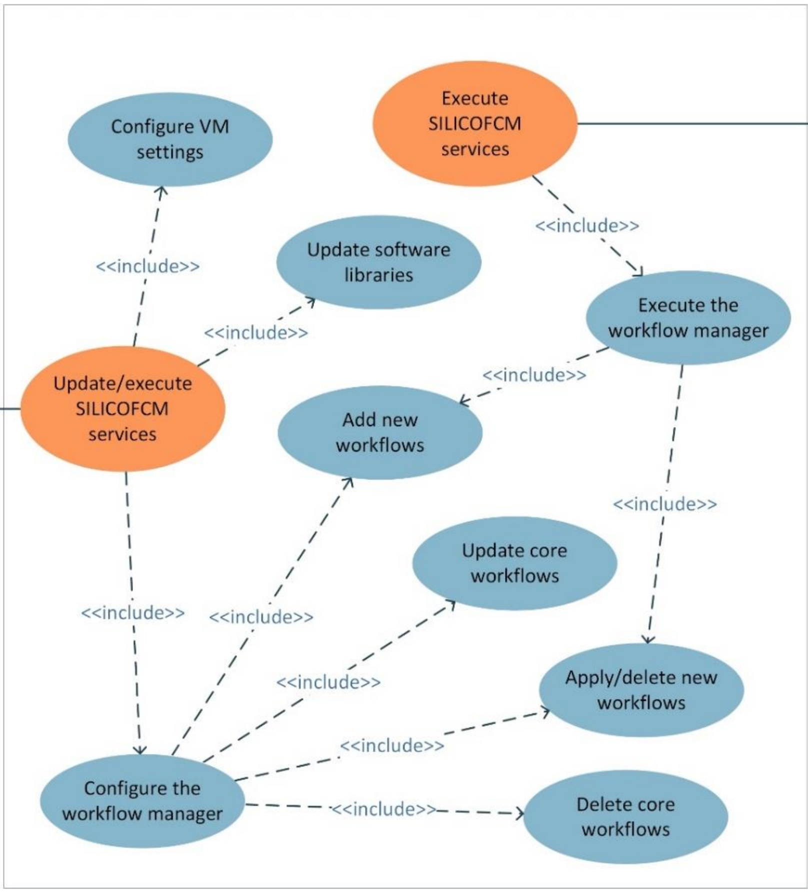

Figure 4: Use-case diagram for the SILICOFCM platform's developer and the outer developer.

2.4 SILICOFCM cloud platform information flows

2.4.1 Overall

The overall information flow of the SILICOFCM architecture is depicted in Figure 5, where the interaction between the two main actors and the platform modules is illustrated. Both the data provider and the typical end-user can connect into the platform through the User Access Management Module. The Workflow Manager Module lies in the heart of the SILICOFCM platform and manages all the modules through appropriate engines. On the right side, the data provider can upload anonymized clinical and genetic data through the Data Management Module. Then, the workflow manager invokes the data quality control engine which sends the workflow(s) to be executed for data quality assessment purposes. On the left side, the typical end-user can log into the platform through the User Access Management Module. Through the workflow module the user can execute three tools which are located in remote sites, i.e., the MUSICO, the PAK solver, and the ALYA solver, using the workflow engine. In addition, the user can execute three more docker-based tools, i.e., the Bioinformatics Tool, the Data Analytics Tool, and Virtual Population Tool, the Multiple Criteria Decision Making Tool using the docker engine. The results of the tools are finally displayed to the end-user through the Visual Analytics Module which receives visual workflow(s) from the visual analytics engine.

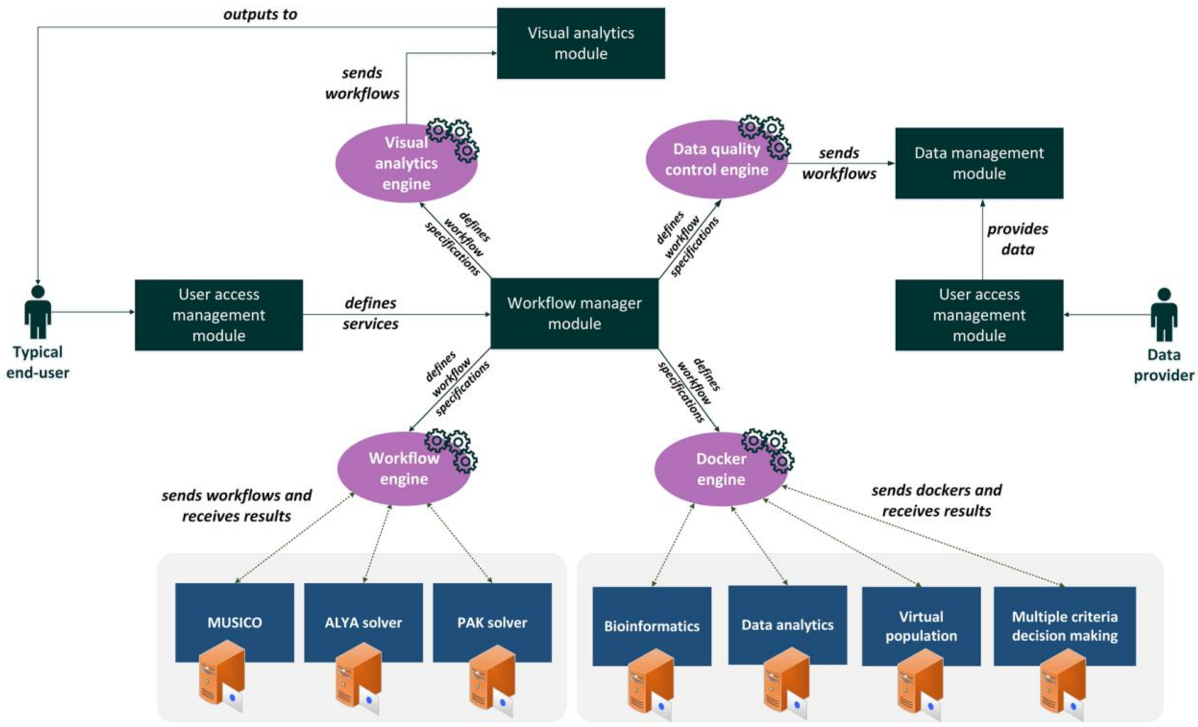

Figure 5: The SILICOFCM overall information flow.

The different type of SILICOFCM stakeholders and their related access to the platform modules/tools is presented below. More details are provided in Section 4 and Section 5.

Table 4: SILICOFCM users and access to platform modules/tools.

Users	Data provider	Cloud provider	Typical end-user	Inner and outer developer
Modules				
User Access Management Module	x	x	x	x
Data Management Module	x			
Workflow manager module		x	x	x
Visual Analytics Module	x		x	x
Tools				
MUSICO Tool			x	x
ALYA Solver Tool			x	x
PAK Solver Tool			x	x
Data Analytics Tool			x	x
Bioinformatics Tool			x	x
Virtual Population Tool			x	x
Multiple Criteria Decision Making Tool			x	

2.4.2 Data provider

The data provider (Figure 6) logs into the platform through the User Access Management Module. Then he/she is able to upload anonymized clinical and genetic data into the platform through the Data Management Module. As soon as the data are temporarily uploaded, the workflow manager invokes the data quality control engine and sends workflow specifications. The data quality control engine interacts with the workflow manager and sends the workflow(s) to the Data Management Module to assess the quality of the data. In addition, the data quality control engine receives status regarding the progress of the quality assessment procedure. The qualified data are finally stored into the data warehouse.

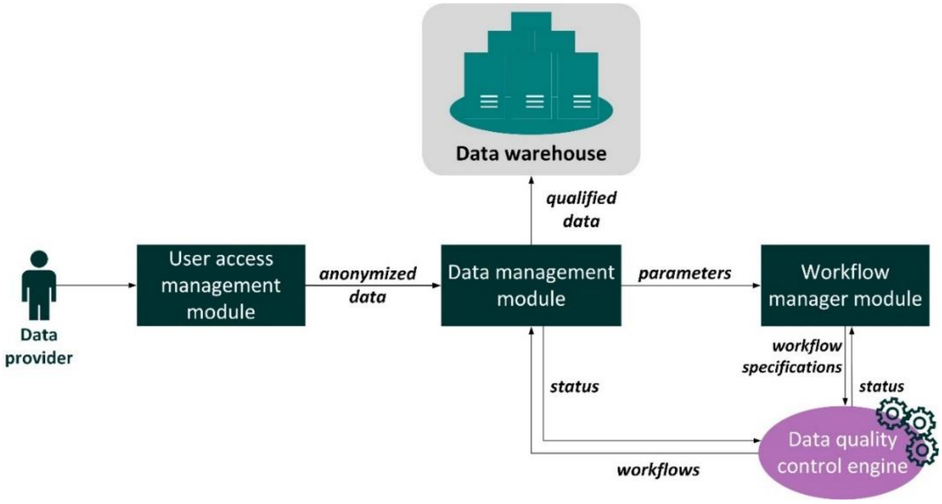

Figure 6: The Data provider's information flow.

2.4.3 Typical end-user

The typical end-user (Figure 7) logs into the platform through the User Access Management Module. Then he/she is able to execute a variety of services through the workflow manager module. According to the specified type of analysis, the workflow manager invokes either the workflow engine or the docker engine.

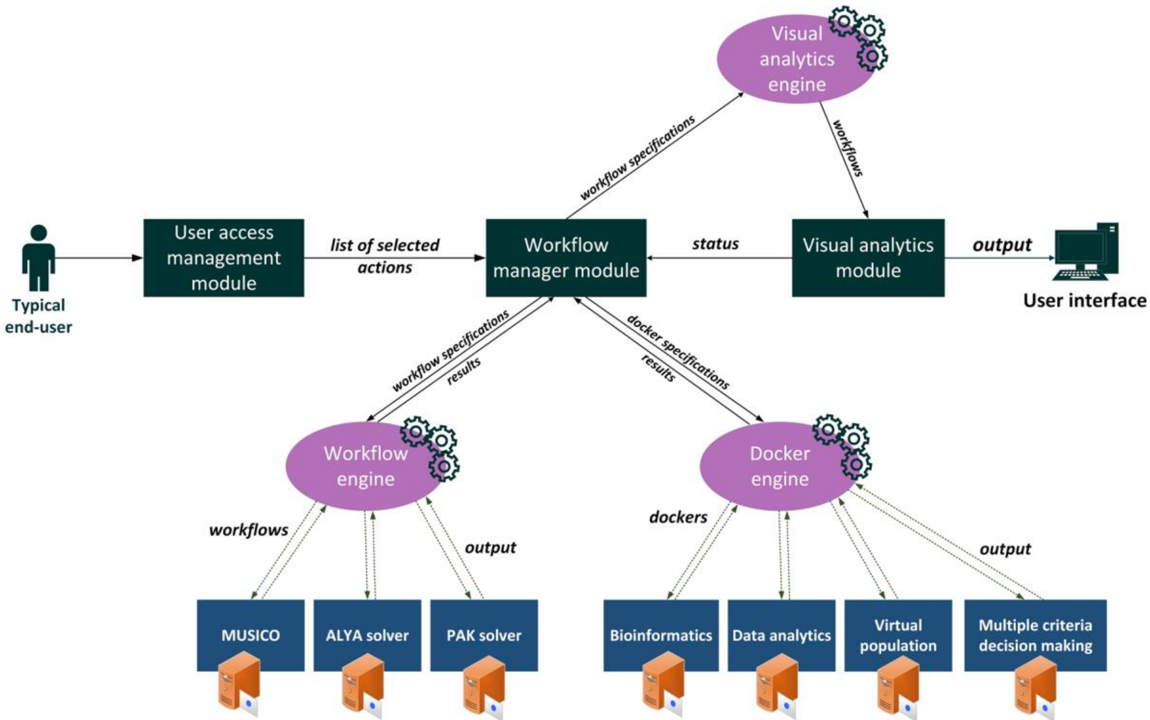

Figure 7: Typical end-user information flow.

The workflow engine is responsible for distributing the specified workflow models to the MUSICO Tool, ALYA Solver Tool, and PAK Solver Tool. The docker engine is responsible for distributing the specified dockers to the docker-based Bioinformatics Tool, Data Analytics Tool, Virtual Population Tool and Multiple Criteria Decision Making Tool. The results are finally assembled to the Workflow Manager Module which sends appropriate visual specifications (visual workflows) to the visual analytics engine. The latter sends the visual workflows to the Visual Analytics Module which processes them and outputs the results to the user's interface.

3. SILICOFCM Conceptual and Detailed Architecture

3.1 SILICOFCM Conceptual Architecture

In Figure 8, the SILICOFCM conceptual architecture is depicted. An overview of the SILICOFCM tools, the engines used and the communication with the client side is depicted.

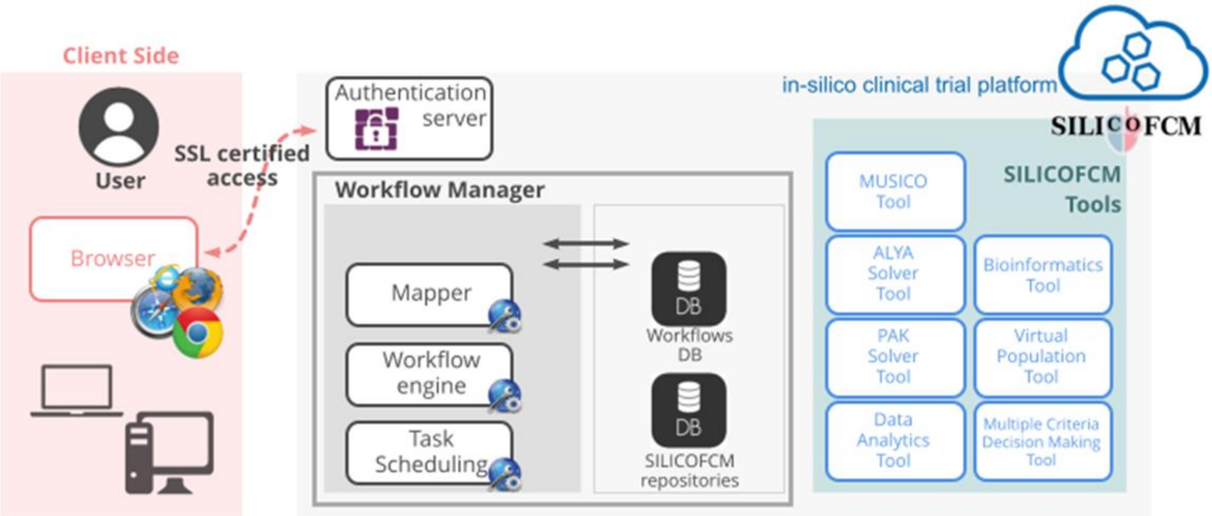

Figure 8: SILICOFCM conceptual architecture.

3.2 SILICOFCM detailed architecture

The SILICOFCM architecture is presented in the following figure with the modules and their corresponding engines and tools. Each connection within the platform is secure since all the operations are performed in a secure private network. The OAUTH2* API framework is used for secure user access management and SSL/TLS protocols are used for the encryption and decryption of sensitive information.

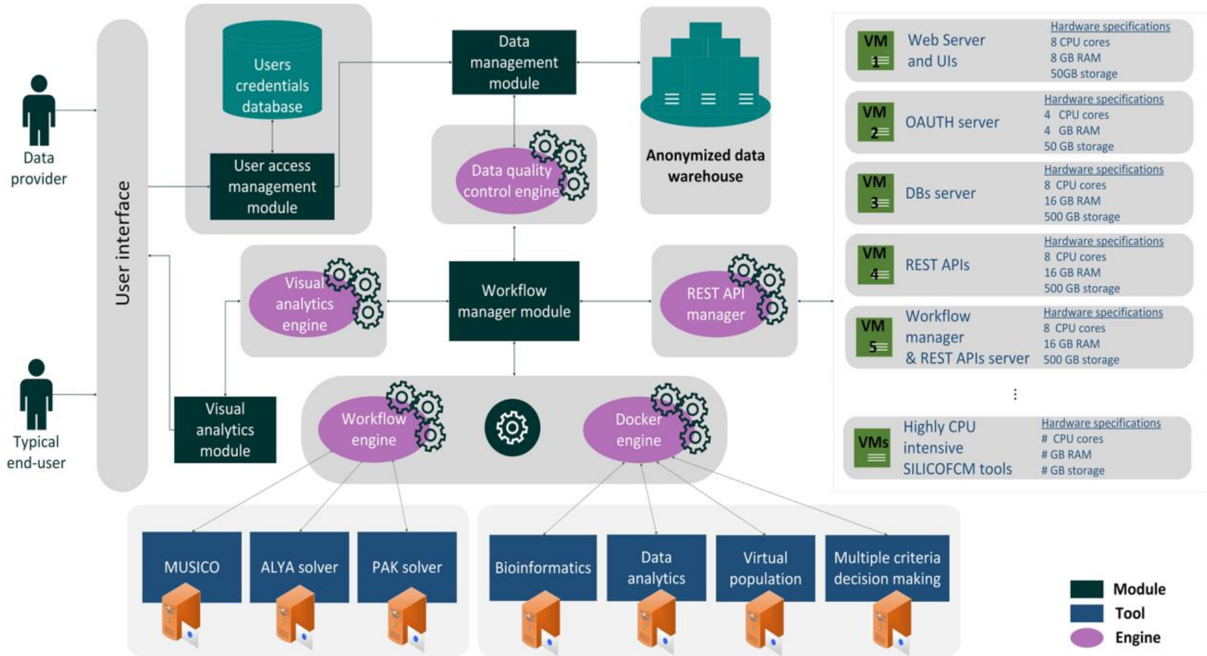

Figure 9: Detailed SILICOFCM cloud platform architecture.

3.2.1 User Access Management Module

The User Access Management Module is an OAUTH (web authorization) API (application programming interface) based framework which handles the user authentication services and is located on a single virtual machine (VM).

3.2.2 Data Management Module

The Data Management Module provides services for anonymized data upload. In addition, it offers data quality assessment services for detecting inconsistencies within the clinical data.

3.2.3 Workflow Manager Module

The Workflow Manager Module is the core module of the SILICOFCM platform. It is responsible for managing the workflow specifications of the rest of the modules and invoking the engines in order to deal with the application of the workflows.

3.2.4 Visual Analytics Module

The Visual Analytics Module is responsible for the visualization of the outputs of the tools and the modules of the platform. It receives the visual workflows from the workflow manager through the visual analytics engine and finally executes them.

3.3 SILICOFCM engines

3.3.1 Data quality control engine

The data quality control engine is raised by the workflow manager when the Data Management Module is enabled. The engine is responsible for executing data quality control workflows in terms of data curation (data cleansing) and overall data quality assessment. The data curation workflow seeks for missing values, outliers, duplicate terms, and further inconsistencies within the clinical data. A data quality assessment report is finally returned to the workflow manager module.

3.3.2 Workflow engine

The workflow engine is invoked by the workflow manager when the user wishes to run SILICOFCM tools such the MUSICO Tool, PAK Solver Tool, and ALYA Solver Tool. The workflow engine receives the workflow specifications from the Workflow Manager Module according to the user's input parameters. Then, the workflow engine executes the workflows on the premises through REST services in secure channels. The results are finally returned to the Workflow Manager Module and sent to the Visual Analytics Module through the visual analytics engine.

3.3.3 Docker engine

The docker engine is invoked by the workflow manager when the user wishes to run the Bioinformatics Tool, the Data Analytics Tool, the Virtual Population Tool and the Multiple Criteria Decision Making Tool. The docker engine receives the docker specifications from the Workflow Manager Module according to the user's input parameters. A docker can be seen as a stand-alone executable package of software that contains all the necessary resources which are needed in order to run the service. The docker is an operation system visualizer (i.e., a software container) which replaces a virtual machine and thus enables faster services execution. The results are finally returned to the Workflow Manager Module and sent to the Visual Analytics Module through the visual analytics engine.

3.3.4 Visual analytics engine

The visual analytics engine receives the visualization specifications from the Workflow Manager Module according to the type of the analysis. Then, the engine constructs the visual workflows and sends them to the Visual Analytics Module for execution. The outcomes are finally displayed to the user interface.

3.3.5 REST API manager

The REST API manager handles the VM resources according to each module's needs. It can be seen as a services scheduler which distributes the VM resources based on the system operations.

3.4 State of the Art

3.4.1 In-Silico Clinical Trials Similar Platforms

The term *in silico* clinical trials (ISCT) [1] refers to the utilisation of individualized computer simulations for designing, developing and evaluating: (i) medicinal products, (ii) medical devices, and (iii) medical interventions. ISCT is a subdomain of *''in silico medicine''* and approaches the adoption of individualized computer simulations for the diseases prevention, diagnosis, prognosis and treatment.

Computer simulation nowadays is widely used in the development and de-risking of a number of ''mission-critical'' products. Currently the process of the biomedical product development and assessment relies on experimental tests and approaches. The time required to perform the *in vitro* tests in animals and the clinical tests in patients pushes development costs to unsustainable levels.

ISCTs is a revolutionary approach for reducing, refining and partially replacing the real clinical trials [1]. This new approach is already being used in the development of biomedical products, as the product design is in a more advanced and mature phase. Pharmaceutical companies use computer models to estimate or simulate the pharmacokinetics and the pharmacodynamics of a new compound.

Developing that kind of reliable computer models of the treatment and its deployment, together with computer models of patient's specific characteristics, we could perform exploratory ISCT (Figure 10). An approach in which virtual patients are generated, could induce a new virtual treatment enabling us to observe through a computer simulation how the drug performs.

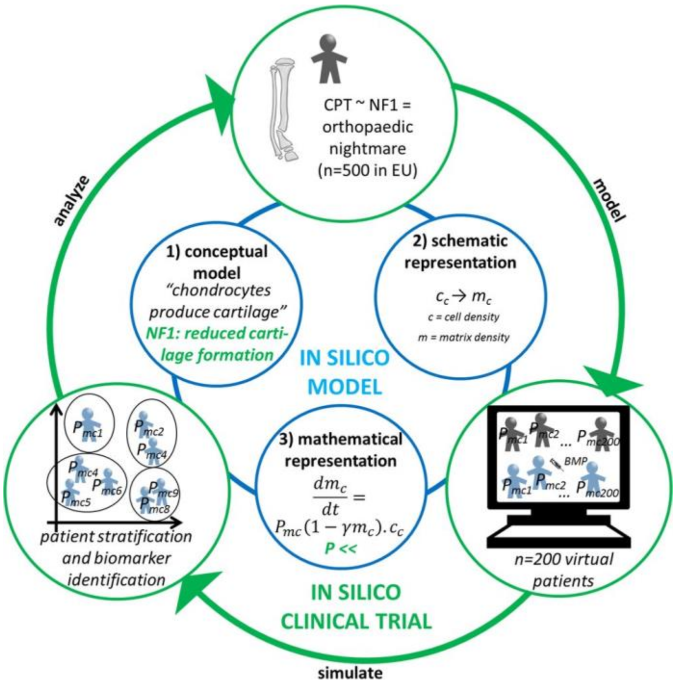

Figure 10: *In Silico* Clinical trials schematic for pediatric orphan diseases [2].

Simcyp

The latest decades, several types of computational models have been used for drug development. Physiologically Based Pharmacokinetic (PBPK) models is a combination of information from drug properties with prior knowledge on the physiology and biology at the organism. This approach implements a mechanistic presentation of the specific drug in biological systems [3]. The Simcyp Population-based Absorption, Distribution, Metabolism and Excretion simulator (ADME), is a framework [4] for *in silico* drug research, development, and generation of a physiologically based pharmacokinetic modelling profiles (Figure 11). It provides the prediction of the metabolically-based interactions among drugs and drug therapies. Accommodating the Pharmacokinetics/Pharmacodynamics modelling, Simcyp is a platform and database for bottom up mechanistic modelling and simulation, integrating discrete different information. Some of the processes refer to oral absorption, tissue distribution and the excretion of drugs. Its major advantage is the combination of the experimental data generated routinely during preclinical drug discovery and the utilization of *in vitro* enzyme and cellular systems (Figure 11).

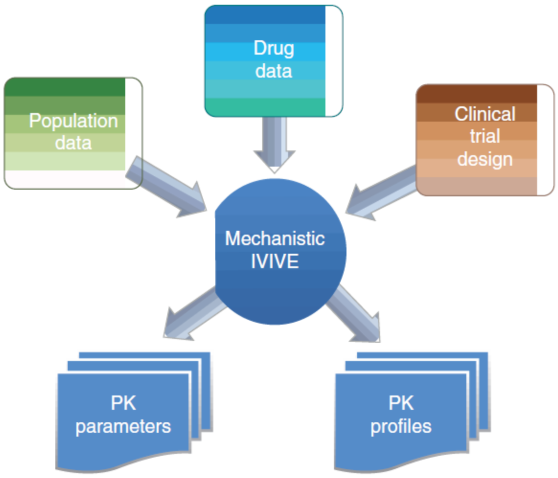

Figure 11: The key elements of Simcyp [4].

Nova Discovery's Virtual Population

The Nova Discovery Virtual population [5] allows the prediction of a disease 's progress through the integration of virtual patients and drug candidates with disease models. The platform uses statistical virtual populations composed by specific patient medical parameters (Figure 12), such as (i) the gender, the age, the weight, the height, (ii) the systolic and diastolic blood pressure, (iii) the total and HDL cholesterol, (iv) the glycaemia, (v) the serum creatinine, (vi) the left ventricular hypertrophy. The virtual population is created from a French population of 26 million individuals.

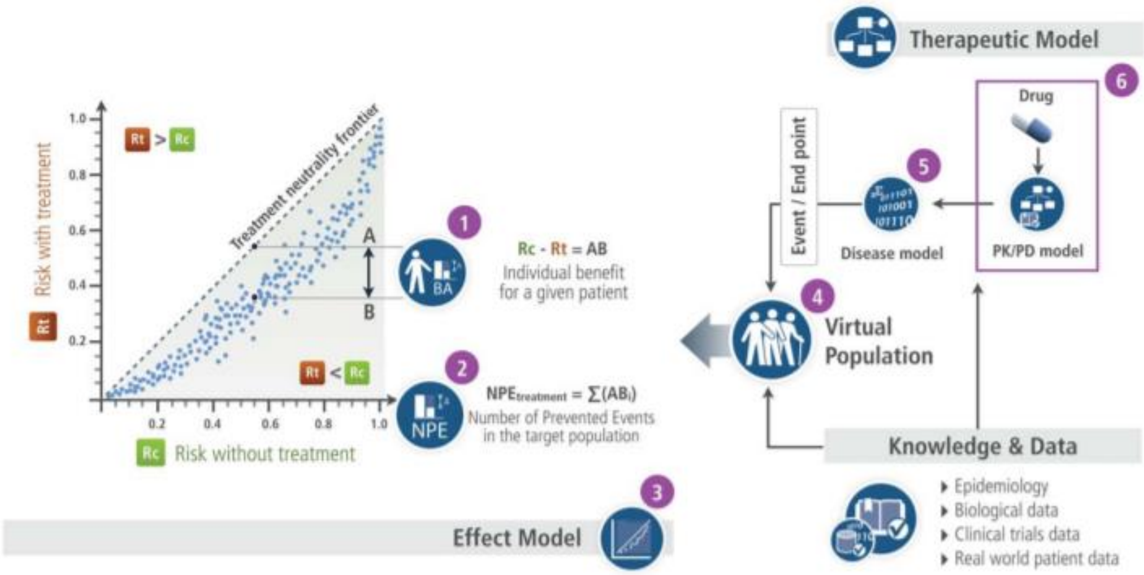

Figure 12: Nova discovery, the Effect Model [5].

EMMA

A web developed system called EMMA [6] (Ex vivo Mathematical Myeloma Advisor), is consisted of patient specific mathematical models parameterized by *ex vivo* data from patients with multiple myeloma (Figure 13). EMMA is a platform which can predict the clinical response of drugs and estimate the efficacy of drug therapies. It has been designed to predict therapeutic responses in myeloma patients and indicate how patients could be treated with combinations of drug therapies. From the general point of view, EMMA is actually an accurate fast *ex vivo* and mathematical tool, for supporting the management and treatment of patients' suffering from myeloma.

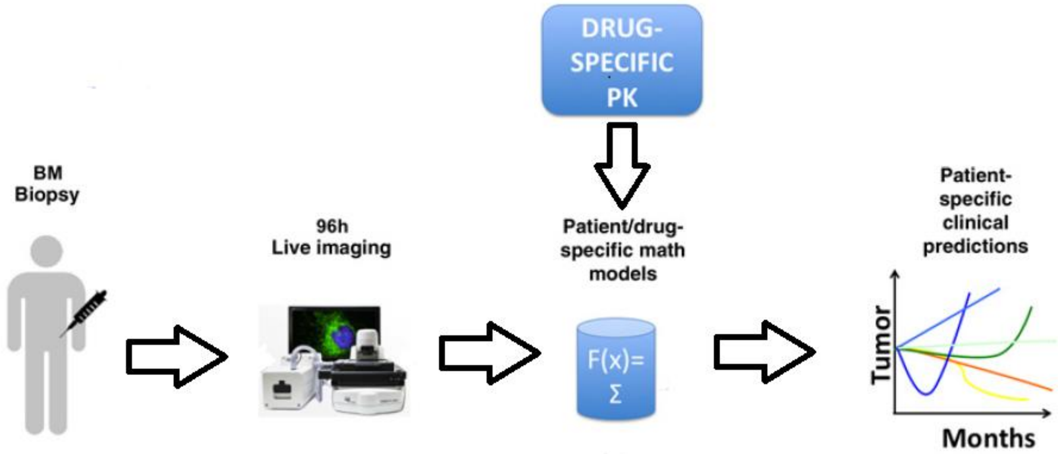

Figure 13: EMMA workflow [6].

3MDAP

The Multi-Modal Medical Data Analysis Platform (3MDAP) [7], is a web-based interface that can handle data and execute the visualization of 3D models. 3MDAP has two major directions: (i) provides to the user the ability to analyze clinical genomic data easily, implement statistical analysis at specific parameters and compare regiments to obtain analysis results, (ii) enables the modelling of different clinical data for developing 3D patient-specific predictive models for assessing the value of specific biomarkers. For each simulation analysis a report of results is been created. The main goal of this platform is to empower researchers to interact with ease with statistical analysis tools and acquire the predictive models through a web platform.

MatchMiner

MatchMiner is an open source computational platform [8] developed to enable the matching of patient's genomic profile to precision cancer medicines at clinical trials (Figure 14). The inputs are based on patient's specific genomic data, clinical data (type of cancer, age, gender) and structured eligibility criteria for clinical trials. The platform automatically does a match at patient specific genomic events and clinical trials, converting the results to available formation for trial researchers and clinicians. MatchMiner is a web application with Python-based programming interface (API) server and AngularJS 1.5 client.

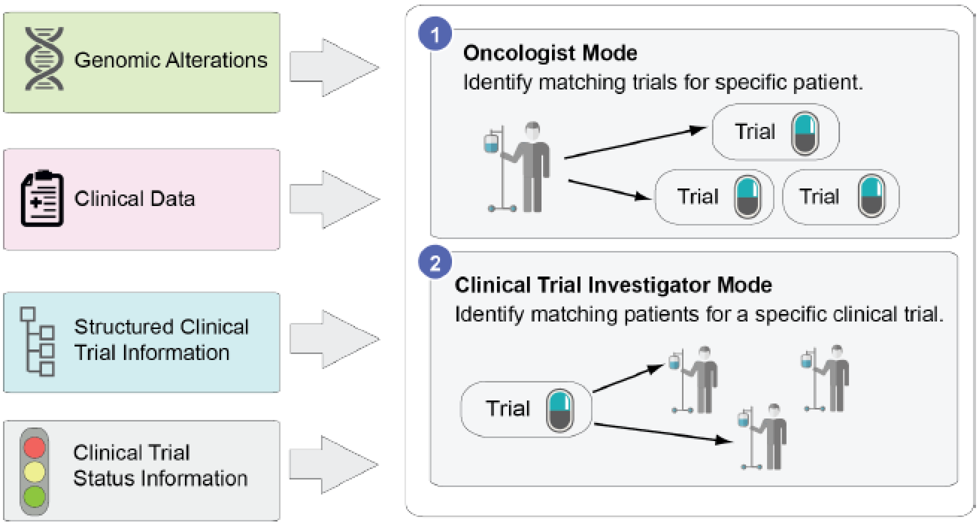

Figure 14: MatchMiner platform [8].

InSilicoTrials.com

Promeditec InSilicoTrials provides medical companies and researchers a web-based platform for the development, evaluation, testing and planning of orthopedic and cardiovascular medical devices (Figure 15). The process for a simulation is based on real clinical trial patient data and different imaging modalities (CT, MRI), from which 3D anatomical model of vascular and bone are created. It enables the *in silico* testing of medical devices on a population and provides the ability to test different surgical options on a single patient. The platform contains solvers for fluid dynamics and finite elements, as tools for the simulation processes.

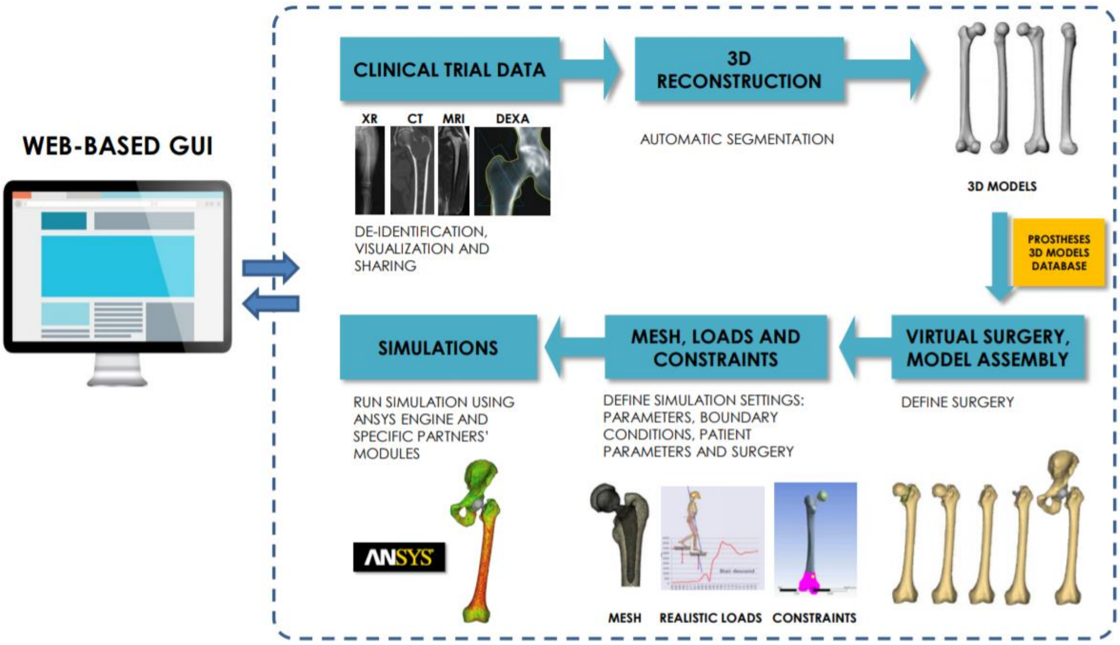

Figure 15: InSilicoTrials platform [9].

DoctorEye

DoctorEye is an easy and flexible open access platform [10] (Figure 16). It includes a user-friendly environment as the graphical interface is based on applications well known from common users such as MSOffice. DoctorEye platform supports the segmentation and annotation of tumor regions. The platform's main advantage is the ability to fast and accurately portray complex areas in medical images. Due to its simplicity, the users should have only some basic knowledge and experience for simulation/segmentation process. Another key feature of the platform is that allows the simulation of *in silico* models of cancer growth and therapies, investigating specific drug therapies.

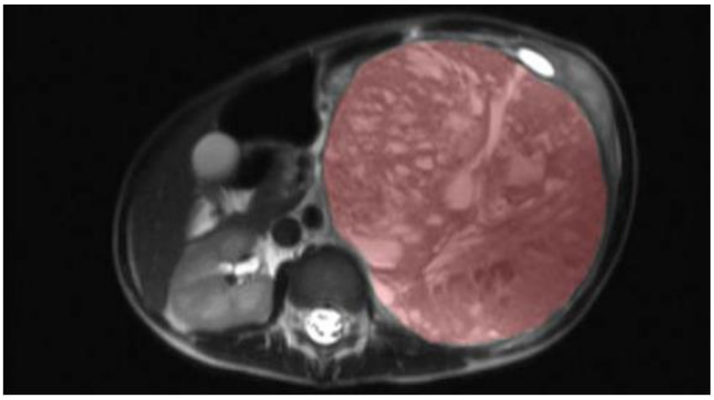

Figure 16: DoctorEye segmentation/annotation tool [10].

Physiolab Platform

A large-scale mathematical model named Entelos and Physiolab Platform [11] focus on the inflammatory and erosive processes in afflicted joints of people suffering from rheumatoid arthritis. The simulation model is deterministic and allows tracking back the mechanism of action for specific simulation result. The model represents different patient phenotypes by different virtual population. Physiolab platform allowed the users to create a virtual population with medical-related data that was in compliance with the real world's population statistics. Physiolab performance enables the systematic and quantitative prediction of the therapeutic effect of several molecular targets.

NONMEM

Non-Linear Mixed Effects Modelling software called NONMEM (Figure 17), [12] is a platform capable for Pharmacokinetics and Pharmacodynamics analysis (PK/PD). It is used to predict the effect of drugs, at specific patient population. It is a computer program designed for analyzing population PK/PD data. These data are collected from clinical studies of drug components. Accurate modeling of these data derive both unexplainable effects and measured effects. This type of mixed modelling is capable for simulation, when the data are few pharmacokinetic measurements for each patient in cohort.

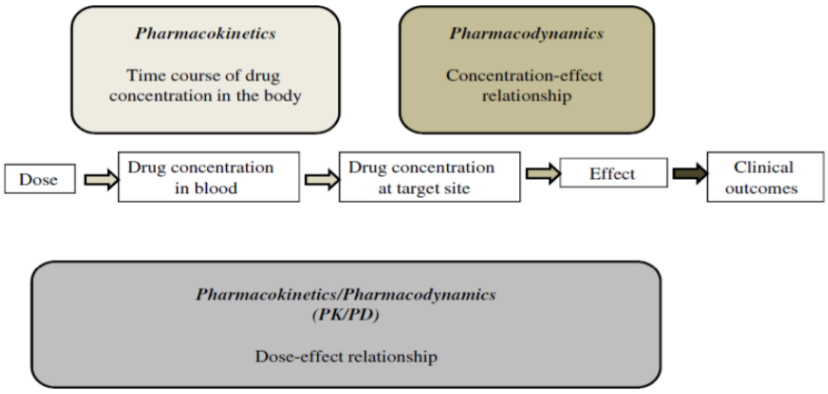

Figure 17: NONMEM flow [12].

DrugGenEx

DrugGenEx is a pharmacology-based platform [13] that enables the prediction of empirical drug-target interactions. Specifically, interaction pairs are integrated into a multi-tiered network analysis and predict the disease-specific drug polypharmacology through on the analysis of systems-based gene expression. It can predict the biological interactions effects at protein structure level, biological pathways and molecular functions. DrugGenEx focuses on known therapeutic drugs for rheumatoid arthritis and inflammatory bowel disease. The platform is currently pursuing to cancer-associated metabolites.

PK-Sim MoBi

A modeling and simulation software platform capable for building and simulating integrated models of various biological scales. It consists of two components: (i) PK-Sim and, (ii) MoBi [14] (Figure 18). PK-Sim is a graphic user interface-based tool, which can model the whole body. It mainly focuses on physiologically based pharmacokinetic modelling (PB/PK modelling). It has been used extensively for decades in the field of toxicological risk assessment. Recently it has been extended towards the research and development area of drugs. PK-Sim enables fast access to clinical patients and animals parameters. The second component of the platform is MoBi [14] which is a systems biology software tool offering multiscale physiological modeling and simulation, such as: (i) biochemical reaction networks, (ii) compartmental disease progression models, or (iii) PBPK models.

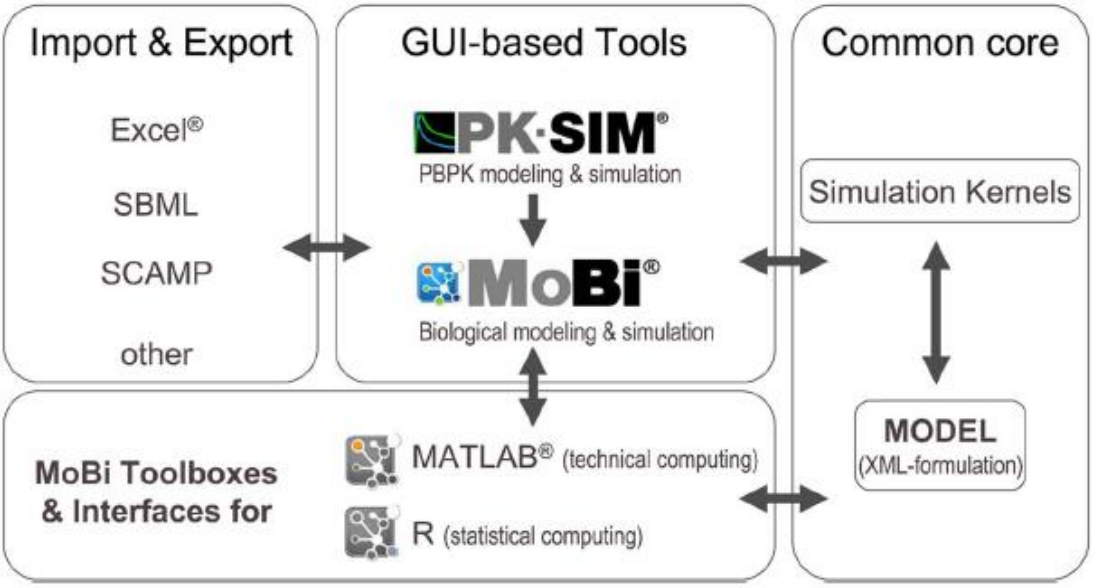

Figure 18: PK-Sim and MoBi simulation flow [14].

The Cancer Genome Atlas

The Cancer Genome Atlas (TCGA) [15] is a platform which can generate comprehensive multidimensional maps of the critical genomic changes for 33 types of cancer. The TCGA dataset describes tumor tissue and matched normal tissues. A pipeline for genomic data analysis has been created for effectively collecting, selecting and analyzing human tissues for gene alterations on a very large scale. The primary goal of this platform is to improve the diagnosis and the proper treatment of cancer.

3.5 Methodological approach

3.5.1 List of standards

The following widely adopted list of standards will be taken into consideration for the SILICOFCM platform development.

- ISO/IEC/IEEE 42010: Systems and software engineering - Architecture description
- ISO27001/2: Information technology – Security techniques – Information security management systems – Requirements
- ISO/IEC/IEEE 12207:Systems and software engineering - Software life cycle processes
- ISO/IEC/IEEE 24765: Systems and software engineering - Vocabulary
- ISO/IEC 27017:2015: Information technology - Security techniques - Code of practice for information security controls based on ISO/IEC 27002 for cloud services
- OAuth: protocol and language for authorizations expressions (to access data or service) and to authorizations exchange between different websites.

3.5.2 Model types

The different model types used within the deliverable to present (i) interactions, the actions and relationships of the user with the system; (ii) the main blocks of the system, their communication and dependencies; (iii) the interaction of objects/systems in time sequence (Appendix A1 – Model types).

4. SILICOFCM modules

4.1 User Access Management Module (UAMM)

The following table describes the User Access Management Module, its dependencies with other modules/tools of SILICOFCM platform and the input and output.

Table 5: Technical overview of User Access Management Module.

#ID _M1	User Access Management Module
Short Description	
Manages the users' access inside the SILICOFCM platform according to the different types of users (data provider, cloud provider, typical end-user, inner and outer developer).	
Scope	
To provide an API for secure web user authentication services.	
Responsibilities and pre-requisites	
Partner(s)	UOI/BIOIRC
Actors	Data provider Administrator Typical end-user Inner and outer developer
Priority	High
Dependencies	
Potential dependencies with the rest of the SILICOFCM modules/tools	Data Management Module Workflow Manager Module
SILICOFCM modules interaction and relationships	Through the User Access Management Module, the data provider can gain access to the user interface and from there to the Data Management Module. Through the User Access Management Module, the administrator can gain access to the platform's infrastructure. Through the User Access Management Module the typical end-user, as well as, the inner and outer developer can gain access to the user interface and from there to the tools and the rest of the platform's modules.
Input and Output	
SILICOFCM input	• User's access credentials (stored in the users' credentials database)
SILICOFCM output	• Temporary access tokens

The architecture of the User Access Management Module is depicted in Figure 19. The module receives as input the user's access credentials (username, password). Then the module communicates with the user's credentials database in order to identify the type of user (data provider, administrator, typical end-user, inner and outer developer) based on the OAUTH API framework which is part of the cloud's infrastructure. The module outputs temporary user access tokens according to the type of the SILICOFCM user.

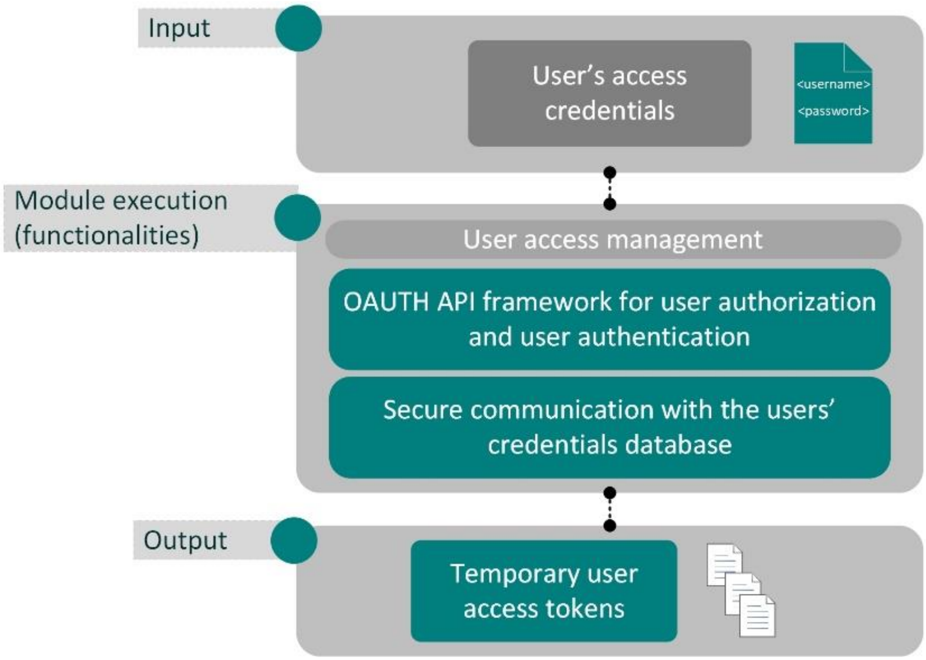

Figure 19: The proposed architecture of the User Access Management Module.

The workflow of the User Access Management Module consists of three stages (Figure 20). In the first stage, the user inserts his/her credentials. The user authentication process comes up which is based on the secure communication of the OAUTH API framework with the users' credentials database to retrieve information according to the type of the user. If the user authentication process fails, the process is terminated. Otherwise, the data authorization process is executed and as a result the user receives temporary access tokens for only those services that are related to his/her type.

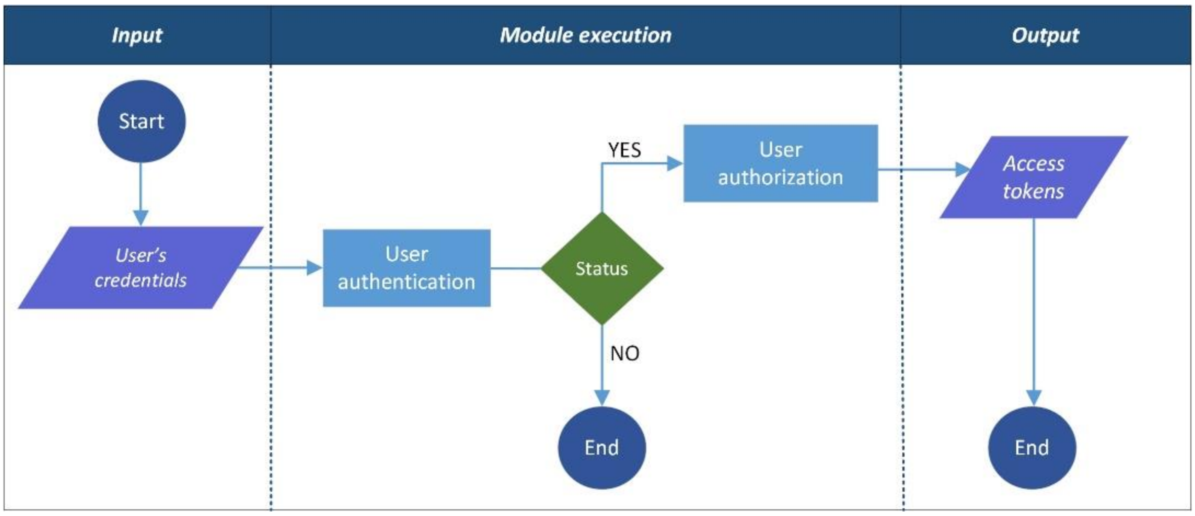

Figure 20: The proposed workflow diagram which depicts the functionality of the User Access Management Module.

4.2 Data Management Module (DMM)

The following table describes the Data Management Module, its dependencies with other modules/tools of SILICOFCM platform and the input and output.

Table 6: Technical overview of Data Management Module.

#ID_M2	**Data Management Module**
Short Description	
Through the Data Management Module the user can upload anonymized clinical and genetic data to the SILICOFCM data warehouse. In addition, the user can execute data quality control services for data curation in order to assess the quality of the data. The data curator serves as an automated diagnostic tool which includes functionalities for incompatibilities check, outlier detection, and identification of duplicate terms, among many others. The data quality assessment consists of the following functionalities: • Metadata extraction (number of attributes, data types, ranges, missing values) • Calculation of descriptive statistics (mean, std, kurtosis, skewness) per attribute • Outliers detection (detection of values that vary from the standard distribution) • Data imputation (detection of missing values and imputing where necessary) • Similarity detection (detection of highly-correlated and duplicated attributes) • Inconsistencies check (detection of unknown values and symbols) <u>Indicative methods for outlier detection</u> 1. z-score and its modified version for Gaussian properties 2. Interquartile range (IQR) 3. Local outlier factor 4. Statistical tests (e.g., Grubb's test) 5. Isolation forests/elliptic envelopes (supervised methods) <u>Indicative methods for data imputation</u> 1. Average/median 2. Random 3. Removal <u>Indicative methods for similarity detection</u> 1. Correlation or Spearman coefficient for detecting attributes with similar distributions. 2. Lexical matching for detecting duplicated attributes.	
Scope	
To provide an API for secure clinical and genetic (anonymized) data upload to the SILICOFCM data warehouse along with proper data quality assessment services.	
Responsibilities and pre-requisites	
Partner(s)	UOI/BIOIRC
Actors	Data provider
Priority	High
Dependencies	
Potential dependencies with the rest of the SILICOFCM modules/tools	Workflow Manager Module

SILICOFCM modules interaction and relationships	The Workflow Manager Module invokes the data quality control engine which interacts with the Data Management Module in order to execute data quality assessment workflow(s).
Input and Output	
SILICOFCM input	• Anonymized clinical and genetic data
SILICOFCM output	• Data quality assessment report(s)

The architecture of the Data Management Module is depicted in Figure 21. The module receives as input the anonymized clinical and genetic data that are going to be uploaded to the SILICOFCM data warehouse. Then, the module offers several functionalities related to: (i) the anonymized clinical and genetic data upload through secure REST services, (ii) the data quality assessment process (outlier detection, inconsistencies check and detection of duplicate and highly-correlated terms). The Data Management Module outputs data quality assessment reports which are displayed to the user through the Visual Analytics Module. The quality assessment reports are generated through appropriate data quality assessment workflows which are distributed to the Data Management Module through the data quality control engine. The latter is invoked by the Workflow Manager Module.

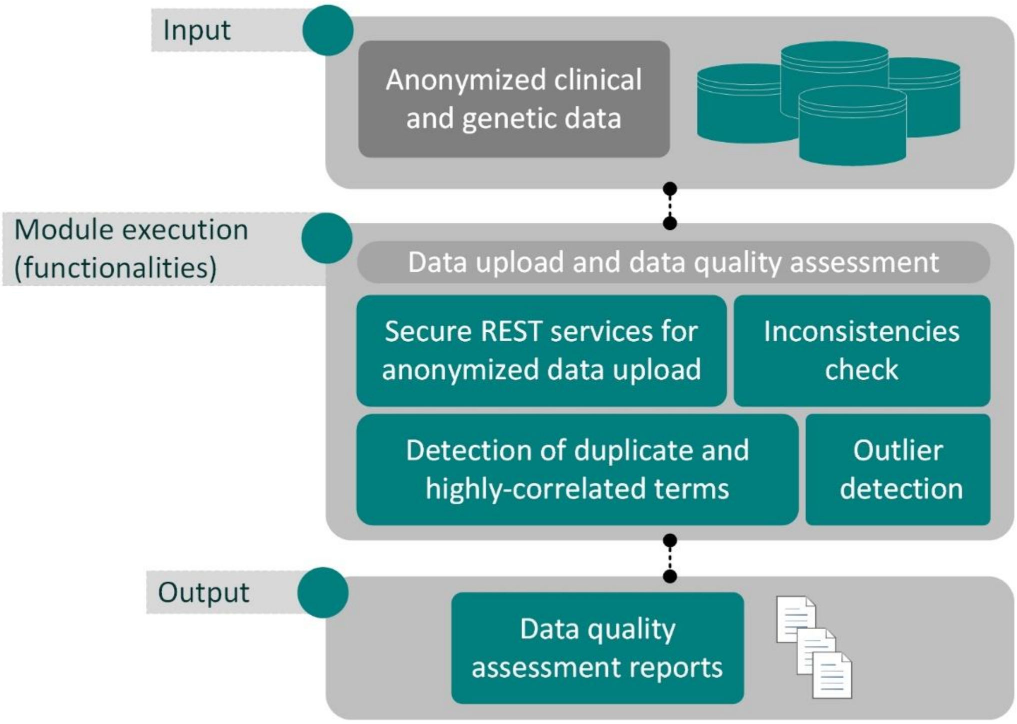

Figure 21: The proposed architecture of the Data Management Module.

The workflow of the Data Management Module consists of three stages (Figure 22). In the first stage, the data provider defines the anonymized clinical and genetic data for upload. In the second stage, the latter are uploaded to the data warehouse. If the data are successfully uploaded to the data warehouse, the data quality assessment services are executed for data curation otherwise the workflow ends. The output of the data management workflow is a data quality assessment report which captures important information related to metadata (i.e., data structure and related vocabularies), outliers, inconsistencies, and duplicate terms within the clinical data. The report is automatically generated and is displayed to the user in a rich text format.

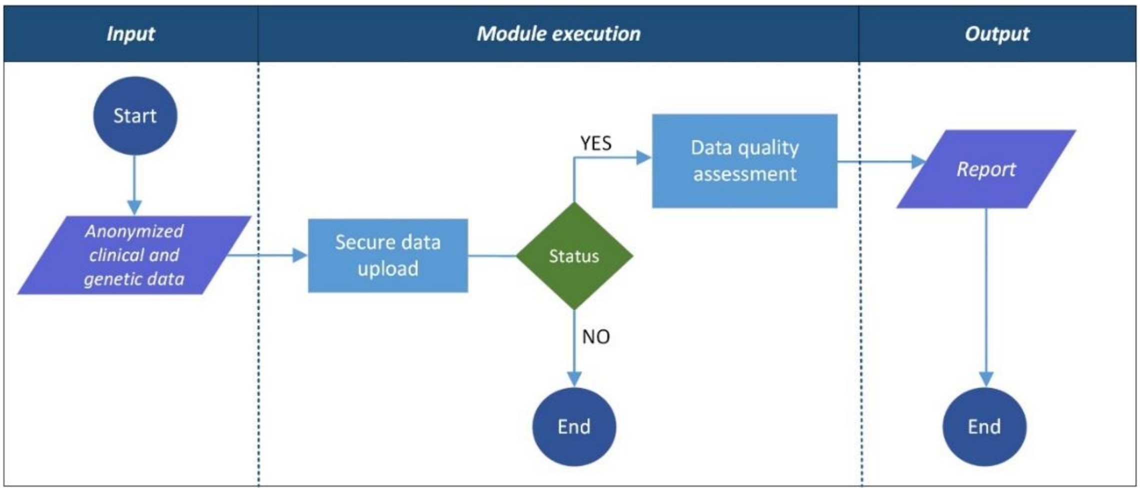

Figure 22: The proposed workflow diagram which depicts the functionality of the Data Management Module.

4.3 Workflow Manager Module (WMM)

The following table describes the Workflow Manager Module, its dependencies with other modules/tools of SILICOFCM platform and the input and output.

Table 7: Technical overview of Workflow Manager Module.

#ID_M3	Workflow Manager Module
Short Description	
The workflow manager lies in the core of the SILICOFCM platform. The Workflow Manager Module composes all the necessary workflows for the execution of the SILICOFCM modules and tools. It is responsible for the management of four basic engines: (i) the data quality control engine, (ii) the workflow engine, (iii) the docker engine, and (iv) the visual analytics engine. The workflow manager: (i) receives the input parameters from the user interface (according to the user's input and type of analysis), (ii) constructs the specifications for the workflows and dockers, and (iii) invokes the corresponding engines according to the type of analysis. In fact, the workflow and docker specifications are sent to the engines, where are composed and finally distributed to the corresponding modules and tools of the SILICOFCM platform for execution. In addition, the Workflow Manager Module includes a REST API manager which is responsible for the resource management of the VMs according to the specifications (needs) of the services that are going to be executed within the platform.	
Scope	
To provide an API for secure clinical and genetic (anonymized) data upload to the SILICOFCM data warehouse along with proper data quality assessment services.	
Responsibilities and pre-requisites	
Partner(s)	UOI/BIOIRC
Actors	Cloud provider Typical end-user Inner and outer developer
Priority	High
Dependencies	

Potential dependencies with the rest of the SILICOFCM modules/tools	**Modules** Data Management Module Visual Analytics Module **Tools** MUSICO Tool PAK Solver Tool ALYA Solver Tool Bioinformatics Tool Data Analytics Tool Virtual Population Tool Multiple Criteria Decision Making Tool
SILICOFCM modules interaction and relationships	• The Workflow Manager Module invokes the data quality control engine which interacts with the Data Management Module for executing the data quality assessment workflows. • The Workflow Manager Module invokes the workflow engine which interacts with the: (i) MUSICO Tool, (ii) PAK Solver Tool, (iii) ALYA Solver Tool, through appropriate REST services in order to execute the workflow(s) that are generated by the users input parameters. • The Workflow Manager Module invokes the docker engine which interacts with the: (i) Bioinformatics Tool, (ii) Data Analytics Tool, (iii) Virtual population Tool, (iv) Multiple Criteria Decision Making Tool through appropriate REST services in order to execute the dockers that are generated according to the users input parameters. • The Workflow Manager Module invokes the visual analytics engine which interacts with the Visual Analytics Module in order to execute the visual analytics workflows according to the type of analysis. • The Workflow Manager Module invokes the REST API manager which interacts with the cloud infrastructure layer in order to manage the VMs usage according to the services that are currently executed.
Input and Output	
SILICOFCM input	• Input parameters from the user interface (according to the user's input).
SILICOFCM output	• Workflows for the following modules: data management (which distributed through the data quality control engine), visual analytics (which are distributed through the visual analytics engine). • Workflows for the following tools: MUSICO, PAK Solver, ALYA Solver (which are distributed through the workflow engine). • Dockers for the following tools: Bioinformatics, Data analytics, Virtual population, the Multiple Criteria Decision Making tool (which are distributed through the docker engine).

The architecture of the Workflow Manager Module is depicted in Figure 23. The module receives as input the parameters from the user interface and offers several functionalities related to: (i) the data quality assessment process under the Data Management Module through the data quality control engine, (ii) the visualization process under the Visual Analytics Module through the visual analytics engine, (iii) the simulation results from the docker-based SILICOFCM tools through the docker engine, (iv) the simulation results from the workflow-based SILICOFCM tools through the workflow engine, and (v) the VM resources management through the REST API manager. The Workflow Manager Module outputs: (i) module-based workflows, (ii) tool-based dockers, and (iii) tool-based workflows, which are used by the rest of the SILICOFCM modules and tools.

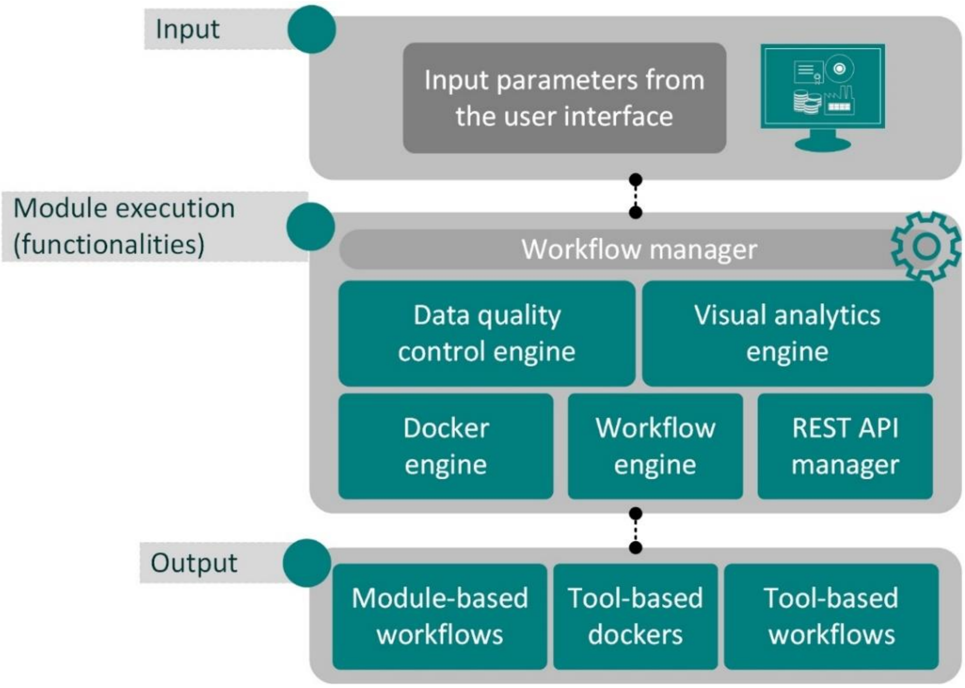

Figure 23: The proposed architecture of the Workflow Manager Module.

The workflow of the Workflow Manager Module consists of three fundamental stages (Figure 24). In the first stage, the module receives input parameters from the user's interface according to the user's input. Then, according to the selected type of analysis, the Workflow Manager Module constructs workflow and docker specifications, which are sent to the engines and from there to the rest of the modules and tools of the SILICOFCM platform. More specifically, if the type of analysis involves one of the following SILICOFCM modules: Data Management Module, and Visual Analytics Module, the data quality control engine and visual analytics engine are invoked, respectively, in order to distribute the workflows to the corresponding modules for execution.

If the type of analysis involves one of the following (workflow-based) tools: ALYA Solver Tool, PAK Solver Tool, MUSICO Tool, the workflow engine is invoked in order to distribute the workflows to these tools through REST services for execution. In addition, if the type of analysis involves one of the following (docker-based) tools: Data Analytics Tool, Virtual Population Tool, and Bioinformatics Tool, the Multiple Criteria Decision Making Tool the docker engine is invoked. Finally, the Workflow Manager Module outputs the results of the modules/tools of the SILICOFCM according to the type of analysis.

For example, if the selected type of analysis involves a SILICOFCM module, i.e., the Data Management Module, the workflow manager constructs the specifications of the data quality assessment workflows and sends them to the data quality control engine (i.e., invokes the data quality control engine) which in turn realizes and distributes the quality assessment workflows to the Data Management Module. The results are finally used by the Data Management Module to compose data quality assessment reports.

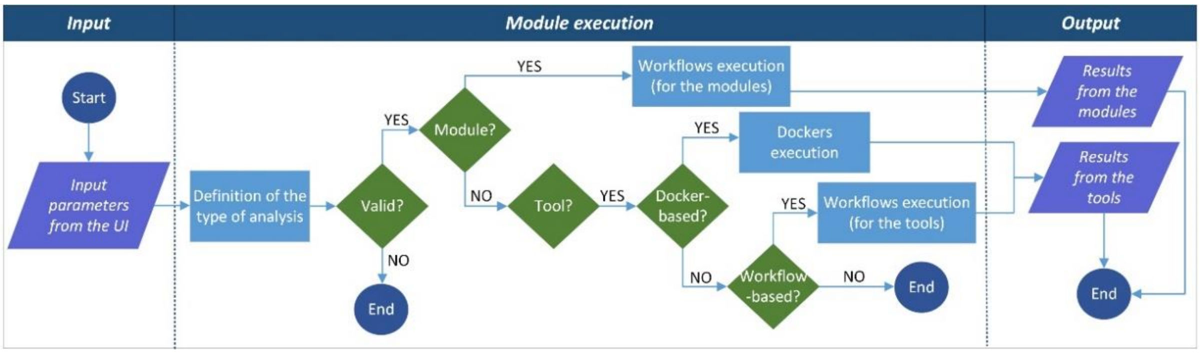

Figure 24: The proposed workflow diagram which depicts the functionality of the Workflow Manager Module.

4.4 Visual Analytics Module (VAM)

The following table describes the Visual Analytics Module, its dependencies with other modules/tools of SILICOFCM platform and the input and output.

Table 8: Technical overview of Visual Analytics Module.

#ID_M4	**Visual Analytics Module**
Short Description	
The Visual Analytics Module handles the graphical visualization interface which depicts the results of the SILIFOCFCM modules and tools.	
Scope	
To provide an API for the graphical visualization needs of the SILICOFCM platform.	
Responsibilities and pre-requisites	
Partner(s)	UOI/BIOIRC
Actors	Data provider Typical end-user Inner and outer developer
Priority	High
Dependencies	
Potential dependencies with the rest of the SILICOFCM modules/tools	Workflow Manager Module
SILICOFCM modules interaction and relationships	The Workflow Manager Module invokes the visual analytics engine which interacts with the Visual Analytics Module in order to execute the visual analytics workflows according to the type of analysis. The workflow manager is responsible for providing the correct visual analytic workflows according to the selected type of analysis.
Input and Output	
SILICOFCM input	• Parameters from the user interface • Anonymized clinical and genetic data • Visual analytic workflows (or dockers)

SILICOFCM output	• Quality assessment and statistical and reports • Results from the modules and tools

Architecture

The architecture of the Visual Analytics Module is depicted in Figure 25. The module receives as input: (i) the parameters from the user interface, (ii) anonymized clinical and genetic data, and (iii) visual analytics workflows (or dockers) from the Workflow Manager Module. Then, the module offers several functionalities related to: (i) the visualization of metadata, (ii) data inspection, (iii) the construction of workflow visualization components, and (iv) the construction of docker visualization components. The Visual Analytics Module outputs: (i) the quality assessment and statistical reports, and (ii) the results from the SILICOFCM modules and tools which are displayed to the user through the user interface.

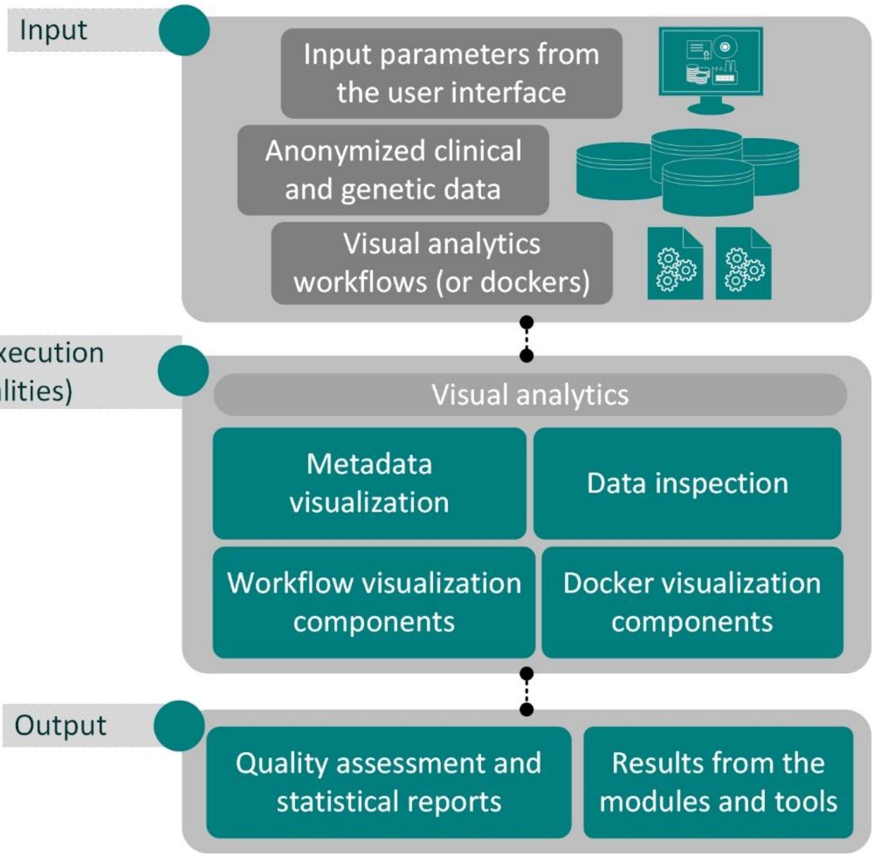

Figure 25: The proposed architecture of the Visual Analytics Module.

The Visual Analytics Module consists of three stages (Figure 26). In the first stage, the module receives the visual analytics workflows and/or dockers from the Workflow Manager Module through the visual analytics engine. According to the SILICOFCM module or the tool that requests the Visual Analytics Module either the workflow or the docker visualization components are executed.

The workflow visualization components refer to the visualization needs of the: (i) Data Management Module (data quality assessment report(s)), (ii) PAK Solver Tool, (iii) ALYA Solver Tool, and (iv) MUSICO Tool. The docker visualization components refer to the visualization needs of the: (i) Bioinformatics Tool, (ii) Data Analytics Tool, and (iii) virtual population Tool, (iv) Multiple Criteria Decision Making Tool for discrimination purposes. The workflow and docker visualization components are finally displayed to the user in a graphical manner through the user interface.

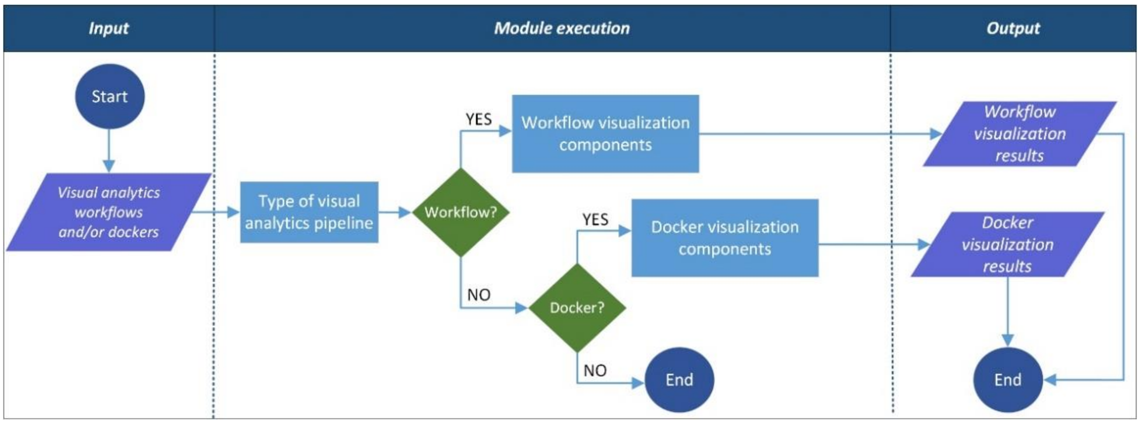

Figure 26: The proposed workflow diagram which depicts the functionality of the Visual Analytics Module.

The dependencies among the SILICOFCM modules and the relevant SILICOFCM modules/tools is summarised in the following table.

	UAMM	DMM	WMM	VAM	MT	AST	PST	DAT	BT	VTP	MCDMT
UAMM		x	x								
DMM	x		x								
WMM	x	x		x	x	x	x	x	x	x	x
VAM			x								

5. SILICOFCM Tools

5.1 MUSICO Tool (MT)

The following table describes the MUSICO Tool, its dependencies with other modules/tools of SILICOFCM platform and the input and output.

Table 9: Technical overview of MUSICO Tool.

#ID_T1	MUSICO Tool
Short Description	
MUSICO (MUscle SImulation COde) is a computational platform for modelling realistic sarcomeric system. It has been developed with the aim to simulate a wide variety of experimental muscle behavior. 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. Furthermore, multiple actomyosin cycle models and calcium regulatory models are incorporated. Nonlinear mechanical behavior of extensible filaments and cross-bridges is addressed using iterative finite element scheme. Moreover, in order to speed-up simulations, it is provided with parallelized computational algorithm.	
Scope	
The tool corresponds to tasks in WP5, where MUSICO has to be upgraded so it can predict the effect of known mutation (defined from in vitro protein studies) on the intact system. It can also do the reverse, take the data from intact muscle fiber studies and predict what molecular properties of the protein components need to have altered to produce the phenotype. It can also predict where in the ensemble of protein potential the targets for drug therapy may be found. Another aim is to make a link between bioinformatics programs developed in Tasks 4.1-4.3 and the MUSICO. 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. The final goal is to develop a link between MUSICO and FE biomechanical simulation. This also includes analyzing data from bioinformatics in integrative modelling solution. Monitored data will be processed with algorithms to calculate and prepare projections in real time for better, faster and more accurate diagnosis establishment and consequently better patient treatment.	
Responsibilities and pre-requisites	
Partner(s)	IIT and BioIRC
Actors	Typical end-user Inner and outer developer
Priority	High
Dependencies	
Potential dependencies with the rest of the SILICOFCM modules/ tools	ALYA Solver Tool PAK Solver Tool Bioinformatics Tool

SILICOFCM modules interaction and relationships	MUSICO Tool is an essential part of the SILICOFCM with a role to make a bridge between genetic data obtained from Gene analysis, sarcomeric protein changes and the functional changes in muscle contractility. The predicted modulated muscle dynamic characteristics are essential input information for simulations of whole heart behaviour using ALYA or PAK finite element solvers. Genetic data, extracted by the use of various Bioinformatics Tools (bioinformatics pipeline variant annotation pipeline), and modified kinetics and structural characteristics of sarcometic proteins will be used as inputs to simulations of modulated muscle function. MUSICO input parameters for the particular genetic variant are read from the predefined lookup table, and further used for redefining kinetics characteristics of sarcomeris protein interactions necessary for simulations of muscle fiber behavior or modulated heart function. Lookup table that maps genetic variants to the related MUSICO parameters will be obtained from the experiments performed in solution, motility assays, muscle fibers and tissues. MUSICO simulations will predict cardiac muscle behavior by matching higher length scale experiments (i.e. muscle fibers and tissues) by adjusting only a few free model parameters. The MUSICO can be used as an independent tool for analyzing impact of genetic variants or drugs on muscle protein functions and their consequences on muscle fiber behavior. In this case, specification of the MUSICO input parameters by the end-user and visualization of the results should be performed through a web GUI, providing an insight into repercussions of specific diseases or therapies on muscle tissue. Note that the web application is not an integral part of MUSICO and should be developed during the project. On the other hand, the results form MUSICO can be used as the input into modules for simulations of heart behavior on macro-scale, such as finite element solvers ALYA or PAK. On macro-scale, the muscle geometry is described by FE mesh, while the instantaneous material properties in each integration (Gaussian) point of each finite element should be calculated by MUSICO. Unfortunately, due to inherent computing complexity of MUSICO, such massive calls from FE solver would lead to unacceptable calculation duration for the simulation of even one hearth beat. Therefore, it is not realistic that MUSICO can be directly coupled with FE solvers. For these purposes MUSICO will be replaced with less calculation demanding modules based on mass-action laws or surrogate models built using machine learning techniques. In the first case, MUSICO will be used as software for the calibration of mass-action models to ensure that these simpler model predictions mimic MUSICO simulations and therefore translate the effects of genetic changes in sarcomeric proteins on cardiac tissue scale. In second case, MUSICO will be used as a generator of a number of input-output pairs, sufficient to teach an adequate regression surrogate model.
Input and Output	

SILICOFCM input

Simulation parameters

General parameters about simulation and the models used to describe different aspects of sarcomere are given in simulation.prm input file.

An example of simulation.prm input file:

```
# Listing of Parameters
# ---------------------
subsection global
  set model                 = Srba
  set model_slow_fileName   = model_srba_slow.prm
  set model_fast_fileName   = model_srba_fast.prm
  set xb_model              = ConstantStiffness
  set modelMyBPC            = DukeMyBPC
  set numerics              = MonteCarlo
  set random_seed           = 1
end
```

Numerical algorithm parameters

Input parameters about the numerical algorithm specified in simulation.prm are given in numerics_<algorithmname>.prm input file.

An example of numerics_mc.prm (for Monte Carlo numerical algorithm) input file:

```
# Listing of Parameters
# ---------------------
subsection monte_carlo
  set activation    = FChain
  set filaments     = 200
  set full_sarcomer = 0
  set geometry      = Vertebrae
  set caActivationModelIndicator = 1
end
```

Sarcomere geometry parameters

Input parameters about vertebrae sarcomere geometry are specified in geom_vertebrae.prm file.

Key geometry parameters are given in the following table:

Parameter	**Input variable**
Length of sarcomere	sarcomere_length
Area of the actin fiber cross section	a_actin1
Distance between two actin binding sites.	dx_actin
Elastic modulus for the actin fiber	e_actin1
Length of actin fiber	length_actin
Distance between actin’s first binding site and M line	a_offset
Distance between the center of the actin fiber and the center of the myosin fiber	d_actin_myosin
Radius of the actin fiber	radius_actin
Radius of the myosin fiber	radius_myosin
Area of the myosin fiber cross section	a_mysoin
Distance between two myosin crowns	dx_myosin
Elastic modulus for the myosin fiber	e_mysoin
Number of myosin crowns	myosin_crowns
Offset for the first myosin crown from M line	myosin_offset

An example of geom_vertebrae.prm input file:

```
# Listing of Parameters
# ---------------------
subsection actin
  set a_actin1          = 38.50000
  set a_actin2          = 38.50000
  set actin_period      = 13
  set dx_actin          = 2.7359
  set e_actin1          = 1.689000e+003
  set e_actin2          = 1.689000e+003
  set   length_actin               =   1099.8318   #   length_actin   =
(num_of_monomer_spacing + 1) * dx_actin
  set a_offset         = 42.4323 # a_offset = 0.5 * sarcomer_length -
length_actin - dx_actin
end
subsection axial
  set d_actin_myosin    = 27.667
  set radius_actin      = 3.500000
  set radius_myosin     = 7.900000
end
subsection myosin
  set a_mysoin          = 196.070000
  set dx_myosin         = 14.300000
  set e_mysoin          = 0.67323000e+003
  set myosin_crowns     = 50
  set myosin_offset     = 88.0000
  set slowHeads_percent = 0
  set fastHeads_percent = 100
end
subsection numerics
  set xamax             = 15.000000
end
subsection nebulin
  set nebulinDeficiency = 0
end
subsection titin
  set titin_enabled   = 0
  set titin_stiffness = 0.1172
end
```

Actomyosin cycle model parameters

Depending on the model chosen in *simulation.prm* input file the model parameters are specified in *model_<modelname>.prm* file.

Key geometry parameters for *Mijailovich-Geeves 6-state* actomyosin model are given in the following table:

Parameter	**Input variable**
Binding factor	G_bind
Myosin-actin binding rate	k_bind (k_{+A})
Myosin-actin detachment rate	k_unbindk_{-A}
ADP release rate	k_ADP (k_{+D})
Working stroke	D
Power stroke energy	GStroke
Second working stroke	delta
Energy released in a full actomyosin cycle	ener_cycle
Eta factor	eta
Temperature times Boltzmann constant	kBT
Myosin stroke rate	k_12 (k_{+Pi})
Myosin reverse stroke cap rate	k_21_cap (k_{-Pi_cap})

ATP binding and detaching myosin from actin	k_45 (k_{+T})
Hydrolysis forward	k_51 (k_{+H})
Hydrolysis backward	k_15 (k_{-H})
From "parked state"	k_61 (k_{+PS})
To "parked state"	k_16 (k_{-PS})
Kps factor	k_ps_0
Kpsmax factor	k_ps_max
Ca_{50} factor	ca_50
B parameter	b_param
Crossbridge stiffness	k

An example of model_srba.prm input file:

```
# Listing of Parameters
# ---------------------
subsection srba
  set D          = 10.5
  set GBind      = -1.742969305
  set GStroke    = 13.0
  set delta      = 1.0
  set ener_cycle = 24.155
  set eta        = 0.0
  set kBT        = 4.0
  set k_12       = 1000.0
  set k_21_cap   = 100.0
  set k_adp      = 80.0
  set k_bind     = 14.0
  set k_45       = 1000000.0
  set k_51       = 100.0
  set k_15       = 10.0
  set k_61       = 100.0
  set k_16       = 200.0
  set k_ps_0     = 10.0
  set k_ps_max   = 400.0
  set ca_50      = 1e-6
  set b_param    = 3.0
end
```

Calcium activation model parameters

Depending on the activation model chosen in *numerics_mc.prm* input file (*caActivationModelIndicator*) the model parameter are specified in different *prm* file. For heart calcium activation model, the parameters are specified in *CaActivation3x2s.prm* input file.

Key geometry parameters for *CaActivation3x2s* activation model are given in the following table:

Parameter	**Input variable**
ε_0	eps0
$\tilde{K}_1$	K_Ca
$\tilde{K}_1/\varepsilon_0$	K_Ca_p
k_1^-	k_Ca_off
$k_1^- \cdot \varepsilon_0$	k_Ca_off_p

$\tilde{k}_1^+$	k_Ca_on
$\lambda \cdot \varepsilon_0$	K_TnB
λ	K_TnB_p
λ^- (from State4 to State1)	k_c_b
λ^- (from State3 to State2)	k_c_b_p
$\lambda^+ \cdot \varepsilon_0$ (from State1 to State4)	k_b_c
λ^+ (from State2 to State3)	k_b_c_p

An example of *CaActivation3x2s.prm* input file:

```
# Listing of Parameters
# ---------------------
subsection Blocket2Closed_regulation
  set K_TnB   = 0.18320     # lambda*eps0, eps0 = 0.01
  set K_TnB_p = 18.3200     # lambda
  set k_c_b   = 375.0       # lambda-
  set k_c_b_p = 375.0       # lambda-
end
subsection Ca_regulation
  set K_Ca       = 154103.9895      # K1tilda
  set K_Ca_p     = 15410398.95      # K1tilda / eps0
  set k_Ca_off   = 88.0             # k1-
  set k_Ca_off_p = 0.88             # k1- * eps0
end
subsection structure
  set segment_length = 7
end
```

Mechanical protocol file

Input data about mechanical protocol applied to sarcomere is given in *protocol.dat* input file.

The protocol file controls the type and time course of mechanical loads which will be prescribed during the simulation run. It contains one or more lines, which are composed of at least 5 entries.

The first parameter defines the time at which the simulation should switch from one mode to another mode, while second parameter defines the size of time step.

After that the type of boundary condition is defined. Currently four boundary conditions are implemented. While this field defines the type of boundary, the value for this boundary condition can currently be defined by three different types of functions (constant, linear, and sine).

One example, which defines isometric conditions followed by isotonic conditions with a prescribes force per filament of 430pN looks like:

```
0.0 1.0e-5 0 0 0
0.5 1.0e-5 1 0 430
1.0 1.0e-5 1 0 430
```

At t = 0.5, the boundary mode is switched from prescribed displacements to

	prescribed forces. The last line defines the end of the simulation. **Calcium activation protocol file (ca_protocol.dat)** Input data about calcium activation protocol applied to sarcomere is given in ca_protocol.dat input file. The protocol file for the time course of calcium concentration is given in the same format as the mechanical protocol.

SILICOFCM output	Outputs from the MUSICO software are typically given in CSV format, and contain the following data for each time step of the simulation:
	• Forces developed
	• Displacements of key sarcomere points
	• Number of cross-bridges in each of actomyosin cycle states
	Data about spatial distribution of cross-bridges in some specific state for chosen time can also be written in separate output files.
	An example of output file containing time course results (result.csv):
	`Time,Force,Displacement_last_myosin_node,Displacement_last_actin_nod e,CB_per_filament,CB_ProteinC_per_filement`
	`0.00001000000, 0.00000e+00, 0.00000e+00, 0.00000e+00, 0.00000e+00,`
	`0.00002000000, 0.00000e+00, 0.00000e+00, 0.00000e+00, 0.00000e+00,`
	`0.00003000000, 0.00000e+00, 0.00000e+00, 0.00000e+00, 0.00000e+00,`
	`0.00004000000, 0.00000e+00, 0.00000e+00, 0.00000e+00, 0.00000e+00,`
	…

Workflow of calculations within MUSICO.

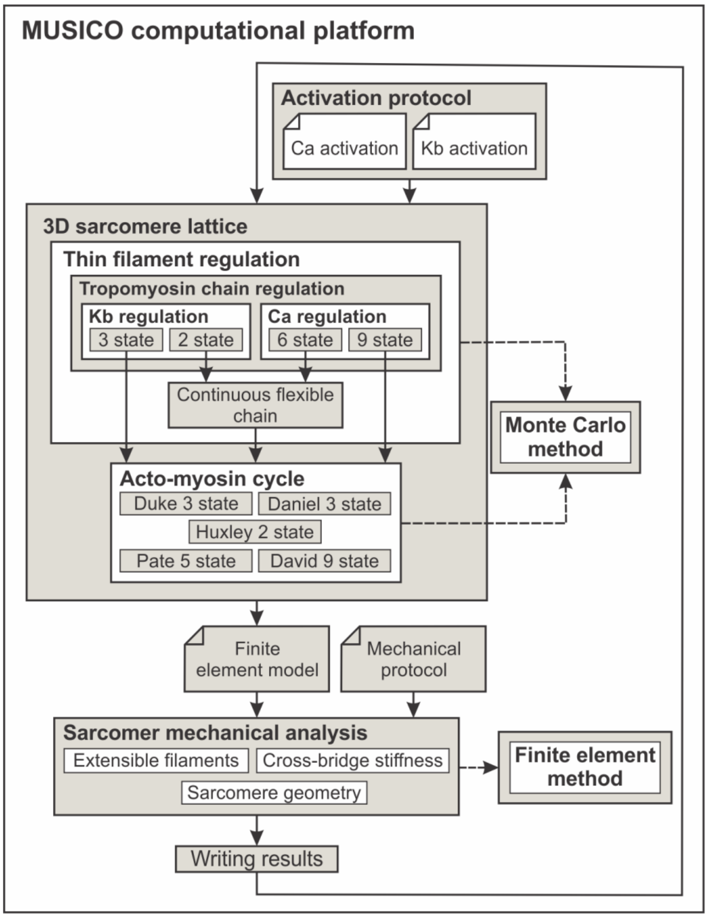

Figure 27: The proposed workflow diagram which depicts the functionality of the MUSICO.

According to the prescribed activation protocol, simulation of the sarcomere behavior is performed in a number of time steps. Within a single time-step, both chemical and mechanical changes are calculated. Chemical transitions are calculated in the modules for thin filament regulation and actomyosin cycle, taking into account current spatial distribution of actin and myosin proteins. Once the myosin and actin protein transitions are calculated, a new constellation of cross-bridges is known, so the mechanical model of the sarcomere can be created using finite element method. After the calculation of equilibrium forces and displacements within the FE model, a new geometry of the sarcomere is obtained. At the end of the time step all relevant state variables, including displacement and forces of key sarcomere points, as well myosin and actin states, are written in output files. Geometry of the sarcomere at the end of the current time step is used as a reference point for the calculation in the next time point (Figure 28).

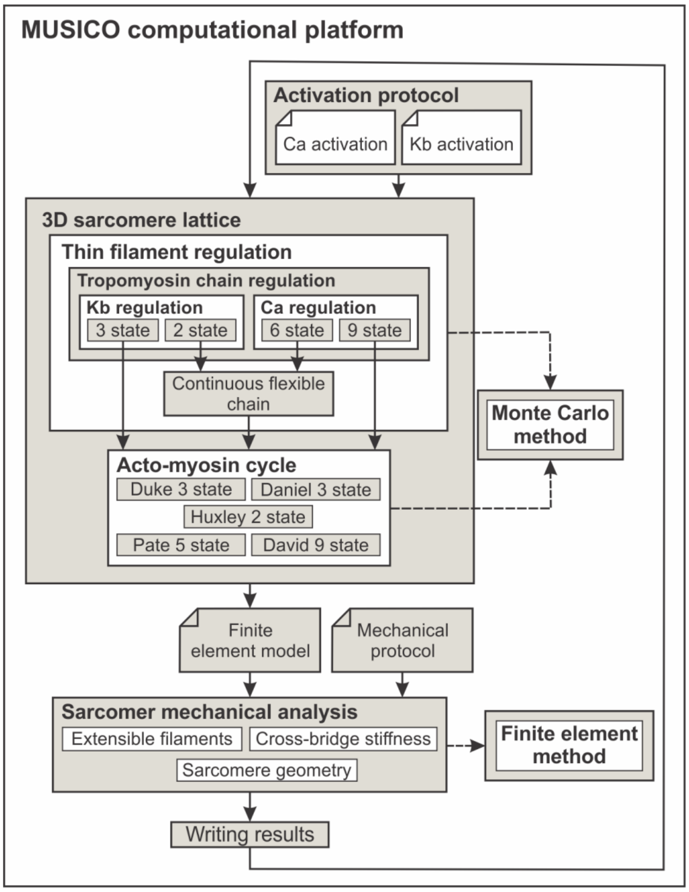

Figure 28: The proposed workflow diagram which depicts the functionality of the MUSICO.

5.2 ALYA Solver Tool (AST)

The following table describes the ALYA Solver Tool (FEA solver), its dependencies with other modules/tools of SILICOFCM platform and the input and output.

Table 10: Technical overview of ALYA Solver Tool.

#ID_T2	**ALYA Solver Tool**
Short Description	
Alya Red is a finite element solver specialised on exploiting high performance computing to create	

mathematical, multiscale, multiphysics computer simulations of the heart and cardiovascular system. It is capable of simulating the electrical cardiac activity, and the cardiac contraction employing state of the art mathematical models in a tightly coupled fashion.	
Scope	
Alya RED is the finite element software selected to be coupled to the software MUSICO to create highly detailed multi-scale simulations of the sarcomere dynamics up to the whole heart behaviour to understand the effect of sarcomeric protein mutations leading to familial cardiomyopathies.	
Responsibilities and pre-requisites	
Partner(s)	BSC
Actors	Typical end-user Inner and outer developer
Priority	High
Dependencies	
Potential dependencies with the rest of the SILICOFCM modules/tools	MUSICO Tool Data Analytics Tool
SILICOFCM modules interaction and relationships	MUSICO is a software tool capable of solving atomistic-to-sarcomere level simulations to study sarcomeric protein mutations. The main aim is to couple MUSICO and ALYA RED, the BSC's finite element code to produce the most detailed cardiac simulations ever created to understand familial cardiomyopathies up to the whole organ function. Regarding the Machine Learning Framework, whole heart simulations of patient-specific mutations will produce a large amount of data that can be analysed for biomarker discovery and patient stratification.
Input and Output	
SILICOFCM input	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 fiber 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 plus manual refinement by experts will be required (potential software that

	could be employed: Seg3D) 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. Fiber 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.
SILICOFCM output	Alya provides an output in the ensight format that can be visualized with software like Paraview or if it is web-based, WebGL could be employed. As output Alya can provide: electrical propagation, stresses, strains, deformation, ejection fraction or any other variable computed at every node or gauss point and at any time step postprocessed.

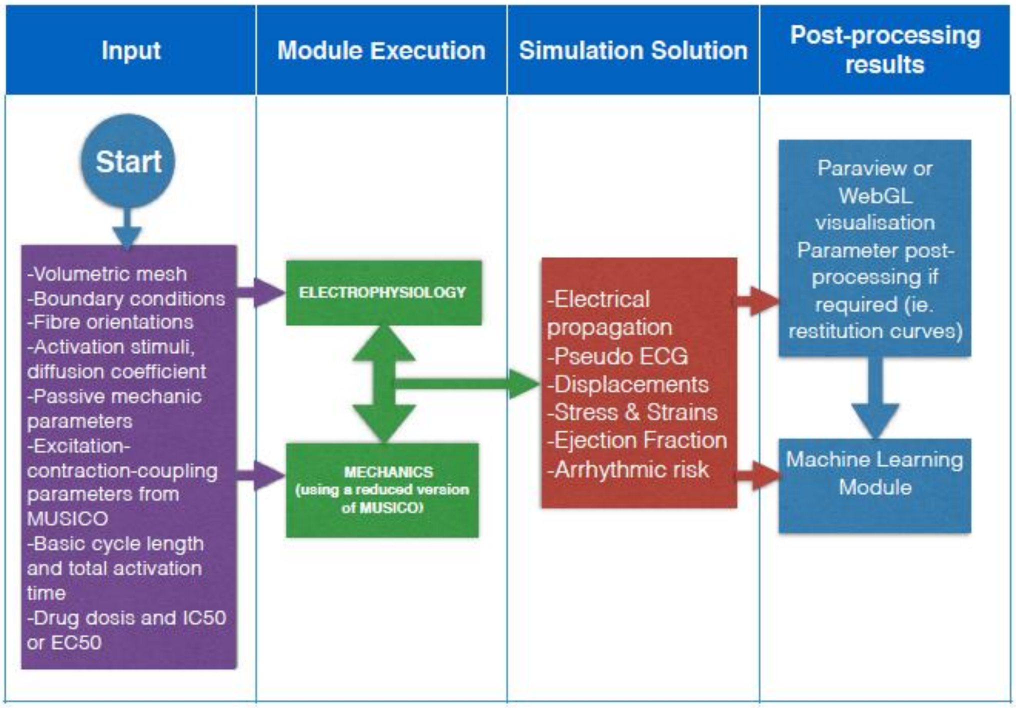

Figure 29: The proposed workflow diagram which depicts the functionality of the Alya Solver.

5.3 PAK Solver Tool (PST)

The following table describes the PAK Solver Tool (FEA solver), its dependencies with other modules/tools of SILICOFCM platform and the input and output.

Table 11: Technical overview of PAK Solver Tool.

#ID_T3	**PAK Solver Tool**
Short Description	
The PAK Solver Tool will provide high performance FEM code to solve complex coupled multi-physics / multi-scale problems in heart tissue. Among different physics solved by PAK will be: fluid flow, non-linear solid mechanics, drug transport, electrophysiology, ionic transport, coupled ionic and electric transport, and mechanics coupled with electric field and drug transport. The outputs of the module will be drug distribution, stress distribution and deformations of heart tissue. The outputs are expected to be used by end users (medical experts in the field of cardiomyopathy) to simulate outcomes of different therapies and provide explanations for therapy outcomes using different drugs.	
Scope	
The module corresponds to tasks in WP5, where one of aims are to: (i) upgrade current FE biomechanical simulation of whole heart, (ii) link MUSICO and FE biomechanical simulation. The goal of the module is to develop FE multiscale simulation tool for predictive modeling and predictive evaluation of drug distribution and mechanical response of heart tissue using data from MUSICO simulation. This also includes data analysis from bioinformatics in integrative modeling solution. The result of these tasks will be visualized medical knowledge that explains interdependencies between input drug distribution, material characteristics and disease occurrences. Computer model simulations will be suited for predicting personalized physiology, functional disorders and other diseases. Simulations will be performed for a number of patients, and prediction will be used for generation of machine learning / data mining predictive models in order to provide an identification of high-risk patients. The work will encompass testing, evaluation and validation of improvements of acquired FE multiscale and multiphysics model.	
Responsibilities and pre-requisites	
Partner(s)	BIOIRC
Actors	Typical end-user Inner and outer developer
Priority	High
Dependencies	
Potential dependencies with the rest of the SILICOFCM modules/tools	MUSICO Tool
SILICOFCM modules interaction and relationships	PAK Solver will be directly coupled with MUSICO in order to predict accurate drug distribution and mechanical deformations of heart tissue during time. PAK module for coupled ionic and electric transport will solve field of Calcium (Ca) concentration within tissue. MUSICO will use current concentration of Ca and deformation to solve stresses in each Gauss point of FE model of heart tissue. Calculated stresses will be used in PAK module

	for mechanics coupled with drug and electric transport for calculation of mechanical response.
Input and Output	
SILICOFCM input	Necessary inputs to the module are: • Geometry input file: Reconstructed 3D geometry of human heart from patient specific data, including heart tissue coronary arteries and veins (STL files and files with 1D centerlines of arteries and veins). • Material properties input file (characteristics of drug transport, ionic transport and electric field, and mechanical characteristics of heart tissue) • Boundary condition input file (prescribed entering drug concentration, ionic concentration, fluid flow velocities, etc) Reconstruction of heart geometry will be performed in pre-processing phase using mesh reconstruction algorithms, and our indoor CAD interface software will be responsible for preparation of PAK Solver execution input file.
SILICOFCM output	The outputs of the tool incudes: • drug concentration in heart model • concentration of ions in heart model • field of electric potentials in different compartments of heart model • results of mechanical deformations of heart tissue Outputs will be written in formats available in CAD (.unv) and Paraview (csv, vtk) visualization software's.

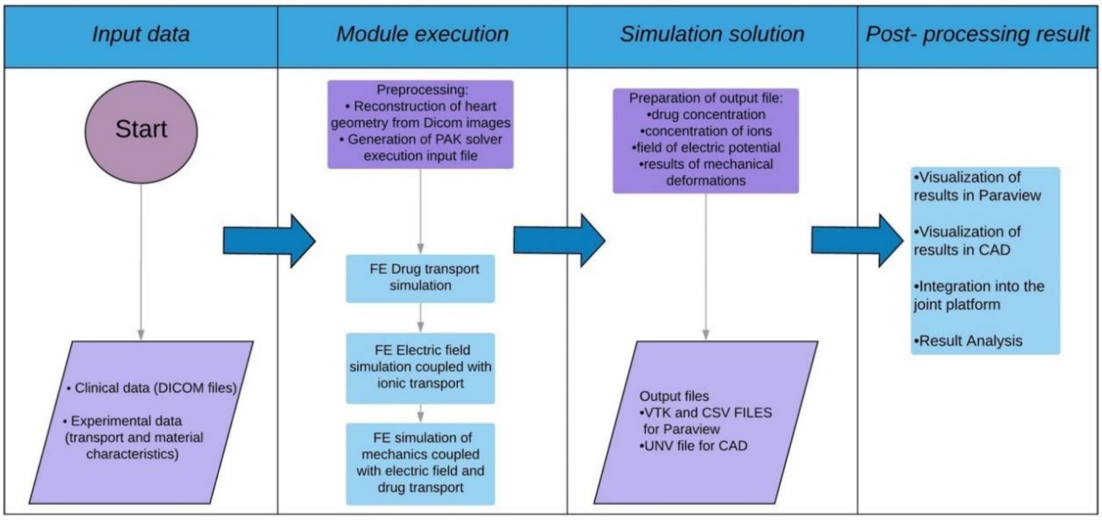

Figure 30: The proposed workflow diagram which depicts the functionality of the PAK Solver.

5.4 Data Analytics Tool (DAT)

The following table describes the Data Analytics Tool, its dependencies with other modules/tools of SILICOFCM platform and the input and output.

Table 12: Technical overview of Data Analytics Tool.

#ID_T4	**Data Analytics Tool**
Short Description	
The Data Analytics Tool provides machine learning / data mining services to end-users by analyzing stored datasets and focusing on two tasks: • providing cardiomyopathy risk stratification of patients (WP4, Task 4.4), • predictive modeling and prediction evaluation for virtual patients (WP6, Tasks 6.3 and 6.4). The outputs of the tool 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.	
Scope	
The tool corresponds to tasks in WP4 and WP6. In WP4, the aim is to develop a cardiomyopathy risk stratification tool based on data mining algorithms. UL with SBG, BIOIRC and UOI will use specialized data mining methods for supervised and unsupervised learning in order to mine heterogeneous patient data and thus provide an identification of high-risk patients (sudden cardiac death or life threating arrhythmias) that will be supplemented by prediction reliability estimates. In WP6, algorithms for explanation of predictive models and predictions will be used to provide efficient and reliable identification of disease patterns from large volumes of heterogeneous and noisy data. The result of this task will be visualized medical knowledge that explains interdependencies between patterns in data and disease occurrences. The work will encompass also testing, evaluation and validation of improvements of acquired machine learning models.	
Responsibilities and pre-requisites	
Partner(s)	UL
Actors	Typical end-user Inner and outer developer
Priority	High
Dependencies	
Potential dependencies with the rest of the SILICOFCM tool/modules	MUSICO Tool ALYA Solver Tool PAK Solver Tool Bioinformatics Tool Virtual Population tool Multiple Criteria Decision Making Tool Docker containers for exchange of code
SILICOFCM modules interaction and relationships	The Data Analytics Tool is not directly dependent on workings of the listed modules, but rather on data that are collected and stored within them. These data are the required input for design, implementation and testing of the data mining tools.
Input and Output	

SILICOFCM input	• data sources that are relevant for patient risk stratification
	  ○ clinical data
	  ○ genetic data
	• data sources containing virtual patients
	  ○ virtual patients repository

	A standard approach for accessing these data sources should be providing, either: • in the form of importable text/binary files (.xls, .csv, .arff, .RData etc.) • as the given access to a database (SQL/Oracle views), • as a provided API for retrieving the data. • as the Docker

SILICOFCM output	The outputs are dependent on the data mining task and shall consist of:
	• **task: patient risk stratification**
	  ○ visualization (.tiff, .jpg, .pdf or similar) that represents clustering (unsupervised learning) of patients into the most apparent risk groups,
	  ○ assignment (given in a form of exportable text/binary files, e.g. .xls, .csv, .arff, .RData etc.) of existing and virtual patients into risk groups, along with reliability estimates for this assignment.
	• **task: modeling virtual patients**
	  ○ graphs (.tiff, .jpg, .pdf or similar), displaying explanation of predictive models and predictions built from the virtual patients data,
	  ○ history of evaluation reports containing performance analysis of the developed predictive models. The repots will be used to iteratively improve prediction quality.

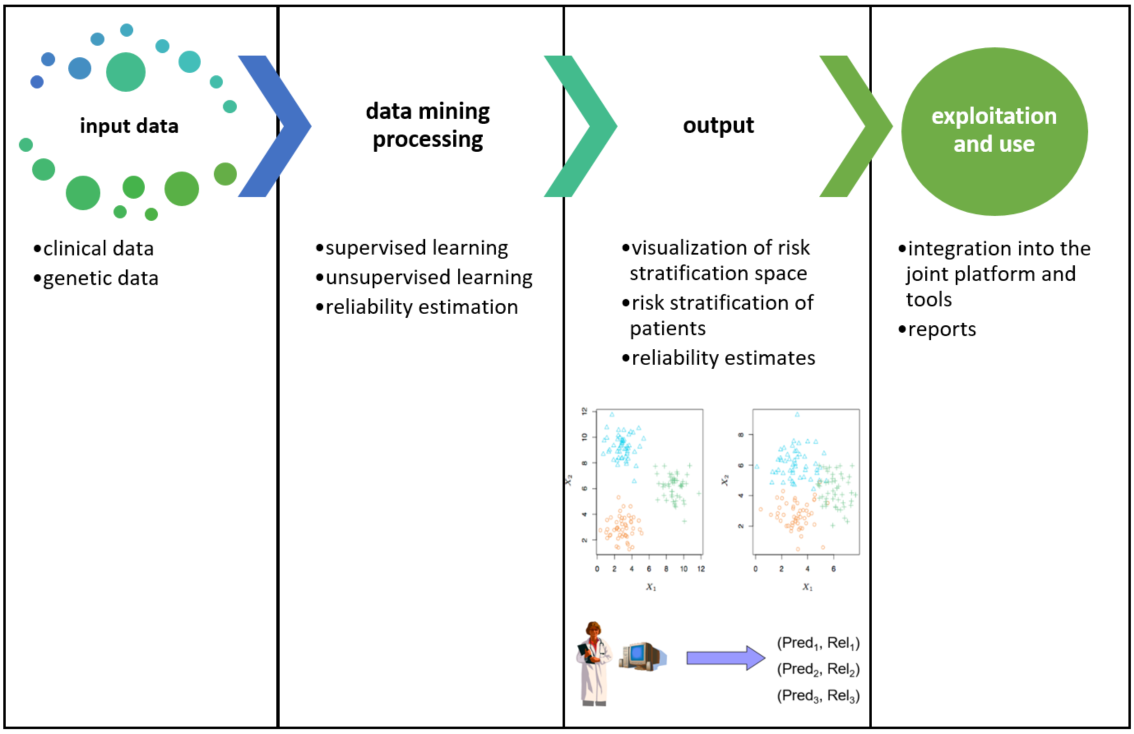

Figure 31: The proposed workflow diagram which depicts the Risk Stratification workflow.

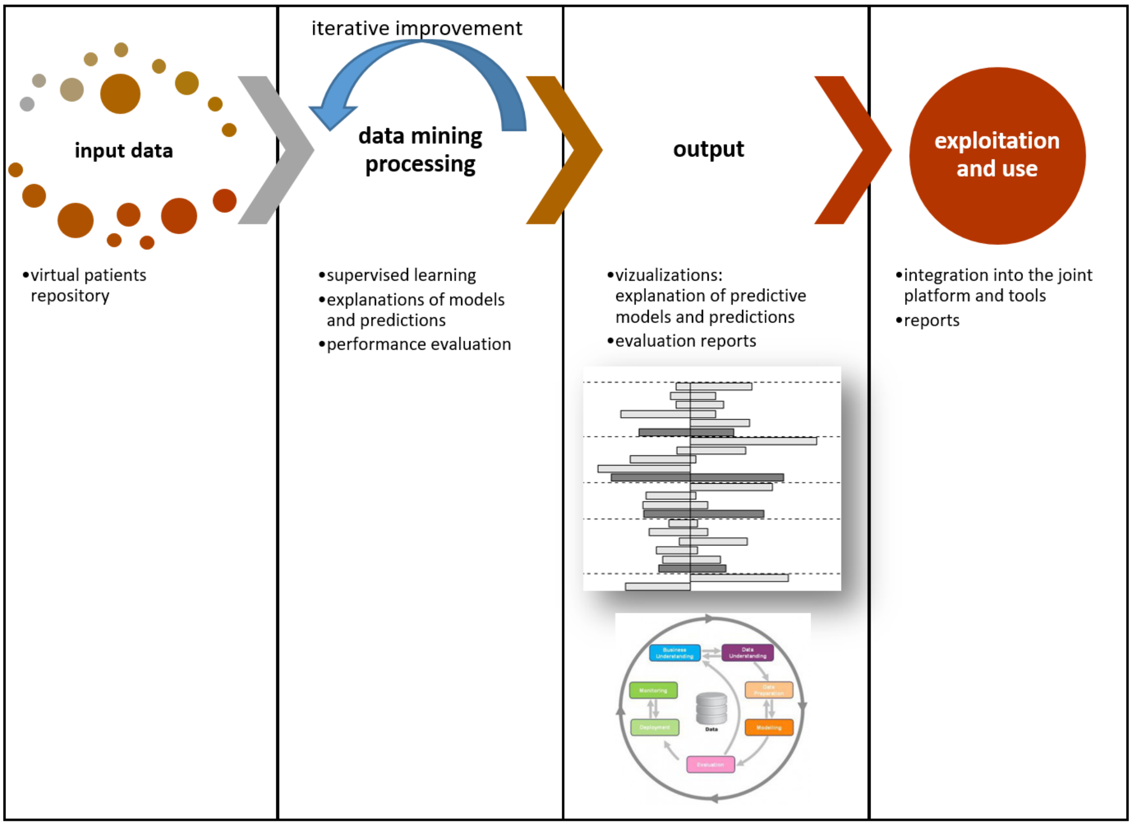

Figure 32: The proposed workflow diagram which depicts the Virtual Population utilization from the data analytics tool.

5.5 Bioinformatics Tool (BT)

This section describes the Bioinformatics Tool integrated into the SILICOFCM platform and the two bioinformatics workflows which will be run on the SILICOFCM platform. The BT will be integrated as a docker image in the platform and it will execute predefined bioinformatics workflows through Common Workflow Language (CWL), with a set of default input parameters and reference inputs.

Table 13: Technical overview of Bioinformatics Tool.

#ID_T5	**Bioinformatics Tool**
Short Description	
Targeted Sequencing GATK workflow is a standard bioinformatics workflow using a linear reference genome and tools from the GATK toolkit. Targeted Sequencing - SBG Graph workflow replaces the linear reference genome with a graph genome incorporating known hypertrophic cardiomyopathy -associated variants. Variant data for building the graph used in this workflow has been collated from multiple sources (Atlas of Cardiac Genetic Variation, published studies, SILICOFCM clinical groups).	
Scope	
Processing of targeted sequencing data from hypertrophic cardiomyopathy patients	
Responsibilities and pre-requisites	
Partner(s)	SBG
Actors	Typical end-user Inner and outer developers
Priority	High
Dependencies	

Potential dependencies with the rest of the SILICOFCM modules/tools	Data Analytics Tool Multiple Criteria Decision Making Tool
SILICOFCM modules interaction and relationships	Outputs of the described module will be used as inputs of the downstream risk-prediction machine learning algorithms.
Input and Output	
SILICOFCM input	• Raw sequencing data (paired-end FASTQ or FASTQ.GZ files) • Reference genome file (FASTA or Graph alternative) • Targeted sequencing gene panel BED file
SILICOFCM output	Identified variants in VCF format (or an adjusted output format suitable for ingestion by machine learning algorithms downstream).

The two workflows are designed to process targeted sequencing data of Hypertrophic Cardiomyopathy patients.

- Targeted Sequencing GATK workflow is a standard bioinformatics workflow using a linear reference genome and tools from the GATK toolkit.
- Targeted Sequencing - SBG Graph workflow replaces the linear reference genome with a graph genome incorporating known hypertrophic cardiomyopathy -associated variants. Variant data for building the graph used in this workflow has been collated from multiple sources (Atlas of Cardiac Genetic Variation, published studies, SILICOFCM clinical groups).

Both workflows use raw sequencing data (FASTQ files) as input, perform alignment and variant calling and output variants in VCF format (possibly modified to accommodate the requirements of downstream machine learning algorithms used by other members of SILICOFCM). Additional inputs include reference files (genome FASTAs, aligner indices, and known variants data) and BED files describing the regions that were targeted. Input FASTQ files and the BED file should be provided by the user.

The workflow will be supplied with a set of default parameters. If you wish for end-users to adjust the parameters used for running the workflow, this is possible, however, SILICOFCM platform would have to design the system to expose this option to the end-users. The default parameters are set to represent reasonable defaults.

The workflows do not require any special input hierarchy or creation of additional virtual environments (aside from Docker containers which are used to run the tools). All outputs are by default created in the working directory of the tools (this can be modified).

5.6 Virtual Population Tool (VPT)

This section describes the Virtual Population Tool integrated into the SILICOFCM platform and a typical workflow which will be run on the SILICOFCM platform.

Table 14: Technical overview of Virtual Population Tool.

#ID_T6	**Virtual Population Tool**
Short Description	

<table>
<tr><td colspan="2">The Virtual Population Tool is a tool integrated in the SILICOFCM platform which wil be used to create virtual populations of patients with FCM where this population eneration involves the production of synthetic characteristics and properties simulation the real ones.</td></tr>
<tr><th colspan="2">Scope</th></tr>
<tr><td colspan="2">The VPT will provide a virtula population repository with virtual patients that should have:
• Physiologically relevance
• Clinically relevance
• Indentifiable from available data
The VPT will create new virtual patients based on the prospective and retrospective data from SILICOFCM such as: Medical history and physical examination; various ventricles geometries form the imaging clinical data; laboratory tests; etc.</td></tr>
<tr><th colspan="2">Responsibilities and pre-requisites</th></tr>
<tr><td>Partner(s)</td><td>UOI, UL</td></tr>
<tr><td>Actors</td><td>Typical end-user
Inner and outer developer</td></tr>
<tr><td>Priority</td><td>High</td></tr>
<tr><th colspan="2">Dependencies</th></tr>
<tr><td>Potential dependencies with the rest of the SILICOFCM modules/tools</td><td>MUSICO Tool
ALYA Solver Tool
PAK Solver Tool
Data Analytics Tool</td></tr>
<tr><td>SILICOFCM modules interaction and relationships</td><td>Outputs of the described tools will be used as inputs of the downstream virtual population generation workflow.</td></tr>
<tr><th colspan="2">Input and Output</th></tr>
<tr><td>SILICOFCM input</td><td>• data sources that are relevant for the virtual population creation: clinical data, laboratory data, ventricle geometries
A standard approach for accessing these data sources should be providing, either:
• in the form of importable text/binary files (.xls, .csv, .dat)
• as the given access to a database
in the form of 3D representation files (.stl, .obj)</td></tr>
<tr><td>SILICOFCM output</td><td>The outputs consists of
• Files in the form of raw format (.csv, .xls, .dat)
• Records of databases (structured and unstructured)</td></tr>
</table>

Workflow

The following figure describes a typical workflow of the Virtual Population Tool executed by the end-user operators of SILICOFCM platform. The platform gives the capability to the end user to select form the repositories real data and fine tune the model input parameters in order for the latter to generate plausible populations for the *in-silico* modelling of FCM through the provided simulation and data informatics tools.

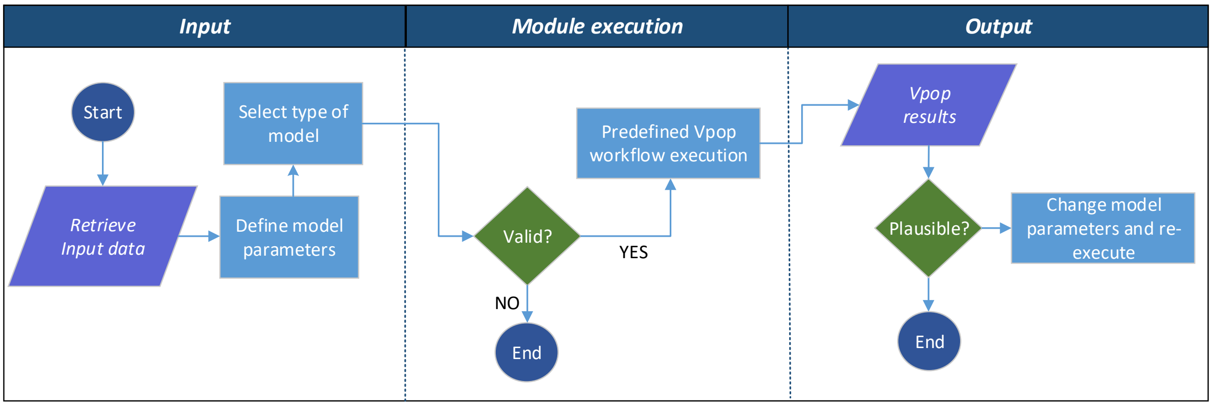

Figure 33 Typical workflow of the virtual population tool

5.7 Multiple Criteria Decision Making Tool (MCDMT)

In this section the Multiple Criteria Decision Making Tool (MCDMT) integrated into the SILICOFCM platform and a typical workflow which will be run on the SILICOFCM platform is described

Table 15: Technical overview of Multiple Criteria Decision Making Tool.

#ID_T7	**Multiple Criteria Decision Making Tool**
Short Description	
Multi-Criteria-Decision-Making Tool is tool integrated in the SILICOFCM platform which will be used to support the selection of different alternative-treatments.	
Scope	
Multi-Criteria Decision-Making Tool (MCDMT) is a discipline aimed at supporting decision makers who are faced with numerous and conflicting decisions. MCDMT aims at deriving a quantitative and unambiguous way to come to an optimal compromise in a transparent process. It will be developed to provide support in the selection of different alternative-treatments against heart diseases, e.g. surgery, medication, therapies etc.	
Responsibilities and pre-requisites	
Partner(s)	R-Tech
Actors	Typical end-user
Priority	High
Dependencies	
Potential dependencies with the rest of the SILICOFCM modules/tools	Bioinformatics Tool Data Analytics Tool
SILICOFCM modules interaction and relationships	Input data for the MCDMT module will be taken from the above tools.
Input and Output	
SILICOFCM input	• Determine set of alternatives • Determine set of relevant criteria • The criteria can be prioritized by assigning weights to them

	• Summing the values - weights or local priorities of the criteria and the alternatives are calculated
SILICOFCM output	The development of MCDMT will support the selection of different alternative-treatments against FCM. The alternative treatments will be studied with respect to a wide range of criteria.

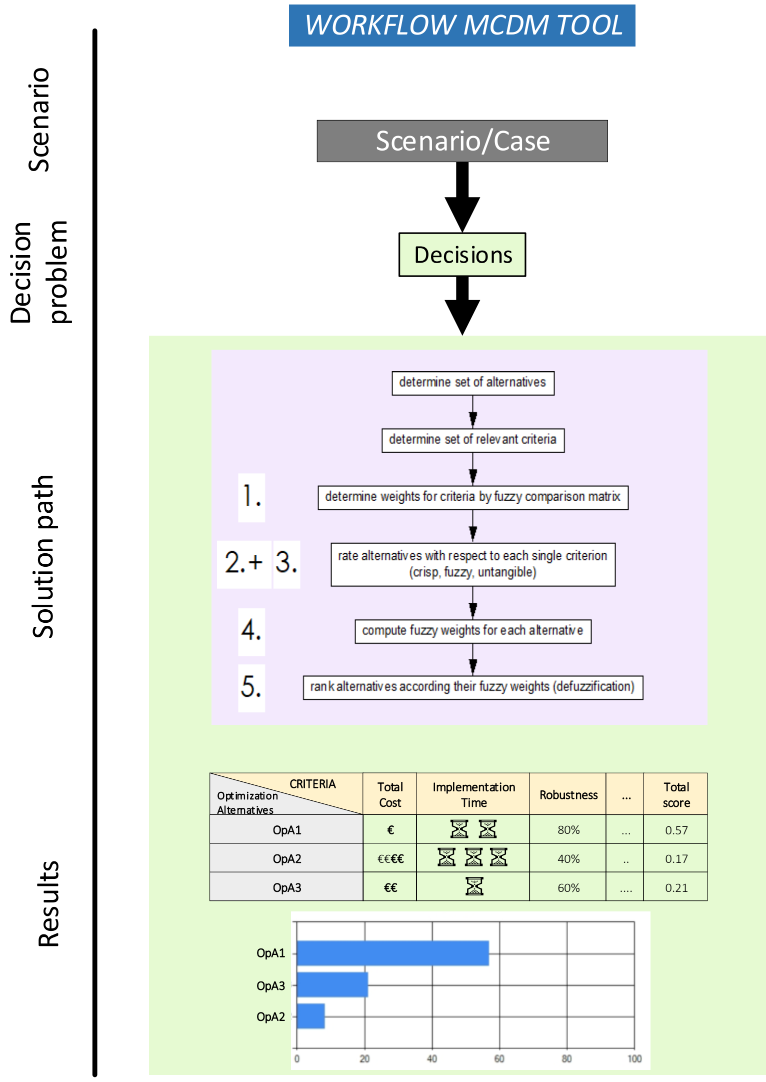

Figure 34: The proposed workflow diagram of the Multiple Criteria Decision Making Tool.

6. SILICOFCM cloud platform architecture

6.1 The SILICOFCM Cloud framework

The SILICOFCM framework can be realized in the form of a conceptual hierarchical multilayer schema (Figure 35). The framework consists of five layers. At the bottom lies the hardware layer where the cloud resources, i.e., CPUs, RAM, VMs, are defined, along with any additional resources. Right above the hardware layer lies the security layer where the OAUTH2 API framework is incorporated along with additional mechanisms for user access management, user authentication and secure communication within the platform. In the third layer lies the workflow layer which is the core of the services. The workflow layer includes all the engines that are coordinated by the Workflow Manager Module. These engines include: (i) the workflow engine, (ii) the docker engine, (iii) the data quality control engine, and (iv) the visual analytics engine. Each one of these engines is directly involved with the SILICOFCM tools and modules that lie on the fourth layer, i.e., the back-end layer. For example, the workflow engine is responsible for the execution of workflows which are related with the MUSICO Tool, ALYA Solver Tool, PAK Solver Tool that comprise the main SILICOFCM tools. In addition, the engines are further involved in the execution of the SILICOFCM modules. For example, the visual analytics engine is invoked when the user wishes to visualize the results of a tool through the Visual Analytics Module. The final layer is the front-end layer which includes the user interface and the visual analytics.

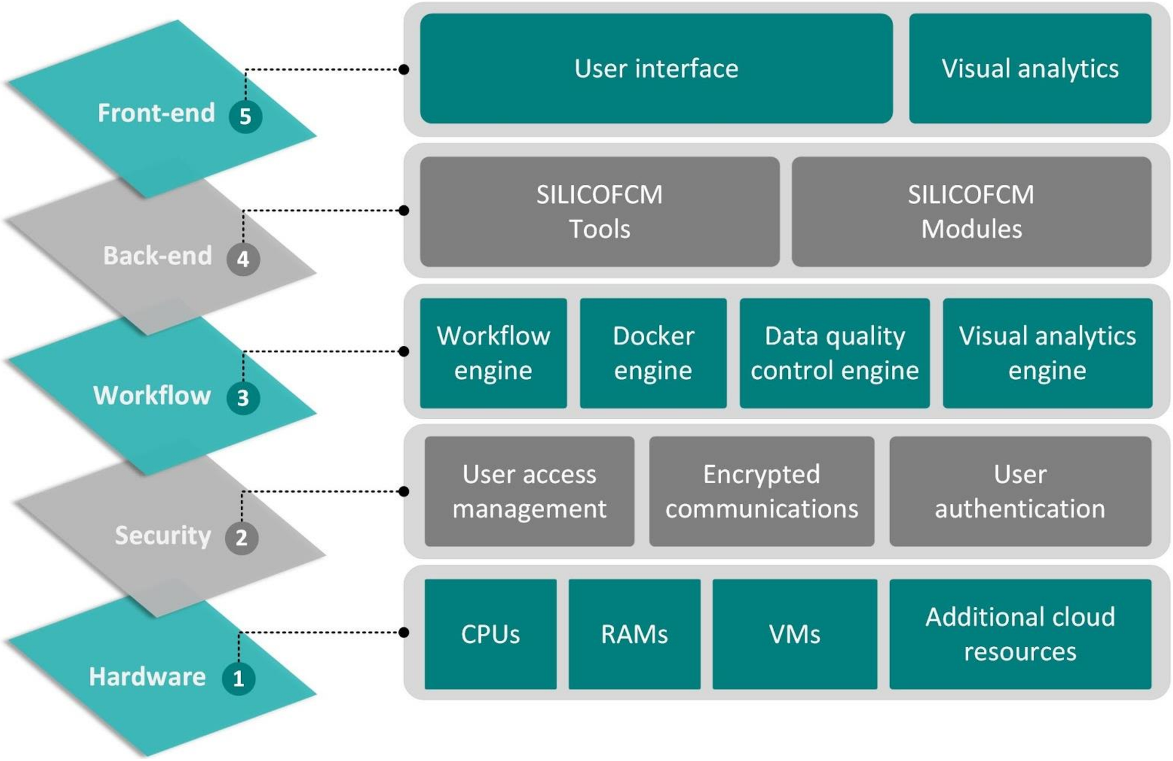

Figure 35: The SILICOFCM conceptual multi-layer hierarchical framework.

According to the types of the cloud computing services, the layers can be classified as follows:

- Front-end layer: Software as a Service (SaaS)
- Back-end layer: Software as a Service (SaaS)
- Workflow layer: Provider as a Service (PaaS)
- Security layer: Provider as a Service (PaaS)
- Hardware layer: Infrastructure as a Service (IaaS)

According to the user's type that is involved with each layer:

- Front-end layer: Cloud administrator, typical end-user.
- Back-end layer: Cloud administrator, inner developer.
- Workflow layer: Cloud administrator, inner developer, outer developer.
- Security layer: Cloud administrator.
- Hardware layer: Cloud administrator.

The typical user access flow is described below:

- The SILICOFCM user gains access into the SILICOFCM graphical user interface from the front-end layer through any web browser. From there, the user can request the SILICOFCM cloud services.
    - The connection and communication between the cloud server and the web browser is performed through the Hypertext Transfer Protocol (HTTP) which sends and receives requests between two hosts through a secure tunnel. In fact, the HTTP protocol is established through an HTTP-within-SSL/TLS or simply HTTPS (see the security layer next).
- The back-end layer receives the user requests, on-demand, and categorizes them according to whether they involve the tools or the modules of the platform.
- The workflow layer receives and handles the requests that are made by the user. The core of this layer is the Workflow Manager Module which lies in the middle of the cloud layers. It invokes:
    - the data quality control engine when a data-provider wishes to assess the quality of the clinical data through the Data Management Module,
    - the visual analytics engine when a data provider wishes to view the results from the data quality assessment or when a typical-end user (or developer) wishes to view the results of the rest of the SILICOFCM modules and tools,
    - the workflow engine or the docker engine when a typical-end user (or developer) wishes to run a SILICOFCM tool (or any data analytics service), where the workflows are executed through REST APIs that transfer the workflows and return the results in JSON formats, and
    - the REST API engine when a SILICOFCM service requires additional cloud resources due to high computational needs.
- The Workflow Manager Module interacts with the security layer for user access management and user authentication, where:
    - the Secure Sockets Layer (SSL)/Transport Layer Security (TLS) protocol is used to encrypt and decrypt sensitive information (e.g., login credentials) between the web browser and the cloud server based on public decryption keys and private encryption keys,
    - the users are classified according to their role as: (i) data providers, (ii) typical end-users, (iii) inner and outer developers, and (iv) cloud administrator(s), through appropriate queries and related interactions with the users' credentials database, and
    - the communication among the cloud layers is accomplished through secure tunnels.
- The hardware layer includes all the necessary hardware infrastructure for the establishment of the VMs, including, networks, servers, storage units, memory units, CPUs, I/O controllers, etc.

6.2 Distribution of the cloud services

The overall schema regarding the distribution of the cloud computing services to the SILICOFCM users is depicted in Figure 36. Only the users that are the actual receivers of the cloud services are depicted. The data provider requests those services that are related to the data management operations, the typical-end user requests the services which are related to the analytics operations, and finally the outer developer can evaluate new workflows (e.g., data models) on the anonymized clinical data. Everything starts from the bottom part which includes the hardware infrastructure and the software components. The hardware infrastructure consists of the hardware resources that have been already described in the hardware layer of Figure 35. whereas the software components include the operating system, as well as, any software programs and sockets that are necessary for the development of the back-end services. The hardware infrastructure is combined with the software components in order to construct VMs which are required for the development of the back-end services. Furthermore, the bottom level includes the security components (i.e., the SSL/TLS protocols and the OAUTH2 framework) which are invoked during the user authentication and user access management procedures (see the security layer in Figure 35 and use any necessary resources from the hardware infrastructure and the software components, as well as, from the users' credentials private database for user authentication.

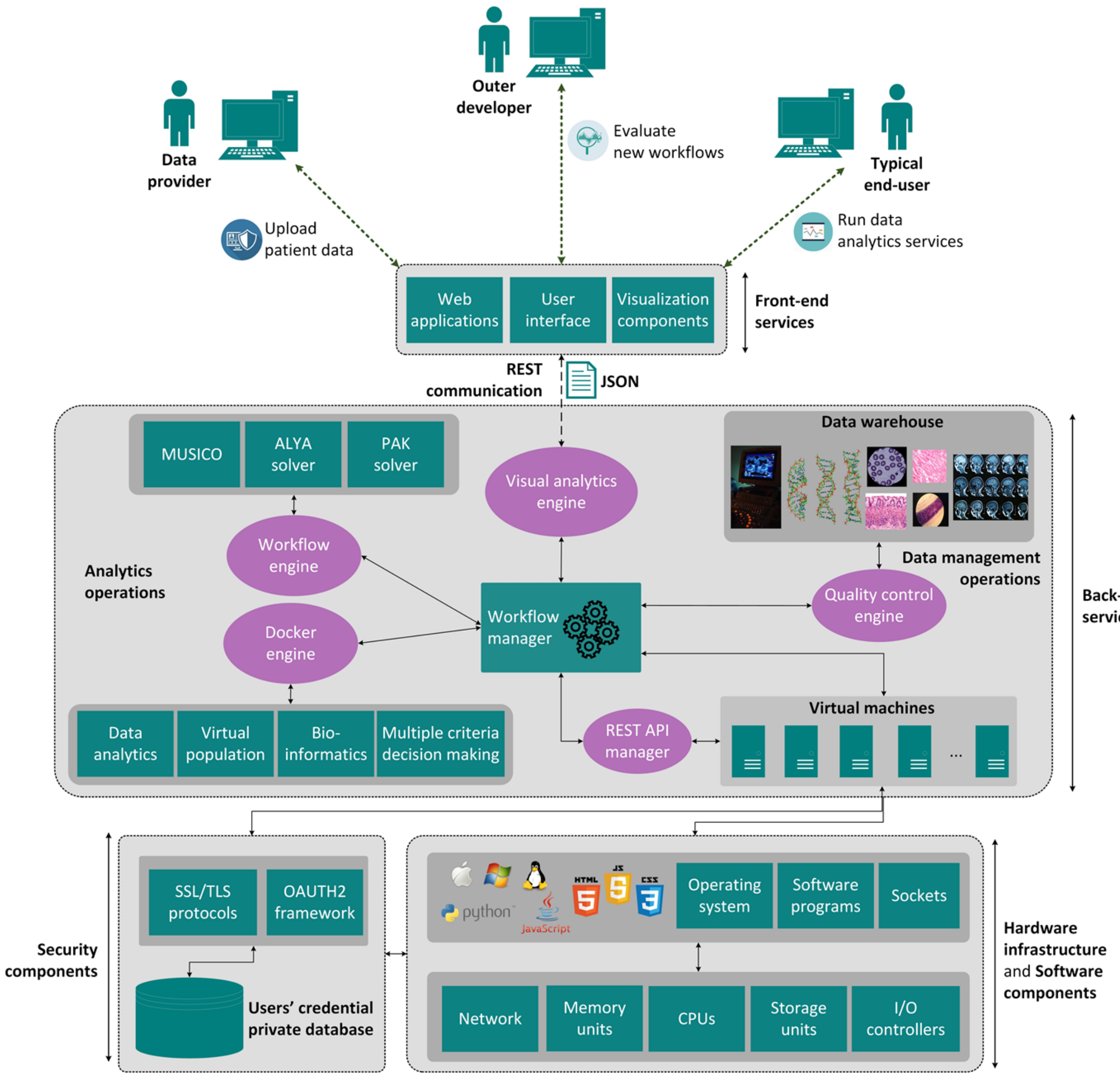

Figure 36: Distribution of the SLICOFCM cloud computing services to the stakeholders.

The back-end services are coordinated by the workflow manager which is located on a specific VM and invokes its four engines, according to the type of service that the user defines through the user interface (UI) that is located in the front-end. More specifically, the quality control engine is invoked when a data management operation (i.e., data quality assessment) is requested by the data provider, the workflow engine and the docker engine are invoked when a data analytics operation is requested by the user, where the workflow engine is invoked by the workflow manager when the type of service involves the execution of the MUSICO Tool or the ALYA Solver Tool or the PAK Solver Tool and the docker engine is invoked by the workflow manager when the type of service involves the execution of the Data Analytics Tool or the Virtual Population Tool or the Bioinformatics Tool or the Multiple Criteria Decision Making Tool. The workflow manager can anytime manage the VM resources according to the needs of the computational needs of the services through the REST API manager. In addition, the REST API manager can assist the development of REST services which can be used to transfer the results of the services to the front-end layer.

The results of the engines are finally gathered to the workflow manager which distributes them through the visual analytics engine to the front-end layer that includes the visualization components. The latter are necessary for the development of web applications that offer graphical representations for the user interactions. The results of the REST-services are transferred in the form of JSON data structures which are parsed by the front-end services and visualized to the users through the user interface.

The cloud computing services and components can be classified to the layers of Figure 35, as follows:

- Cloud computing services:
    - Front-end services: Front-end layer.
    - Back-end services: Back-end layer, Workflow layer.
- Cloud computing components:
    - Hardware infrastructure: Hardware layer.
    - Software components: Security layer, Workflow layer, Back-end layer.
    - Security components: Security layer.

6.3 Functional specifications of the platform

The functional specifications of SILICOFCM platform are discriminated in 11 key groups characterized by the module or tool that refer to: 1) User Access Management Module (UAMM), 2) Data Management Module (DMM), 3) Workflow Manager Module (WMM) , 4) Visual Analytics Module (VAM), 5) MUSICO Tool (MT), 6) ALYA Solver Tool (AST), 7) PAK Solver Tool (PST), 8) Data Analytics Tool (DAT), 9) Bioinformatics Tool (BT), 10) Virtual Population Tool (VPT), 11) Multiple Criteria Decision Making Tool (MCDMT).

The corresponding id is generated as follows: [F]_[initials of key groups]_[ascending numbering]. The “F” refers to the functional specifications, the UAMM, DMM, WMM, VAM, MT, AST, PST, DAT, BT, VPT, MCDMT to the key groups. The priority of each requirement is characterized as:

- **Mandatory specification:** This specification must be followed
- **Desirable specification:** This feature should be built into the final platform unless the latter demands high cost and effort.
- **Optional specification:** This feature is good to ‘implement’.
- **Possible future enhancement:** This feature is beyond the current scope but could be an added value for future exploitation.

Based on the analysis, the following specifications have been identified:

Table 16: Functional specification (F_UAAM_1).

Specification ID	**F_UAAM_1**	**Priority***	Mandatory
Specification title	User authentication according to the user's type	**Stakeholders involved**	Cloud provider Inner and outer developer Typical end-User
Description	In order to access the SILICOFCM platform the credentials of the user must be verified. Such credentials are the name and the necessary password. SILICOFCM platform incorporates a security management system for not allowing the access to unauthorized logins. It logs all the logins and failed login attempts and keeps the records in a dedicated DB.		
Rationale/Goal	The authentication of the user for the protection of the SILICOFCM data and the prevention of malicious access		
Means of verification	Successful login to the cloud platform.		
Acceptance Measures	The correct UI and services of SILICOFCM are accessible		
Dependencies:	N/A		

Table 17: Functional specification (F_UAAM_2).

Specification ID	**F_UAAM_2**	**Priority***	Mandatory
Specification title	User authorization according to the user's access to the SILICOFCM's services.	**Stakeholders involved**	Cloud provider Inner and outer developer Typical end-User
Description	The SILICOFCM access control and security manager provides different roles to the operators that login. Through the management the operators could gain access to different UIs, to the cloud hardware infrastructure, to the services and the provided SILICOFCM simulation tools.		
Rationale/Goal	To provide different type of access to the SILICOFCM operators.		
Means of verification	Login to the cloud platform. After valid authentication the operators have access to the services according to their roles.		
Acceptance Measures	Cloud platform forbids access to an operator in a service with no permissions describe for his role.		
Dependencies	F_UAAM_1		

Table 18: Functional specification (F_UAAM_3).

Specification ID	**F_UAAM_3**	**Priority***	Mandatory
Specification title	User logout after a specific amount of time or when he wants to.	**Stakeholders involved**	Cloud provider Inner and outer developer Typical end-User
Description	The SILICOFCM access control and security manager provides the ability to the operator to logout whenever he/she wants. Moreover, provides the ability to automatically log out the platform after certain time of inactivity of the latter for security purposes.		
Rationale/Goal	To provide the logout capability in the cloud platform.		

Means of verification	Logout of the cloud platform. After certain time of inactivity –automatic logout of the user.
Acceptance Measures	After a successful log out the user can login again using only his owned credentials.
Dependencies	F_UAAM_1

Table 19: Functional specification (F_UAAM_4).

Specification ID	**F_UAAM_4**	**Priority***	Mandatory
Specification title	The admin can either accept or reject pending approvals	**Stakeholders involved**	Cloud provider Inner and outer developer
Description	The SILICOFCM access control and security manager provides the ability to the Admin to access or reject any pending approvals regarding the requests for upgrading authentication levels of operator in the various SILICOFCM provided services, tools		
Rationale/Goal	To provide the adequate service/UI		
Means of verification	An admin approval will enable the access to the requested service (or the opposite)		
Acceptance Measures:	Successful upgrade/downgrade of access levels.		
Dependencies:	N/A		

Table 20: Functional specification (F_DMM_1).

Specification ID	**F_DMM_1**	**Priority***	Mandatory
Specification title	Data upload/donwload	**Stakeholders involved**	Inner and outer developer Typical end-User
Description	The SILICOFCM cloud platform provides a specific UI and service for uploading new data (anonymized clinical or/and genetic data) to the platform through a safe and encrypted way in order to be stored and further processed. In addition the same backend engine provides the capability to download simulations reports and results		
Rationale/Goal	To provide the capability to upload related data on the platform.		
Means of verification	Through the dedicated UI the operator uploads anonymized data in the adequate form.		
Acceptance Measures	Uploaded data with no CRC errors.		
Dependencies	F_UAAM_1		

Table 21: Functional specification (F_DMM_2).

Specification ID	**F_DMM_2**	**Priority***	Optional
Specification title	Cyclic redundancy check of the uploaded data	**Stakeholders involved**	Inner and outer developer Typical End-User

Description	The SILICOFCM cloud platform provides a cyclic redundancy check (CRC) header that allows clients to verify the integrity of object contents. At the end of each copy operation, the platform validates automatically that the checksum of the source file/object matches the checksum of the destination file/object.
Rationale/Goal	To check the data integrity of the uploaded data.
Means of verification	Checksum comparison
Acceptance Measures	Uploaded data with no CRC errors.
Dependencies	F_DMM_1

Table 22: Functional specification (F_DMM_3).

Specification ID	**F_DMM_3**	**Priority***	Mandatory
Specification title	Data quality assessment	**Stakeholders involved**	Inner and outer developer Typical End-User
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. The data curator is a diagnostic tool and provides functionalities for incompatibilities check, outlier detection, and identification of duplicate terms.		
Rationale/Goal	To provide a data cleansing functionality		
Means of verification	The operator logins to the platform, proceeds to the upload UI, uploads the anonymized data and proceed to data quality assessment. Data quality report includes various metrics regarding the quality of the data.		
Acceptance Measures	No duplicates, or other data incompatibilities existence in the report.		
Dependencies	F_DMM_1, F_DMM_2		

Table 23: Functional specification (F_DMM_4).

Specification ID	**F_DMM_4**	**Priority***	Mandatory
Specification title	Data conversion to predefined formats	**Stakeholders involved**	Inner and outer developer Typical end-User
Description	The SILICOFCM cloud platform provides a specific UI and service for Converting well established/standard file/data formats for dedicated for external/internal solvers		
Rationale/Goal	To provide the capability to transform data simulation types.		
Means of verification	Through the dedicated UI the operator transform data files from one data file type to another.		
Acceptance Measures	No errors in conversion. The exported file works for the dedicated purpose		
Dependencies	F_DMM_1		

Table 24: Functional specification (F_WMM_1).

Specification ID	**F_WMM_1**	**Priority***	Mandatory
Specification title	Execution of dockers for data analytics	**Stakeholders involved**	Cloud provider Inner and outer developer Typical End-User
Description	The cloud platform provides the capability to execute the dedicated docker image of the Data Analytics Tool through the docker engine.		
Rationale/Goal	To provide the data analytics capabilities to the operator.		
Means of verification	The operator logins to the platform and selects a data analytics workflow from the WMM.		
Acceptance Measures	The data analytics workflow will be executed without any reported "execution eror"		
Dependencies	F_WMM_2, F_DAT_1, F_DAT_2, F_DAT_3		

Table 25: Functional specification (F_WMM_2).

Specification ID	**F_WMM_2**	**Priority***	Mandatory
Specification title	Execution of dockers for bioinformatics	**Stakeholders involved**	Cloud provider Inner and outer developer Typical End-User
Description	The cloud platform provides the capability to execute the dedicated docker image of the Bioinformatics Tool through the docker engine.		
Rationale/Goal	To provide the bioinformatics capabilities to the operator.		
Means of verification	The operator logins to the platform and selects bioinformatics workflow from the WMM.		
Acceptance Measures	The bioinformatics workflow will be executed without any reported "execution error"		
Dependencies	BT_1, BT_2		

Table 26: Functional specification (F_WMM_3).

Specification ID	**F_WMM_3**	**Priority***	Mandatory
Specification title	Execution of dockers for virtual population Tool	**Stakeholders involved**	Cloud provider Inner and outer developer Typical End-User
Description	The cloud platform provides the capability to execute the dedicated docker image of the Virtual Population Tool through the docker engine.		
Rationale/Goal	To provide the Virtual Population Tool capabilities to the operator.		
Means of verification	The operator logins to the platform and selects the Virtual Population Tool workflow from the WMM.		
Acceptance Measures	The virtual population workflow will be executed without any reported "execution error"		

Dependencies	F_WMM_1, F_WMM_6, VPT_1, VPT_2

Table 27: Functional specification (F_WMM_4).

Specification ID:	**F_WMM_4**	**Priority*:**	Optional
Specification title:	Execution of executable tool outside the SILICOFCM cloud infrastructure	**Stakeholders involved:**	Cloud provider Inner and outer developer Typical End-User
Description:	The WMM of SILICOFCM will provide the capability to create secure and encrypted tunnels over which will execute the computational demanding tools/solvers in other HPC servers.		
Rationale/Goal:	To run demanding simulating workflows in other HPC servers and retrieve the results		
Means of verification:	The operator provides the necessary credentials for the external HPC center and the workflow manager creates the secure tunnel and executes the appropriate workflow.		
Acceptance Measures:	The secure tunnel is alive and the simulation instance runs with errors in the external HPC center.		
Dependencies:	F_WMM_6		

Table 28: Functional specification (F_WMM_6).

Specification ID	**F_WMM_6**	**Priority***	Mandatory
Specification title	Execution of workflows for SILICOFCM tools reside in VMs.	**Stakeholders involved**	Cloud provider Inner and outer developer Typical End-User
Description	The cloud platform provides the capability to execute the dedicated workflow of the different provided tools that are installed in different VMs.		
Rationale/Goal	To provide the various simulation/calculation capabilities to the operator		
Means of verification	The operator logins to the platform and selects simulation tool workflow from the WMM.		
Acceptance Measures	The virtual population workflow will be executed without any reported “execution error”.		
Dependencies	N/A		

Table 29: Functional specification (F_WMM_7).

Specification ID	**F_WMM_7**	**Priority***	Mandatory
Specification title	Execution of data visualization workflow.	**Stakeholders involved**	Cloud provider Inner and outer developer Typical End-User
Description	The cloud platform provides the capability to visualize the results of any executed workflow which is integrated in the SILICOFCM.		
Rationale/Goal	To provide the capability of to execute data visualization workflows.		

Means of verification	The operator logins to the platform and selects a visualization workflow from the WMM.
Acceptance Measures	The virtual population workflow will be executed without any reported “execution error”
Dependencies	F_WMM_1, F_WMM_6

Table 30: Functional specification (F_WMM_8).

Specification ID	**F_WMM_8**	**Priority***	Optional
Specification title	Management of the platform cloud resources.	**Stakeholders involved**	Cloud provider Inner and outer developer Typical end-user
Description	The SILICOFCM platform provides the capability though the Workflow Manager Module to manage all the computational and storage resources though a dedicated dashboard.		
Rationale/Goal	To manage the cloud resources in an easy and responsive manner.		
Means of verification	The operator logins into the dedicated dashboard and tethers the resources that needs and is authenticated to.		
Acceptance Measures	The selected resources are not in the available resources pool.		
Dependencies	N/A		

Table 31: Functional specification (F_WMM_9).

Specification ID	**F_WMM_9**	**Priority***	Mandatory
Specification title	Selection of the type of analysis	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	The SILICOFCM platform provides the capability to the operator to select predefined simulations workflows of the available tools.		
Rationale/Goal	To select predefined available SILICOFCM tools.		
Means of verification	The operator logins to the platform and selects an available tool (predefine workflow).		
Acceptance Measures	The workflow is executed with no “execution error”.		
Dependencies	F_WMM_1, F_WMM_2, F_WMM_6, F_WMM_10		

Table 32: Functional specification (F_WMM_10).

Specification ID	**F_WMM_10**	**Priority***	Mandatory
Specification title	Definition of workflows for the tools	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	The platform provides the capability to the user to define parameters for constructing the workflows according to the selected tool.		
Rationale/Goal	Parametric workflow definition.		
Means of verification	The operator logins to the platform and selects an available predefined workflow where he could change predefined parameters to conduct his experiment/simulation.		

Acceptance Measures	The workflow execution creates no execution error.
Dependencies	F_WMM_9

Table 33: Functional specification (F_WMM_11).

Specification ID	**F_WMM_11**	**Priority***	Optional
Specification title	Define workflows for the modules	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	The platform provides the capability to the operator to define parameters for constructing the workflows according to the selected platform's module.		
Rationale/Goal	Parametric workflow definition.		
Means of verification	The operator logins to the platform and selects an available predefine workflow where he could change predefined parameters of the selected platform modules		
Acceptance Measures	The workflow execution creates no execution error		
Dependencies	F_WMM_12		

Table 34: Functional specification (F_WMM_12).

Specification ID	**F_WMM_12**	**Priority***	Mandatory>
Specification title	Workflow Manager Module configuration	**Stakeholders involved**	Inner and outer developer
Description	The inner developer can configure the settings of the Workflow Manager Module.		
Rationale/Goal	Configuration of WMM dashboard		
Means of verification	The operator (inner developer) logins and changes the configuration dashboard of the WMM		
Acceptance Measures	No execution errors		
Dependencies	N/A		

Table 35: Functional specification (F_WMM_13).

Specification ID	**F_WMM_13**	**Priority***	Optional
Specification title	Upload of new workflow(s)	**Stakeholders involved**	Inner and outer developers
Description	The platform provides the capability to an authenticated outer developer upload a new simulation workflow for evaluation		
Rationale/Goal	To upload new simulation workflows from authenticated third parties		
Means of verification	The operator logins into the platform and uploads a new simulation workflow using the tools of the SILICOFCM.		
Acceptance Measures	The execution of the uploaded workflow reports no errors.		
Dependencies	N/A		

Table 36: Functional specification (F_VAM_1).

Specification ID	**F_VAM_1**	**Priority***	Mandatory

Specification title	Visualization of the results of the various SILICOFCM tools	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	The SILICOFCM platform provides the capability to the end user to visualize the simulated results provided by the various incorporated tools. The visualization includes various 2D plots, contours or/and 3D geometry or contour visualization.		
Rationale/Goal	To visualize the simulated results		
Means of verification	The operator conduct a simulation and selects a visualisation option from the provided list.		
Acceptance Measures	Correct and lucid simulation result visual representation. No artefacts included.		
Dependencies	F_WMM_1, F_WMM_3, F_WMM_6, F_WMM_7, F_WMM_10		

Table 37: Functional specification (F_VAM_2).

Specification ID	**F_VAM_2**	**Priority***	Optional
Specification title	Visualization of metadata.	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	The SILICOFCM platform provides the capability to visualise the results of a statistical meta-analysis of the stored SILICOFCM data.		
Rationale/Goal	To visualize the metadata of stored data in clear and understandable way.		
Means of verification	The operator performs a meta-analysis and then starts the visualization module.		
Acceptance Measures	Correct and lucid visual representation of the meta-analysis		
Dependencies	F_WMM_7, F_WMM_10, F_DAT_1, F_DAT_2, F_DAT_3		

Table 38: Functional specification (F_VAM_3).

Specification ID	**F_VAM_3**	**Priority***	Mandatory
Specification title	Visualization of statistical reports regarding the data structure.	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	The SILICOFCM platform provides the capability to visualize the basic statistical metrics for the stored or new uploaded data to the platform in a predefined report.		
Rationale/Goal	To visualize statistical metrics of a structured data pool		
Means of verification	The operator selects the features of the stored or newly uploaded data and execute a basic statistical workflow		
Acceptance Measures	The visualization report depicts no artifact.		
Dependencies	F_DMM_1, F_DMM_2, F_DMM_3		

Table 39: Functional specification (F_VAM_4).

Specification ID	**F_VAM_4**	**Priority***	Optional
Specification title	Visualization of new created workflow	**Stakeholders involved**	Inner and outer developer

Description	The SILICOFCM platform provides the capability to the outer developer to visualize a new created simulation workflow as a flow diagram
Rationale/Goal	To visualize workflows in a flow diagram manner
Means of verification	The outer developer creates/develops a new simulating workflow by updating the SILICOFCM tools (adds new functionalities) and the latter is represented as a flow diagram
Acceptance Measures	Correct representation of the workflow including the necessary inputs and outputs.
Dependencies	F_WMM_9, F_WMM_10, F_WMM_11, F_WMM_13

Table 40: Functional specification (F_MT_1).

Specification ID	**F_MT_1**	**Priority***	Mandatory
Specification title	Calculation of sarcomere mechanical response to the prescribed protocol.	**Stakeholders involved:**	Inner and outer developer Typical End-User.
Description	MUSICO will provide a console application that runs calculation of sarcomere mechanical behaviour under the prescribed protocol. Input parameters are given in few ASCII files, while the results are exported into one or more CSV files, depending on the requirements.		
Rationale/Goal	Using this functionality, the inner and outer developers of the SILICOFCM platform will develop cloud based application that enables end-user to test the influence of various diseases and therapies on muscle fibre function. This functionality will help the typical end user and inner and outer developers to create surrogate models that can adequately replace computationally demanding MUSICO platform within finite element simulations of the heart.		
Means of verification	Comparison with other relevant models and experimental results.		
Acceptance Measures	MUSICO results are not significantly different from the results of relevant models and experimental measurements, and are physiologically explainable.		
Dependencies	F_WMM_6		

Table 41: Functional specification (F_AST_1).

Specification ID	**F_AST_1**	**Priority***	**Mandatory**
Specification title	ALYA Solver Tool coupling with MUSICO Tool	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	The SILICOFCM platform will provide the capability to run FEA simulation workflows of a functioning heart coupled (loose or strong) with the multiscale solver MUSICO which calculates the sarcomere mechanical behavior.		
Rationale/Goal	Prescribed coupled FEA analysis workflows will be executed and results will be visualized using VAM.		
Means of verification	Performance and accuracy evaluation metrics		
Acceptance Measures	Adequate performance in simulation. Robust simulation exhibiting no solution divergence.		
Dependencies	F_WMM_6		

Table 42: Functional specification (F_PST_1).

Specification ID	**F_PST_1**	**Priority***	Mandatory
Specification title	FE simulations of mechanics coupled with electric field and drug transport	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	The typical end user is able to execute/run typical FE simulation on the SILICOFCM stored data and visualize outcomes of different therapies for identifying high Risk individuals.		
Rationale/Goal	The relevant FE simulation will be executed and results will be visualized using visualization tool.		
Means of verification	Performance and accuracy evaluation metrics		
Acceptance Measures	Adequate performance in simulation. Robust simulation exhibiting no solution divergence.		
Dependencies	F_WMM_6		

Table 43: Functional specification (F_DAT_1).

Specification ID	**F_DAT_1**	**Priority***	Mandatory
Specification title	Machine learning/ data mining: Risk Stratification tool	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	The end users are able to: • visualize and display statistics of various cardiomyopathy patients risk groups, • make reliability-supplemented predictions of a new patient for his cardiomyopathy risk level		
Rationale/Goal	The aim is to develop a cardiomyopathy risk stratification tool based on data mining algorithms. Identification of high-risk patients (sudden cardiac death or life threating arrhythmias) will be provided and supplemented by prediction reliability estimates.		
Means of verification	• Machine learning performance evaluation measures. • Qualitative evaluation by clinicians.		
Acceptance Measures	• Adequate machine learning performance. • Acceptance to use by clinicians.		
Dependencies	F_DMM_1, F_DMM_2, F_DMM_3, F_WMM_3, F_WMM_6, BT_1, BT_2, VPT_1, VPT_2		

Table 44: Functional specification (F_DAT_2).

Specification ID	**F_DAT_2**	**Priority***	Mandatory
Specification title	Machine learning / data mining: Virtual Patients Repository Modeling	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	The end users are able to: • visualize explanation of predictive models that describe cardiomyopathy outcomes for virtual patients, • study reports on prediction performance for different type of data sources for virtual patients.		

Rationale/Goal	The aim 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.
Means of verification	• Machine learning performance evaluation measures. • Qualitative evaluation by clinicians.
Acceptance Measures	• Adequate machine learning performance. • Adherence to known medical phenomena. • Acceptance to use by clinicians.
Dependencies	F_DMM_1, F_DMM_2, F_DMM_3, F_WMM_3, F_WMM_6, BT_1, BT_2, VPT_1, VPT_2

Table 45: Functional specification (F_DAT_3).

Specification ID	**F_DAT_3**	**Priority***	Mandatory
Specification title	Machine learning algorithms on FCM clinical & genetic data	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	The typical end user is able to execute/run typical machine learning algorithms on the SILICOFCM stored data and for identifying high Risk individuals.		
Rationale/Goal	The relevant supervised machine learning pipeline will be executed		
Means of verification	Performance evaluation metrics		
Acceptance Measures	Adequate performance in classification.		
Dependencies	F_DMM_1, F_DMM_2, F_DMM_3, F_WMM_3, VPT_1, VPT_2		

Table 46: Functional specification (F_BT_1).

Specification ID	**F_BT_1**	**Priority***	Mandatory
Specification title	Bioinformatics workflows for genetic analyses	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	The typical end user is able to execute/run CWL 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		
Acceptance Measures	Comparable test results as seen on Seven Bridges Platform		
Dependencies	F_WMM_2, F_DAT_3		

Table 47: Functional specification (F_BT_2).

Specification ID	**F_BT_2**	**Priority***	Mandatory

Specification title	Genetic data upload and storage	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	SILICOFCM provides the ability to upload genetic data and access them to be used as input files in bioinformatics workflows. End-users and developers are furthermore able to store output data from bioinformatics workflows on the platform and feed into downstream Data Analytics Tool.		
Rationale/Goal	Raw genetic data will be stored on the SILICOFCM platform		
Means of verification	Successful usage of test data stored on SILICOFCM platform as input files		
Acceptance Measures	Successful completion of CWL workflows using test dataset stored on SILICOFCM platform as input files and feeding output data into risk stratification tool		
Dependencies:	F_DMM_1, F_DMM_2, F_DMM_3		

Table 48: Functional specification (F_VPT_1).

Specification ID	**F_VPT_1**	**Priority***	Mandatory
Specification title	Visualisation of vritual patients geometries	**Stakeholders involved**	Inner and outer developer Typical End-User
Description	SILICOFCM platform provides the visualization capability (VAM) of the geometries generated by the virtual population Tool.		
Rationale/Goal	Geometries and statistics with the geometric metrics of the virtual patients will be provided.		
Means of verification	The operator starts the corresponding VAM workflow and the specifica UI starts including the appropriate 3D views.		
Acceptance Measures	No artifacts in the visualisation		
Dependencies	F_WMM_7, F_VAM_1		

Table 49: Functional specification (F_MCDMT_1).

Specification ID	**F_MCDMT_1**	**Priority***	Mandatory
Specification title	MCDMT functions implementation through SQL	**Stakeholders involved**	Inner and outer developer
Description	SILICOFCM platform provides capability to the developers of MCDMT to implement the decision making features through Structured Query Language.		
Rationale/Goal	Implementation of tool features through Structured Query Language.		
Means of verification	The MCDMT developer will account on the SQL functions of the DBs integrated into the SILICOFCM platform.		
Acceptance Measures	The MCDMT features are fully fucntional		
Dependencies	F_BT_1, F_BT_2, F_DAT_1, F_DAT_2		

A summary of all functional requirements and the associated dependencies is presented below.

Table 50: Functional requirements and associated dependencies.

ID	Title	Dependencies (#)
F_UAAM_1	User authentication according to the user's type	N/A
F_UAAM_2	User authorization according to the user's access to the SILICOFCM's services.	F_UAAM_1
F_UAAM_3	User logout after a specific amount of time or when he wants to	F_UAAM_1
F_UAAM_4	The admin can either accept or reject pending approvals	N/A
F_DMM_1	Data upload	F_UAAM_1
F_DMM_2	Cyclic redundancy check of the uploaded data	F_DMM_1
F_DMM_3	Data quality assessment	F_DMM_1, F_DMM_2
F_DMM_4	Data conversion of data file types	F_DMM_1
F_WMM_1	Execution of dockers for data analytics	F_WMM_2, F_DAT_1, F_DAT_2, F_DAT_3
F_WMM_2	Execution of dockers for bioinformatics	BT_1, BT_2
F_WMM_3	Execution of dockers for virtual population Tool	F_WMM_1, F_WMM_6, VPT_1, VPT_2
F_WMM_4	Execution of executable tool outside the SILICOFCM cloud infrastructure	F_WMM_6
F_WMM_6	Execution of workflows for SILICOFCM tools reside in VMs.	N/A
F_WMM_7	Execution of data visualization workflow.	F_WMM_1, F_WMM_6
F_WMM_8	Management of the platform cloud resources.	N/A
F_WMM_9	Selection of the type of analysis	F_WMM_1, F_WMM_2, F_WMM_6, F_WMM_10
F_WMM_10	Definition of workflows for the tools	F_WMM_9
F_WMM_11	Define workflows for the modules	F_WMM_12
F_WMM_12	Workflow Manager Module configuration	N/A
F_WMM_13	Upload of new workflow(s)	N/A
F_VAM_1	Visualization of the results of the various SILICOFCM tools	F_WMM_1, F_WMM_3, F_WMM_6, F_WMM_7, F_WMM_10
F_VAM_2	Visualization of metadata.	F_WMM_7, F_WMM_10, F_DAT_1, F_DAT_2, F_DAT_3
F_VAM_3	Visualization of statistical reports regarding the data structure.	F_DMM_1, F_DMM_2, F_DMM_3
F_VAM_4	Visualization of new created workflow	F_WMM_9, F_WMM_10, F_WMM_11, F_WMM_13
F_MT_1	Calculation of sarcomere mechanical response to the prescribed protocol.	F_WMM_6
F_AST_1	ALYA Solver Tool coupling with MUSICO Tool	F_WMM_6
F_PST_1	FE simulations of mechanics coupled with electric field and drug transport	F_WMM_6
F_DAT_1	Machine learning / data mining: Risk Stratification tool	F_DMM_1, F_DMM_2, F_DMM_3, F_WMM_3, F_WMM_6, F_BT_1, F_BT_2, F_VPT_1,

F_DAT_2	Machine learning / data mining: Virtual Patients Repository Modeling	F_DMM_1, F_DMM_2, F_DMM_3, F_WMM_3, F_WMM_6, F_BT_1, F_BT_2, F_VPT_1,
F_DAT_3	Machine learning algorithms on FCM clinical & genetic data	F_DMM_1, F_DMM_2, F_DMM_3, F_WMM_3, F_VPT_1,
F_BT_1	Bioinformatics workflows for genetic analyses	F_WMM_2, F_DAT_3
F_BT_2	Genetic data upload and storage	F_DMM_1, F_DMM_2, F_DMM_3
F_VPT_1	Visualisation of vritual patients geometries	F_WMM_7, F_VAM_1
F_MCDMT_1	MCDMT functions implementation through SQL	F_BT_1, F_BT_2, F_DAT_1, F_DAT_2

6.4 Non-functional specifications of the platform

The non-functional specifications (NFSs) of the SILICOFCM cloud based platform are presented in the following sections. The NFSs describe the features of SILICOFC platform not related to the functionality and will outline the architecture of the platform solution. These are related to any layer of the SILICOFCM cloud stack (e.g, IaaS, platform, SaaS) and have impact on different users.

- **Availability (NFS1):** Refers to the time fraction the SILICOFCM services will be online and available to the end-users.
- **Scalability (Elasticity) (NFS2):** Refers to the capability of the platform to scale-up or down the hardware resources in a dynamic manner in order to adjust the abovementioned to te requested workload changes, maximizing the use of resources.
- **Interoperability (NFS3):** Refers to the ability of the platform tools/modules/applications to communicate between different cloud providers
- **Security (NFS4):** Refers to the security levels that the cloud platform offers since large amount of various data types are managed and processed.
- **Adaptability/Maintainability (NFS5):** Refers to the ability of the cloud platform to easily adopt new services, change/update/enhance existing ones and/or connect to external APIs.
- **Performance (NFS6):** Refers to the cloud platform ability to handle all the deployed workload
- **Usability (NFS7):** Refers to the design of the User Interfaces (UIs) and the ease of use of the offered cloud services by the end-users.
- **Storage (NFS8):** Refers to the heterogeneous and big amount of data which will be stored in relational and non-relational Databases produced by virtual population data, information for the simulation workflows, log of events, platform usage, etc.

6.4.1 Availability (NFS1)

Availability is the ratio of time a system or component is functional to the total time required or expected to function and usually is described as percentage of online or downtime in terms of weekly, monthly or yearly averages. The SILICOFCM cloud platform is an *in-silico* cloud platform which implies a cloud simulation platform. The availability of such infrastructure is as a direct proportion (for example, 9/10 or 0.9) or as a percentage (for example, 90%). It can also be expressed in terms of average downtime per week, month or year or as total downtime for a given week, month or year. Sometimes availability is expressed in qualitative terms, indicating the extent to which a system can continue to work when a significant component or set of components goes down. Moreover the

SILICOFCM platform will be deployed at the end on a cloud provider were a service-level agreement (SLA) will be drawn up between the service provider and the client (SILICOFCM).

6.4.2 Scalability (NFS2)

A cloud platform must be expandable in terms of hardware and software components. The cloud infrastructure and especially the hardware layer of the SILICOFCM platform is easily adjustable. Any changes in the hardware infrastructure are tracked by the REST API manager which is controlled by the Workflow Manager Module which lies in the core of the SILICOFCM platform. The REST API manager monitors the availability of the hardware and software components and distributes them according to the needs of the cloud computing services. In addition, the REST API manager can be easily adjusted through the Workflow Manager Module (see the Adaptability/Maintainability).

6.4.3 Interoperability (NFS3)

The diversity of offers combined with cloud services going mainstream will lead to scenarios of distributed Software as a Service (SaaS) applications whose parts are hosted on different cloud platforms and will therefore need to interoperate and cooperate through efficient and reliable protocols. The SILICOFCM platform accounts for such scenarios, in cases where the type of analysis involves the execution of tools that are located outside the platform. Secure REST services are going to be used in order to transfer the workflows for local execution in the premises where the tools are located (e.g., ALYA Solver Tool, PAK Solver Tool, MUSICO Tool) and finally receive the results in appropriate JSON data structures that are going to be parsed for visualization purposes. This integration of services is the main vision of the SILICOFCM platform.

6.4.4 Security (NFS4)

Data security comprises the biggest barrier of cloud computing. The lack of data security results to data leakage, data abuse, loss of data integrity and control over the hosted data and the cloud applications. The SILICOFCM platform uses an OAUTH2 authorization framework for ensuring secure user authentication and access management and secure access to the information and services of the platform. The flow of sensitive information outside the platform (e.g., user credentials) is encrypted and decrypted through Secure Sockets Layer (SSL)/Transport Layer Security (TLS) protocols using public decryption keys and private encryption keys. The inner information flows are performed through secure firewalls and virtual private networks which enhance the reliability of the platform.

6.4.5 Adaptability/Maintainability (NFS5)

A cloud platform must be easily scalable in terms of hardware expandability and software updates. The SILICOFCM is highly-scalable since it includes an operations coordinating system that is referred to as the workflow manager. The workflow manager is the SILICOFCM's core module and is responsible for the execution of all the cloud computing services that lie in the back-end layer, as well as, for the distribution of the visualization components that are necessary for the development of the front-end services. In addition, the Workflow Manager Module includes a REST API manager which handles the cloud resources according to the computational needs of the requested services. The workflow manager interacts with all the modules of the SILICOFCM platform through appropriate engines. An update in the workflow manager can enable the update of all the cloud computing services of the platform through the engines.

6.4.6 Performance (NFS6)

A cloud platform shall be able to adjust its hardware and software components according to the needs of the cloud computing services. The SILICOFCM platform can make use of the REST API manager to control the distribution of the cloud resources to the services that require high computational power. The REST API manager is controlled by the Workflow Manager Module which lies in the heart of the SILICOFCM platform. The REST API manager receives information from the Workflow Manager Module regarding the computational requirements of the requested services. Then, the REST API manager uses provisioning rules in order to distribute the available hardware and software components of the cloud infrastructure according to the computational power needs of the provided list of services.

6.4.7 Usability (NFS7)

A cloud platform must provide user-friendly menus and visualization graphs. The SILICOFCM platform accounts for such needs using visualization components that are easily scalable and coordinated by the Workflow Manager Module. Based on the type of cloud computing service, the visualization components are properly adjusted by the visual analytics engine. The latter is controlled by the Workflow Manager Module and receives visualization workflows which depend on the type of service. These workflows are sent to the Visual Analytics Module which makes use of the front-end services in order to parse the results and provide user-friendly graphical illustrations of the ensuing results of the services.

6.4.8 Storage (NFS8)

In the SILICOFCM cloud platform various, heterogeneous and big amount of data will be stored which means that a number of repositories are needed to be designed and integrated. SILICOFCM integrates simulation tools which produce calculation results varying from MBs to several GBs. SILICOFCM will integrate relational and non-relational Databases for storing heterogeneous anonymized clinical data, produced virtual population data, information for the simulation workflows, log of events, platform usage, authentication information, roles and credentials of the platform users and dedicated file server for storing input and output raw data files from the various SILICOFCM simulation tools. Since it is foreseen that the simulation results are characterized of large volume and in order to overcome the possible interconnection bottleneck, where needed, only simulation metadata will be transferred though VMs or through external secure tunnel.

6.5 Mapping User Requirements to Functional & Non-Functional Specifications

The following table depicts the mapping of the collected user requirements in Task 1.1 (D1.1) to the functional and non-functional specifications of the SILICOFCM cloud *in-silico* platform.

Table 51 User requirements mapping to the functional and non-functional requirements.

ID	Title of User Requirements	Priority (according to D1.1)	Platform Functional & Non-Functional Specification
URNF1	Ease of use	Mandatory	NFS7
URNF2	Ease of learning	Mandatory	NFS7

ID	Title of User Requirements	Priority (according to D1.1)	Platform Functional & Non-Functional Specification
URNF3	Platform time response	Desirable	NFS2, NFS6
URNF4	Simulation time acceptance	Desirable	NFS2, NFS6
URNF5	Expandable Platform Storage	Mandatory	NFS2, NFS8
URNF6	Reliable simulation results	Desirable	F_MT_1, F_AST_1, F_PST_1, F_DAT_1, F_DAT_2, F_DAT_3, F_BT_1, F_BPT_1, F_MCDMT_1
URNF7	Available SILCOFCM platform service	Desirable	NFS1
URNF8	SILICOFCM model validation	Desirable	F_MT_1, F_AST_1, F_PST_1, F_DAT_1, F_DAT_2, F_DAT_3, F_BT_1, F_BPT_1, F_MCDMT_1
URNF9	Notification messages	Mandatory	F_UAAM_1, F_UAAM_2, F_UAAM_3, F_UAAM_4
URNF10	Data privacy	Mandatory	NFS4, F_DMM_1, F_DMM_2, F_DMM_3
URNF11	Different roles	Mandatory	F_UAAM_1, F_UAAM_2, F_UAAM_3, F_UAAM_4
URNF12	Controlled Data access	Mandatory	F_UAAM_1, F_UAAM_2
URNF13	OAUTH and API services for secure web user authentication and authorization	Mandatory	NFS4
URNF14	Https Communications	Mandatory	NFS4
URNF15	Big data management	Mandatory	NFS8, F_DMM_1, F_DMM_2, F_DMM_3
URNF16	System administration	Mandatory	F_UAAM_4
URNF17	IPR Protection	Mandatory	NFS4
URNF18	Capability for new services inclusion	Optional	NFS5, F_WMM_1, F_WMM_2, F_WMM_3
URNF19	Capability for new computational resources	Optional	NFS2, NFS6
URNF20	Compliance of the SILICOFCM content and the scope with EU directives	Mandatory	NFS4
URF1	Input/output Data Format	Mandatory	NFS5, F_WMM_1, F_WMM_2, F_WMM_3
URF2	Data Vocabulary	Mandatory	F_DMM_3
URF3	Metadata	Mandatory	NFS8
URF4	Data Anonymization	Mandatory	F_DMM_3
URF5	Upload of New Data	Mandatory	F_WMM_1

ID	Title of User Requirements	Priority (according to D1.1)	Platform Functional & Non-Functional Specification
URF6	Data Consistence and Completeness	Mandatory	F_WMM_2, F_WMM_3
URF7	Data Updates	Mandatory	F_WMM_1
URF8	Scheduled Backup od SILICOFCM Data	Mandatory	NFS8
URF9	Notification about Data Usage	Mandatory	F_UAAM_5
URF10	Data Access Logging and Auditing	Mandatory	F_UAAM_5
URF11	A list of available SILICOFCM tools	Mandatory	F_WMM_9
URF12	A list of available virtual patients/models and clinical/genetic data	Mandatory	F_WMM_9
URF13	A list of available computational resources per tool	Optional	F_WMM_8
URF14	UI which allows user to complete all needed tasks for running the simulation	Mandatory	NFS7
URF15	Conversion of SILICOFCM simulation/experiment setup to a workflow	Mandatory	F_WMM_9, F_WMM_10, F_WMM_11
URF16	Workflows should be defined in a standard workflow definition language	Desirable	F_WMM_10, F_WMM_11
URF17	Validate the SILICOFCM tool workflow execution capability	Desirable	NFS7
URF18	The task flowcharts should be handled and recovered from task failure	Desirable	F_WMM_1, F_WMM_2, F_WMM_3, F_WMM_4, F_WMM_5, F_WMM_6, F_WMM_7, F_WMM_8
URF19	Communication between remote-based tools	Mandatory	NFS4, F_WMM_8
URF20	Communication between docker-based tools	Mandatory	NFS4, F_WMM_8
URF21	Conversion of solvers' files	Mandatory	F_WMM_4
URF22	Incorporate a convergence criteria per case	Desirable	

ID	Title of User Requirements	Priority (according to D1.1)	Platform Functional & Non-Functional Specification
URF23	Parallel execution of simulations	Mandatory	NFS2, NFS6, F_WMM_8
URF24	Estimation of simulation duration	Optional	NFS7
URF25	Calculation of sarcomere mechanical response	Mandatory	F_MT_1
URF26	Linking the MT with BT, ALT, PST	Mandatory	F_MT_1, F_PST_1, F_AST_1
URF27	Mesh validation	Desirable	F_PST_1, F_AST_1
URF28	Imaging Data Processing	Optional	-
URF29	Set up the Boundary Conditions	Mandatory	F_WMM_10
URF30	Set up the Material Properties	Mandatory	F_WMM_10
URF31	Heart mechanics coupled with electric field and drug transport	Mandatory	F_MT_1, F_PST_1, F_AST_1
URF32	Genetic Data Processing	Mandatory	F_WMM_2
URF33	Machine Learning Algorithms usage	Mandatory	F_WMM_1
URF34	Creation of virtual populations (cohort) of FCM patients	Mandatory	F_WMM_3
URF35	Post-processing of results	Mandatory	F_VAM_1, F_VAM_2, F_VAM_3, F_VAM_4
URF36	Visualization of 2D- and 3D-case results in browser	Mandatory	F_VAM_1, F_VAM_2, F_VAM_3, F_VAM_4
URF37	Visualization of evaluation reports	Mandatory	F_VAM_1, F_VAM_2, F_VAM_3, F_VAM_4
URF38	Browsing and filtering with an interactive visual access	Mandatory	F_VAM_1, F_VAM_2, F_VAM_3, F_VAM_4, NFS7
URF39	Visualization of Virtual Patients Cohort	Optional	F_VPT_1
URF40	Visual and statistical comparison of sub-cohorts	Desirable	F_VAM_2, F_VAM_3
URF41	Capability to Save/Load Working Progress	Desirable	F_WMM_1, F_WMM_2
URF42	Data Download	Desirable	F_DMM_3
URF43	Integration with other SILICOFCM services	Optional	-

ID	Title of User Requirements	Priority (according to D1.1)	Platform Functional & Non-Functional Specification

* Functional and non-Functional Specification that are not presented in the mapping table are inferred due to dependencies between to specification.

6.6 Hardware specifications

The hardware specifications of the SILICOFCM infrastructure are provided in the following table. These specifications derived from the T1.2 and the corresponding deliverable D1.2

Table 52: Hardware specifications of SILICOFCM platform infrastructure [listing from D1.2].

	Hardware Requirements				
Tools	**CPUs (cores)**	**GPUs**	**Memory (GB)**	**Storage (GB)**	**Additional Information**
AST	2000	N/A	1.8 per CPU	90	N/A
Authentication Server	4	N/A	4	N/A	N/A
Web Server	8	N/A	8	N/A	
REST API Server	8	N/A	8	N/A	
DB Server	8	N/A	16	N/A	
File Storage Server	4	N/A	8	2048	
VPT	12	N/A	32x12	1000-2000	
MT	200	N/A	1	0.5	Depending on the problem simulated MUSICO can run in few different modes: 1) simple analysis on one CPU; 2) many independent analyses simultaneously on up to 200 CPUs; 3) parallel execution of one analysis on 200-1000 CPUs.

	Hardware Requirements				
Tools	**CPUs (cores)**	**GPUs**	**Memory (GB)**	**Storage (GB)**	**Additional Information**
DAT	At least 8	Nvidia server enabled	256	1024	Intel Xeon Silver Octacore 2.10GHz 12GB RAM or 11GB.
MCDMT	No special hardware infrastructure needed	No special hardware infrastructure needed	No special hardware infrastructure needed	No special hardware infrastructure needed	No special hardware infrastructure needed
PST	250-500	N/A	16-64 per core	2000-4000	Although the calculations are feasible with smaller number of processors, the parameters specified are justified to provide reasonable duration of calculations.
BT	36	Not required	60	1024	N/A

6.7 UI analysis

6.7.1 UI Relevant technologies

The SILICOFCM platform as an *in-silico* clinical trial cloud based platform comprises by various UIs starting from the authentication page till the visualisation UIs, the simulation job type etc. SILICOFCM will translate all of the visual elements the SILICOFCM users will need into actual screen and pages. The developed UIs will be characterized by:

- Simplicity and consistency. Simplicity is the cornerstone of great user experience. The UIs should consist only with the necessary buttons and icons (links) and include only the necessary information per UI functionality. In addition, the SILICOFCM UIs will be characterised by consistency leaving away the "chaos" of multiple colour palette between them.
- Good understanding by the operators. The UIs will be tailored to the need of the target audience of such cloud platform.
- Visual hierarchy. To create some elements and features more clear and distinctive by other if is needed more attention by the operator.

- Include feedback messages. Feedback messages are necessary components of a good UI design. SILICOFCM will include where necessary. These messages will be updated and refined and improved during the testing-refinement period of the platform.
- Formed by simple layouts. The design of SILICOFCM UI layouts will be characterised by simple layouts with minimal number of fields for the user to complete.

The SILICOFCM UI design will be based in open source UI frameworks that are available nowadays. The final decision of the most appropriate for the project will be based on metrics such as:

- Performance: Time for rendering the UI to the end user
- Size: How big (size) will be the front end

The most popular UI frameworks are:

- **Bootstrap**: Bootstrap is an open source toolkit for developing with HTML, CSS, and JS[1].
- **React:** A JavaScript library for building interactive user interfaces such as VAT[2].
- **Angular:** Angular is an open framework that empowers the developers to build web applications. It combines declarative templates, end to end tooling, and best practices. The resulting environment is extraordinarily expressive, readable, and quick to develop[3].
- **ParaviewWeb:** Is a framework for bringing scientific visualization to the Web. It offers many capabilities from visualise data onto various 2D plots, visualise and handle 3D objects and visualise 3D scientific contours, iso-surfaces, 3D vector graphs etc[4].

6.7.2 UI mockups

6.7.2.1 User Access Management Module

One of the basic SILICOFCM module is the UAMM (User Access Management Module) and one of the front end representation is the SILICOFCM login page. In Figure 37, a draft mockup of the login page is depicted. The mockup provides:

- a login panel (with fields for the username and password),
- a button for password retrieval
- information for contacting the administrator.

[1] Bootstrap · The most popular HTML, CSS, and JS library in the world.” [Online]. Available: https://getbootstrap.com
[2] “React – A JavaScript library for building user interfaces.” [Online]. Available: https://reactjs.org/.
[3] Angular, https://angular.io/
[4] ParaViewWeb, the JavaScript library, https://www.paraview.org/web/

Figure 37: UI mockup of SILICOFCM login page.

6.7.2.2 Data Management Module

One of the DMM functionalities is the data upload and the data cleansing to the SILICOFCM platform. Figure 38 depicts a proposed mockup of one page of DMM. The mockup provides:

- a button for data upload (with browse option),
- a small panel for writing a short description for the data,
- a state of the SILICOFCM guidelines concerning the quality and structure of the data,
- a button for executing the data quality assessment service,
- a panel to view the summary data (with the ability to download them), and
- a button for data re-upload.

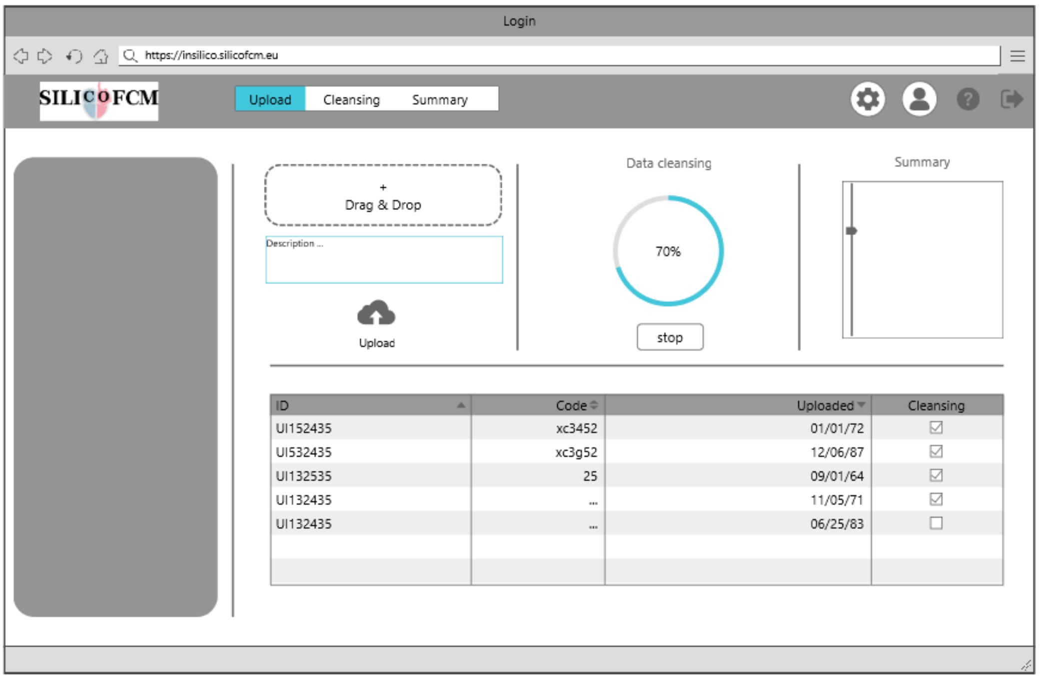

Figure 38: UI mockup of one page of the SILICOFCM DMM.

6.7.2.3 Workflow Manager Module

One of the core components of SILICOFCM cloud platform is the Workflow Manager Module where most of the simulation workflows are orchestrated. One UI page of the WMM is depicted in Figure 40.

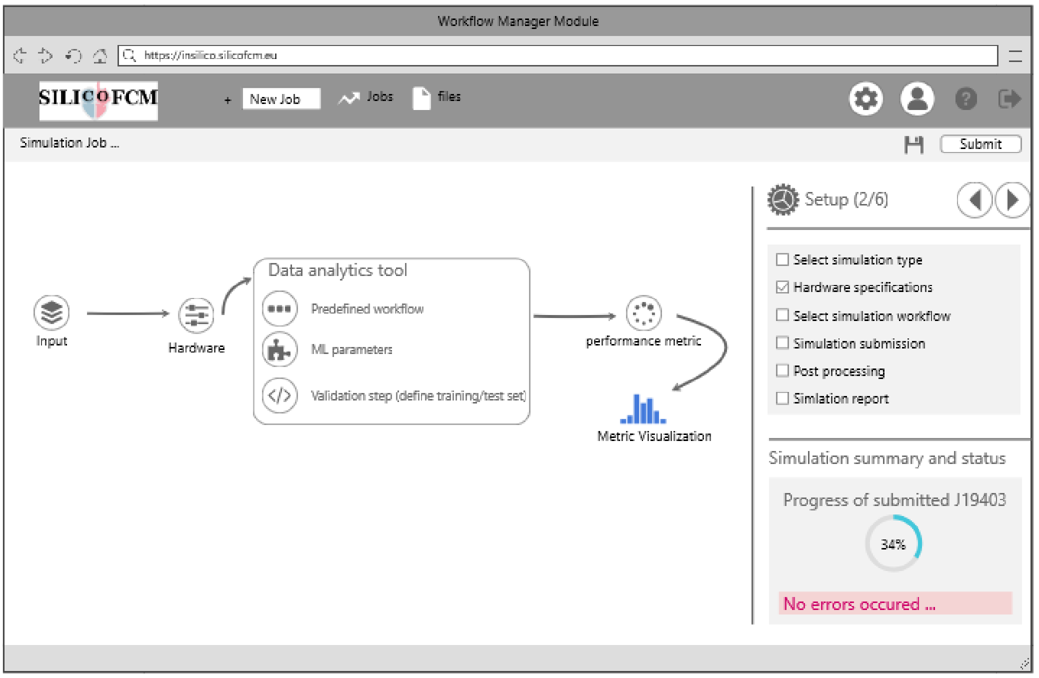

Figure 39: UI mockup of one page of the SILICOFCM WMM.

The mockup provides:

- a drop-down menu where the user can define the type of analysis,
- boxes and/or drop-down menus for selecting input parameters,
- a button for executing the workflow or the docker according to the type of analysis,
- a panel to view the processing status,
- a button to save the results, and
- a button to upload a model (workflow) according to the type of analysis.

6.7.2.4 Visual Analytics Module

Another component necessary for *in silico* platforms is the visualisation of the simulation results of the incorporated tools and predefined simulation pilelines in SILICOFCM. Figure 40 and Figure 41 present the proposed mockup layouts for 3D visualization and 2D plots respectively.

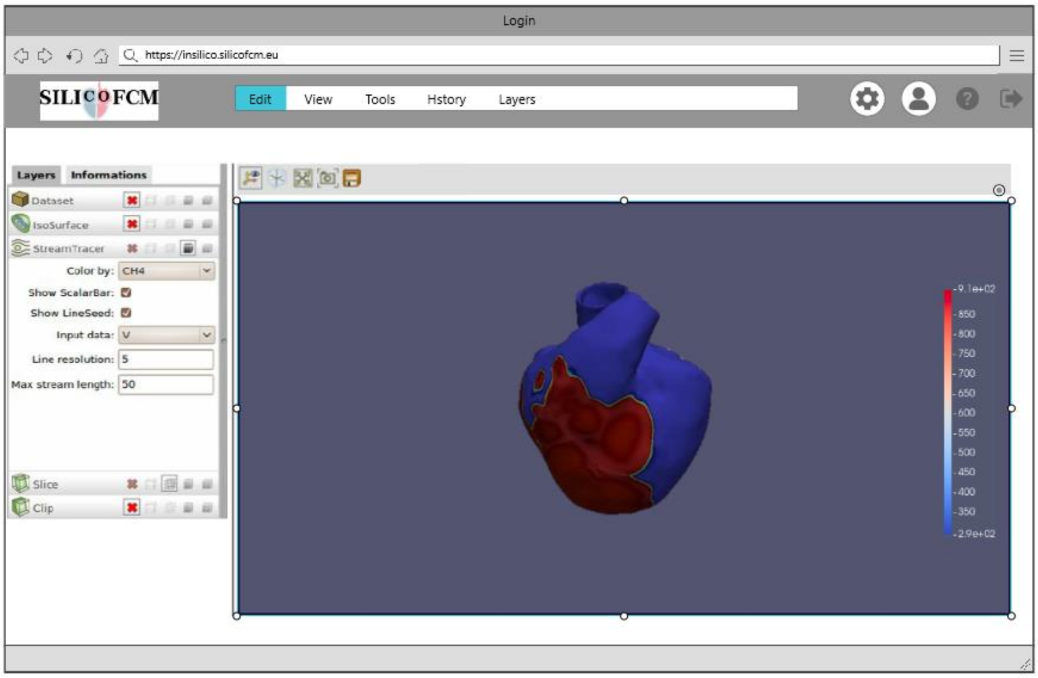

Figure 40: UI mockup of a page of the SILICOFCM VAM (3D contour representation).

Figure 41: UI mockup of a page of the SILICOFCM VAM (2D plots).

6.8 UML Sequence diagrams

6.8.1 Overall

An overall UML sequence diagram for the undergoing services of the SILICOFCM platform is depicted in Figure 42. The user can gain access (login) into the web platform through the user authentication service which checks for the validity of the credentials and from there to the web interface. Through the web interface, the user can execute the SLICOFCM services (i.e., the modules and/or tools) through appropriate queries that are executed in the background. These queries are handled by the Workflow

Manager Module. Depending on the type of each query (i.e., the type of analysis) the workflow manager invokes the related engines (e.g., the data quality control engine for the data quality assessment module). Status flags are returned at each stage which denote either the successful execution of each stage or not. The internal loops at each stage denote the operation that is executed by each individual stage. For example, during the user access management stage, an internal check with the users' credential database is performed in order to validate and identify the type of the user that wishes to access the platform. After the successful validation of the user, appropriate access tokens are provided for accessing the web interface of the SILICOFCM platform, as well as, for executing a variety SILICOFCM of services through appropriate queries. The latter are handled by the Workflow Manager Module. A deeper look into the way that the services are executed through the workflow manager is presented in Figure 45.

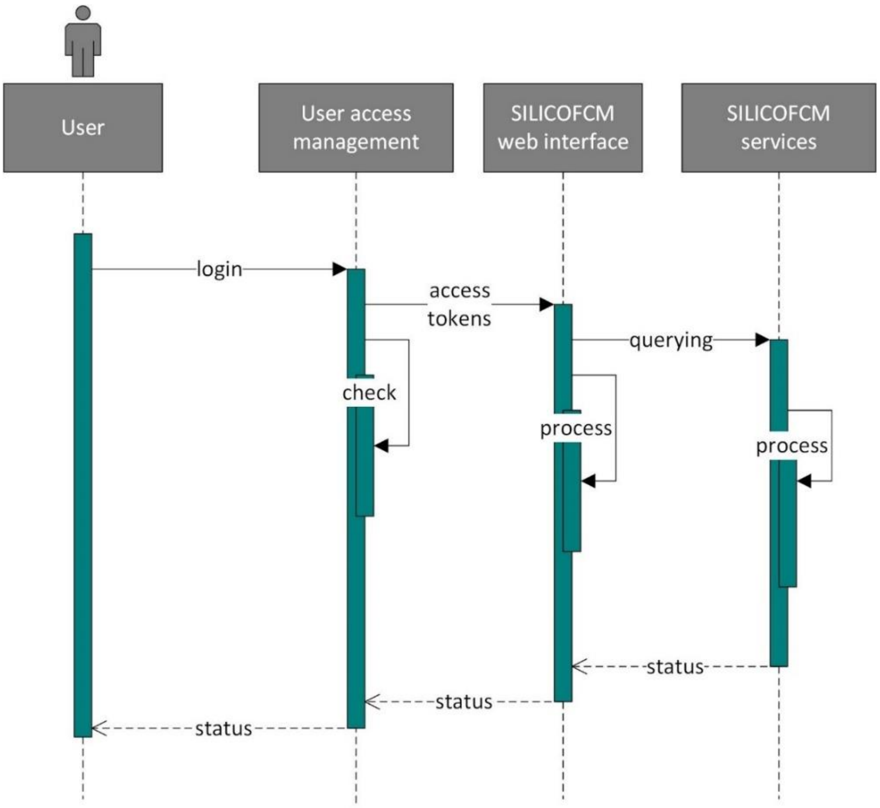

Figure 42: An overall sequence diagram.

6.8.2 User access management (All users)

The sequence diagram for the user access management process is presented in Figure 43. The user types his or her credentials into the login page and requests access to the platform. The user credentials are sent to the user authentication stage for validation with the users' credentials database. The login status determines whether the user will be successfully authorized and gain access to the appropriate services of the SILICOFCM platform or not. In the former case, the user obtains access tokens which enable the execution of only those types of services that are under his or her privileges according to the Workflow Manager Module (e.g., the data provider is the only one who is able to interact with the Data Management Module whereas the typical end-user is the only one who interacts with the SILICOFCM tools). The types of services are presented to the user through the SILICOFCM web interface. In any other case, the returned status denotes an unsuccessful login and the user's access is prohibited.

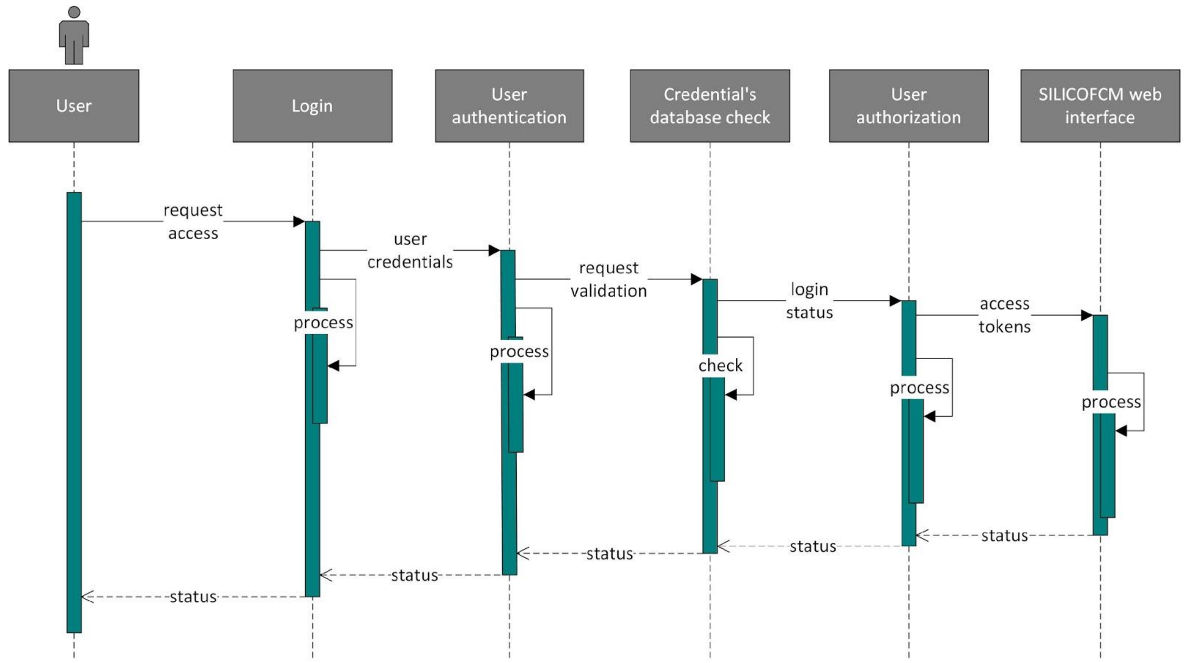

Figure 43: The user access management sequence diagram.

6.8.3 Data Management Module (Data provider)

The sequence diagram for the data management process is depicted in Figure 44. The actor of the depicted diagram is the data provider who initially logs into the platform through the user access management service. Then the data provider is able to upload anonymized data in a secure way. The uploaded data are evaluated by a regulatory committee who is responsible for the relevance and completeness of the data. The quality of the data is then evaluated through the data quality assessment process which is handled by the workflow manager through the data quality control engine. The outcomes of the data quality assessment procedure are appropriate data quality assessment reports which provide important information concerning the accuracy of the clinical and genetic data, as well as, the anonymity of such data. Additional status flags are returned at each stage which denote either the successful or the unsuccessful execution of the user access management, data upload and data quality assessment stages.

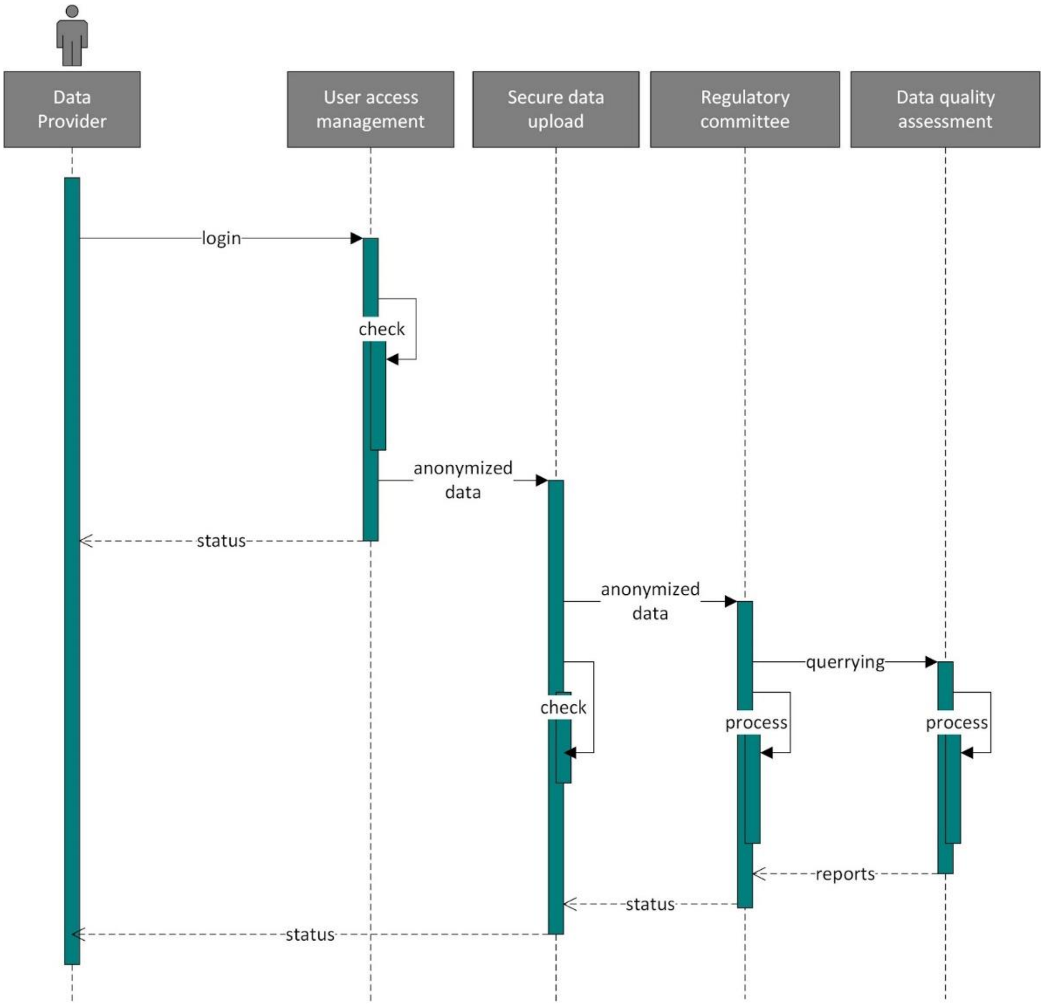

Figure 44: The data management sequence diagram.

6.8.4 Workflow Manager Module (Core services for all users)

The Workflow Manager Module is a core module which is responsible for the execution of the SILICOFCM services (modules and tools). The Workflow Manager Module is invoked anytime a user logs into the SILICOFCM platform through the User Access Management Module. The actor of the sequence diagram can be a data provider, a SILICOFCM typical end-user or a developer. According to a typical sequence diagram (Figure 45), the workflow manager receives input from the user (i.e., the typical-end user) and then constructs appropriate workflows and/or dockers according to whether the analysis involves a module (where the workflow manager invokes the workflow engine) or a tool (where the workflow manager invokes the docker engine). The same stands for the case where the user is the data provider. In this case, the workflows for the Data Management Module are constructed and handled by the data quality control engine. The workflows and/or dockers are executed by the corresponding engines that are invoked by the workflow manager and the results are finally sent to the Visual Analytics Module which outputs the visual components that are necessary for the visualization purposes. The visualization components are finally displayed to the user through the UI. Additional status flags are returned at each stage which denote either the successful or the unsuccessful execution of the stages.

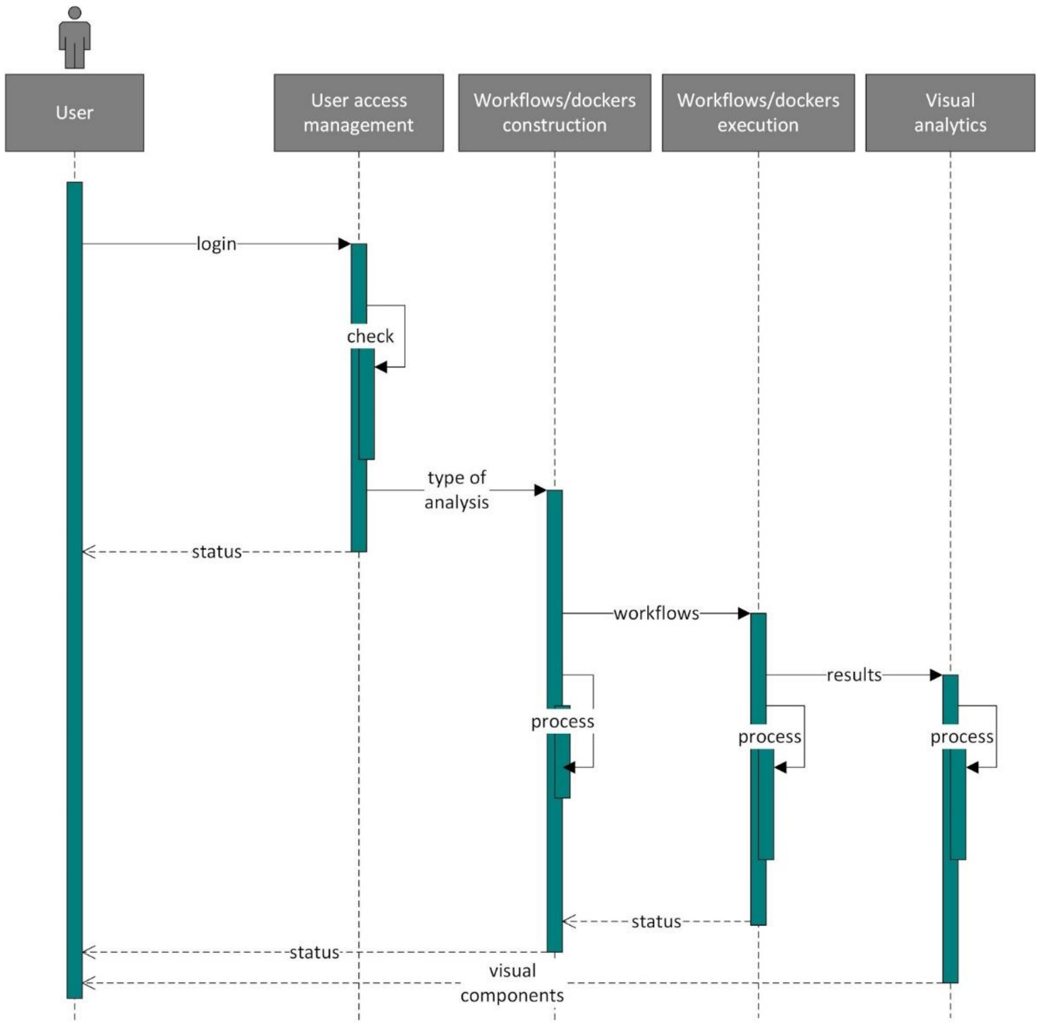

Figure 45: The services execution sequence diagram.

6.8.5 Diagrams for the actions of the inner and outer developers

The sequence diagrams for the actions that are executed under the privileges of the inner and outer developers are presented in Figure 46 and Figure 47, respectively. Both of them can gain access into the platform through the User Access Management Module. Through the SILICOFCM web interface the inner developer can either update, edit, or delete any workflows and/or dockers, through the Workflow Manager Module. On the other hand, the outer developer can only upload and execute new (or existing) workflows. Additional status flags are returned at each stage which denotes either the successful or the unsuccessful execution of the stages.

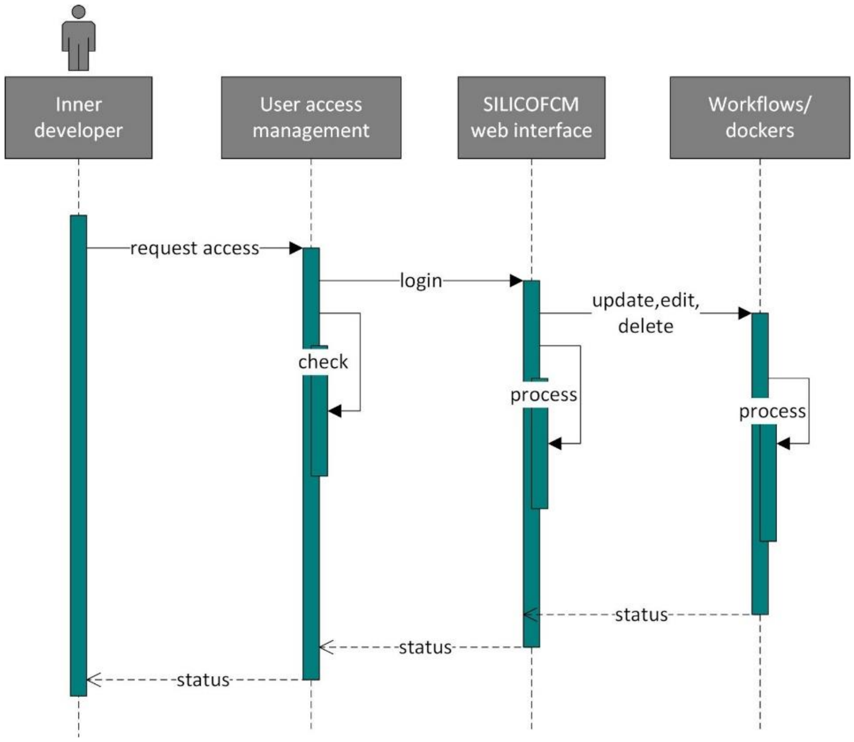

Figure 46: The sequence diagram for the actions of the inner developer.

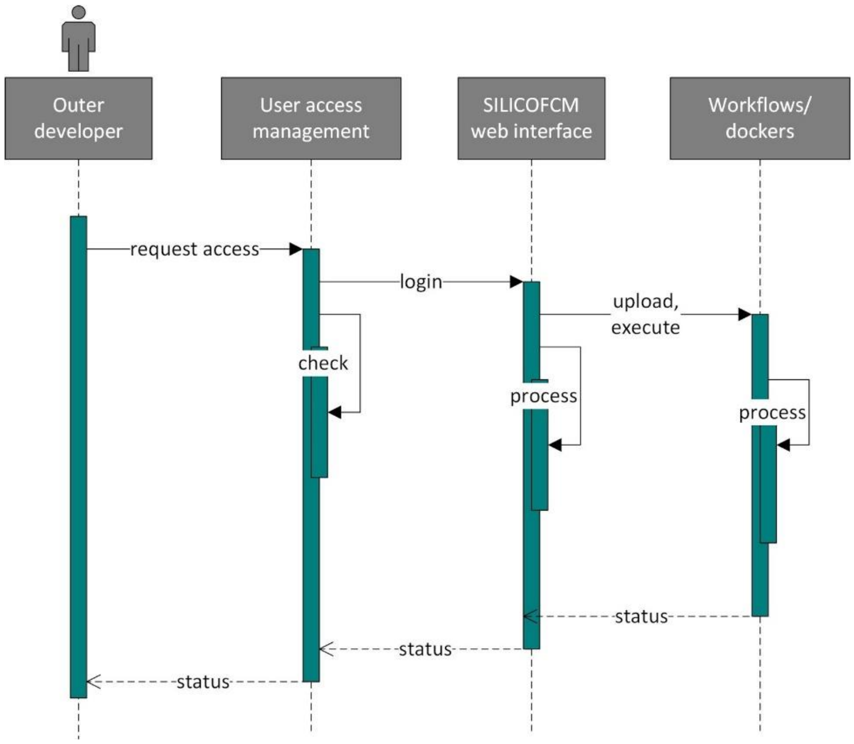

Figure 47: The sequence diagram for the actions of the outer developer.

7. Deviation from the work plan

There is no deviation from the workplan for the current deliverable.

8. Conclusions

"D1.3 - SILICOFCM Reference Architecture'', corresponds to the work, outcomes and results of "Task 1.3 - SILICOFCM Reference Architecture" which started on M1 and ended on M6. The objective was to define, design and document an innovative, generic approach and reference architecture that will facilitate the deployment of a system for *in-silico* clinical trials for the drug efficacy for FCM. To achieve this and taking into consideration the definition of the different type of users (Data providers, Cloud providers, Typical End-users, Inner and Outer developers), the requirement gathering and analysis achieved within Task 1.1: State-of-the-Art and Requirements Analysis (D1.1 - Requirements Analysis, M6) and the system specifications achieved within Task 1.2 - SILICOFCM Specification (D1.2 - SILICOFCM Cloud Platform, M6): (i) several use cases have been created to serve as a basis for the SILICOFCM architecture design and development, (ii) overall and detailed information flows of the different users with SILICOFCM modules have been designed, (iii) the design conceptual architecture and the detailed SILICOFCM architecture with the different modules, tools and engines have been designed, (iv) a state of the art analysis in *in silico* clinical trials similar platforms and proposed methodological approach have been performed, (v) the SILICOFCM modules and tools with the input, output, potential dependencies and workflows have been described, (vi) a conceptual hierarchical multilayer approach of the SILICOFCM framework, the cloud computing services distribution to the SILICOFCM users, the functional and non-functional specifications of the system, hardware specifications and User Interface analysis and mockups have been defined and presented, (vii) UML sequence diagram for the services of the SILICOFCM platform have been designed.

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10. Appendix A1 – Model types

10.1 Use-Case Diagram

A use case diagram shows the interactions, the actions and relationships of the user with the system. This diagram defines the different type of the use cases that can be realised. An example of a use case diagram is presented in Figure 48.

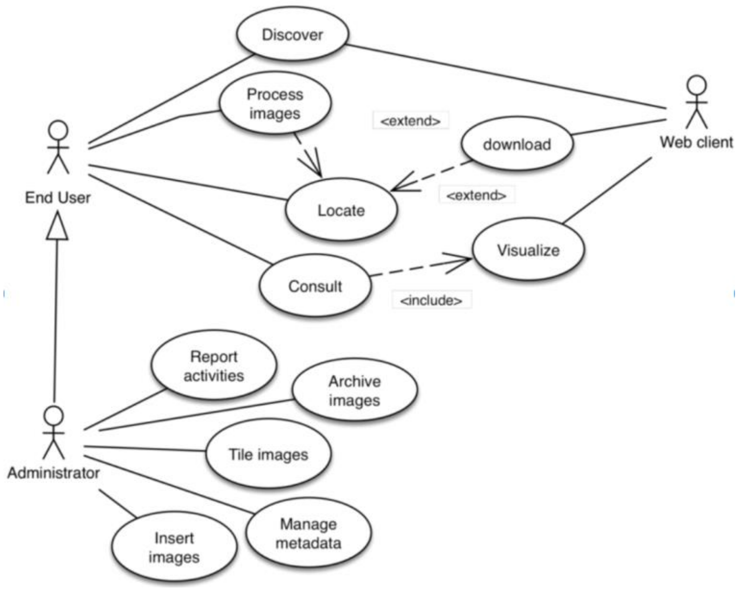

Figure 48: Example of Use Case Diagram[5].

10.2 Layer Diagrams

A layer diagram illustrates the main blocks of the system, their communication and dependencies. An example of a layer diagram is presented in Figure 49.

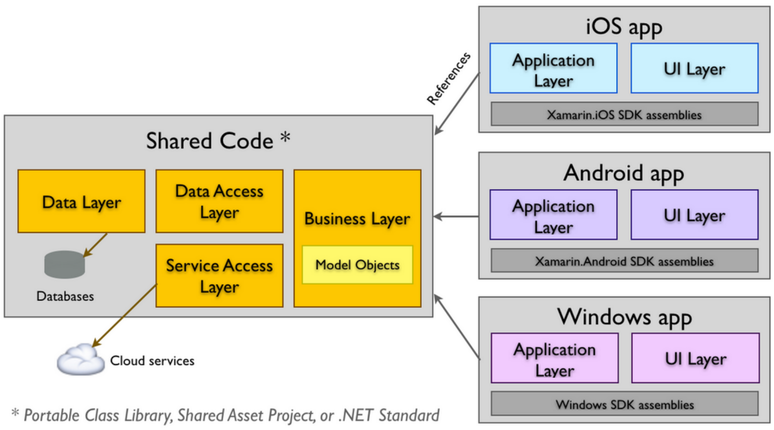

Figure 49: Example of Layer Diagram[6].

5 https://www.researchgate.net/figure/Main-use-cases-of-the-GEOSUD-platform-UML-use-case-diagram_fig3_312529320.
6 https://docs.microsoft.com/en-us/visualstudio/modeling/layer-diagrams-reference.

10.3 Sequence Diagrams

A sequence diagram includes the interaction of objects/systems in time sequence. These diagrams concern the realisation of use cases in the Logical View of the system. In a sequence diagram: (i) the parallel vertical lines (lifelines) present the processes that simultaneously take place, (ii) the horizontal arrows present the message that is exchanged in order to allow the process to be executed. An example of a sequence diagram is presented in Figure 50.

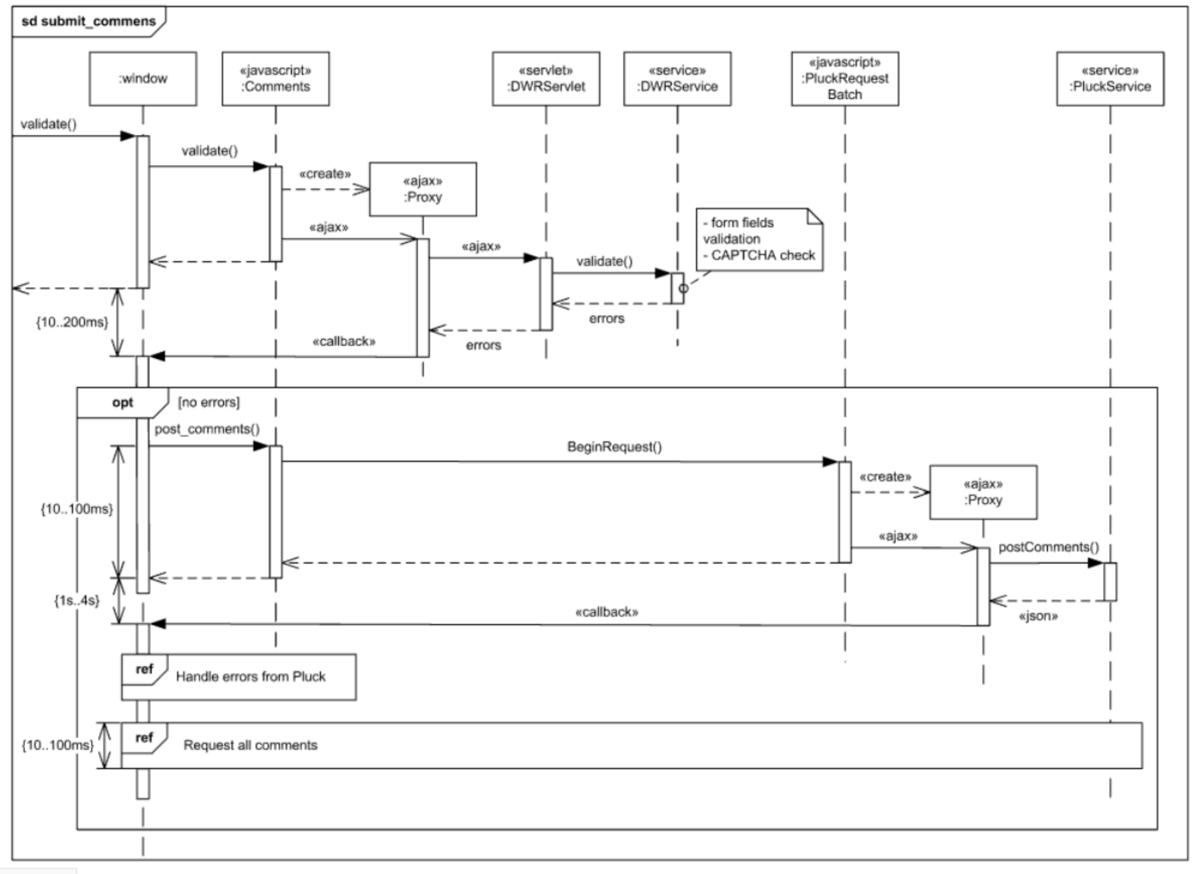

Figure 50: Example of sequence diagram[7].

11. Appendix A2 - Detailed user requirements listing

The following table depicts the detailed listing of the collected user requirements during T1.1 and it is integrating also in the current document for the completeness of it.

ID	D1.1 coding	User Requirements	Description
URNF1	NF_GUR_1	Ease of use	The SILICOFCM platform functionalities the 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.

[7] https://www.uml-diagrams.org/pluck-comments-uml-sequence-diagram-example.html

URNF2	NF_GUR_2	Ease of learning	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 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.
URNF3	NF_GUR_3	Platform time response	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.
URNF4	NF_GUR_4	Simulation time acceptance	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).
URNF5	NF_GUR_5	Expandable Platform Storage	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.
URNF6	NF_GUR_6	Reliable simulation results	The results produced by the SILICOFCM platform on user requests should be accurate and reliable.
URNF7	NF_GUR_7	Available SILCOFCM platform service	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.
URNF8	NF_GUR_8	SILICOFCM model validation	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. The each stage of the model will be validated by comparing model predictions with observation at higher level organization.
URNF9	NF_GUR_9	Notification messages	The appropriate messages (warnings, notification, error messages etc.) are presented to the users in case of improper/unexpected functioning of the system.
URNF10	NF_GUR_10	Data privacy	Any collected data must me anonymized and protected from unauthorized access.
URNF11	NF_GUR_11	Different roles	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.
URNF12	NF_GUR_12	Controlled Data access	Only authorized users should access the SILICOFCM platform integrated data. Different users should have access to different Platform's functionalities and data sets.
URNF13	NF_GUR_13	OAUTH and API services for secure web user authentication and authorization	The SILICOFCM platform should OAUTH and API services for secure web user authentication and authorization.
URNF14	NF_GUR_14	Https Communications	In order to ensure secure communication between users and SILICOFCM platform, all communications should be performed only in https with appropriate certificates.

URNF15	NF_GUR_15	Big data management	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.
URNF16	NF_GUR_16	System administration	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.
URNF17	NF_GUR_17	IPR Protection	IPRs related to SILICOFCM architecture, UI design, development, and implementation, as well as to created and shared data, should be ensured
URNF18	NF_GUR_18	Capability for new services inclusion	The platform should supply inclusion of new services, or increase of existing ones.
URNF19	NF_GUR_19	Capability for new computational resources	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
URNF20	NF_GUR_20	Compliance of the SILICOFCM content and the scope with EU directives	All components and practices developed within SILICOFCM should be in accordance to the project's ethics and EU directives.
URF1	F_DGR_1	Input/output Data Format	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.
URF2	F_DGR_2	Data Vocabular	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.
URF3	F_DGR_3	Metadata	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.
URF4	F_DGR_4	Data Anonymisation	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.
URF5	F_DGR_5	Upload of New Data	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.
URF6	F_DGR_6	Data Consistence and Completeness	The data within the SILICOFCM platform should be accurate and valid, as well as complete, i.e. predefined set of parameters must be included.
URF7	F_DGR_7	Data Updates	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.
URF8	F_DGR_8	Scheduled Backup od SILICOFCM Data	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.

URF9	F_DGR_9	Notification about Data Usage	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.
URF10	F_DGR_10	Data Access Logging and Auditing	The access to the SILICOFCM services should be logged by recording information regarding which user had access, through which service and at which timepoint.
URF11	F_STUR_1	A list of available SILICOFCM tools	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.
URF12	F_STUR_2	A list of available virtual patients/models and clinical/genetic data	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.
URF13	F_STUR_3	A list of available computational resources per tool	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.
URF14	F_STUR_4	UI which allows user to complete all needed tasks for running the simulation	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.
URF15	F_STUR_5	Conversion of SILICOFCM simulation/experiment setup to a workflow	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. A task includes, meshing, data-conversion, simulation, post-processing, data-transfer etc.
URF16	F_STUR_6	Workflows should be defined in a standard workflow definition language	The SILICOFCM workflows for tools/modules are core of the platform and should be defined in a standard workflow definition language.
URF17	F_STUR_7	Validate the SILICOFCM tool workflow execution capability	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.
URF18	F_STUR_8	The task flowcharts should be handled and recovered from task failure	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.
URF18	F_STUR_9	Communication between remote-based tools	The user should be able to execute three tools which are located in remote sites, i.e., the MUSICO, the PAK solver, and the ALYA solver. The SILICOFCM system must provide appropriate workflow engines.
URF20	F_STUR_10	Communication between docker-based tools	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.
URF21	F_STUR_11	Conversion of solvers' files	The SILICOFCM will provide all needed tools in order to convert solvers' files. This is important for the SILICOFCM tools linking.
URF22	F_STUR_12	Incorporate a convergence criteria per case	The SILICOFCM platform should incorporate a default or user defined convergence acceptance criteria related to the SILICOFCM tools.

URF23	F_STUR_13	Parallel execution of simulations	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
URF24	F_STUR_14	Estimation of simulation duration	The SILICOFCM platform should provide the estimation of time required to get results for given specific simulation.
URF25	F_STUR_15	Calculation of sarcomere mechanical response	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.
URF26	F_STUR_16	Linking the MT with BT, ALT, PST	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
URF27	F_STUR_17	Mesh validation	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.
URF28	F_STUR_18	Imaging Data Processing	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.
URF29	F_STUR_19	Set up the Boundary Conditions	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.
URF30	F_STUR_20	Set up the Material Properties	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.
URF31	F_STUR_21	Heart mechanics coupled with electric field and drug transport	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.
URF32	F_STUR_22	Genetic Data Processing	The SILICOFCM platform should enable the user to run CWL 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.

URF33	F_STUR_23	Machine Learning Algorithms usage	The SILICOFCM platform should provide Machine learning algorithms for Risk Stratification, Virtual Patients Repository Modeling, and mining of FCM clinical and genetic data stored within the SILICOFCM database. This 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.
URF34	F_STUR_24	Creation of virtual populations (cohort) of FCM patients	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.
URF35	F_VAUI_1	Post-processing of results	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.
URF36	F_VAUI_2	Visualization of 2D- and 3D-case results in browser	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.
URF37	F_VAUI_3	Visualization of evaluation reports	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.
URF38	F_VAUI_4	Browsing and filtering with an interactive visual access	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.
URF39	F_VAUI_5	Visualization of Virtual Patients Cohort	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.
URF40	F_VAUI_6	Visual and statistical comparison of sub-cohorts	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.
URF41	F_VAUI_7	Capability to Save/Load Working Progress	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.

URF42	F_VAUI_8	Data Download	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.
URF43	F_VAUI_9	Integration with other SILICOFCM services	Is 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.

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